Literature Review

Primary Myelofibrosis

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Primary myelofibrosis (PMF) is a Philadelphia negative myeloproliferative neoplasm characterized by bone marrow fibrosis, splenomegaly, anemia, constitutional symptoms, and extramedullary hematopoiesis. As a clonal hematopoietic stem cell disorder, it is often accompanied by a disease-initiating driver mutation and shortened survival. Diagnosis is often based on bone marrow findings. Diagnosis is supported by the presence of janus kinase 2 (JAK2), calreticulin (CALR), or thrombopoietin receptor protein (MPL) mutation, found in approximately 90% of patients. In 2016, the World Health Organization divided PMF into pre-fibrotic and overt categories to aid in distinguishing PMF from essential thrombocythemia. Several prognostic systems, using a variety of clinical and genetic features, have been developed to aid in therapeutic decision-making. Treatment focuses on alleviation of symptoms and an increase in overall survival. Treatment options have historically been limited. However, the therapeutic landscape is changing with the development of new JAK inhibitors.

Key words: Myelofibrosis, myeloproliferative neoplasm, prefibrotic myelofibrosis, primary myelofibrosis, overt myelofibrosis.

Introduction

Primary myelofibrosis (PMF) is the least frequent Philadelphia chromosome negative (Ph negative) myeloproliferative neoplasm (MPN).[1] PMF is an aggressive and chronic hematologic disease characterized by bone marrow fibrosis resulting in extramedullary hematopoiesis and splenomegaly.[2,3] Additional disease features include anemia, inflammatory cytokine production, constitutional symptoms, and transformation to acute leukemia.[3,4]

In 1951, hematologist William Dameshek included PMF among a group of diseases that he termed myeloproliferative disorders.[5,6] In the past, PMF has had several names including agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, and myelofibrosis with myeloid metaplasia with the latest being primary myelofibrosis.[5] The 2008, 4th edition, of the World Health Organization (WHO) *Classification of Tumors of Hematopoietic and Lymphoid Tissues* modified the term myeloproliferative disorders to myeloproliferative neoplasms. The disease name chronic idiopathic myelofibrosis was replaced with PMF.[7] In addition, MPNs were classified based on bone marrow morphology, clinical features, and genetic information.[7]

In 2016, the WHO revised the 4th edition resulting in changes to the classification of MPNs. As described above, the classification of MPNs are still based on bone marrow morphology, clinical features and genetics, yet the revised edition has more integration of molecular genetic data due to the discovery of new somatic mutations.[8] PMF is further subcategorized into prefibrotic/early primary

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myelofibrosis (pre-PMF) and overt PMF.[8] This subcategorization allows for distinction between "true" essential thrombocythemia (ET) and pre-PMF.[9,10] Additionally, myelofibrosis can follow a diagnosis of ET and polycythemia vera (PV) and is known as post-ET/post-PV MF (or secondary myelofibrosis).[9]

Epidemiology

The annual incidence rate of PMF is approximately 1 per 100,000 based on reports in Australia, Europe, and North America making it the least frequent Ph negative MPN.[6] The prevalence rate of PMF ranges from 1.76 to 4.05 per 100,000.[11] PMF has been reported in all ages, yet it is most often found in middle aged and elderly patients with the majority of patients greater than 50 years old at diagnosis.[1,2] Some studies have indicated that men are affected more frequently than women, however other studies indicate that both sexes are nearly equally affected.[1] In general, median overall survival for PMF is 5-7 years post-diagnosis with primary causes of death including leukemia transformation, vascular events, and infections.[1,6]

Etiology and Pathogenesis

The majority of PMF patients have one of three disease-initiating driver mutations that over-activate the janus kinase 2 and signal transducer and activator of transcription (JAK2-STAT) pathway resulting in unregulated myeloproliferation. Approximately 50-65% of PMF patients have a mutation in the JAK2 gene, specifically the JAK2V617F exon 14 mutation.[12-14] These patients are associated with older age, higher hemoglobin levels and white blood cell (WBC) counts, and lower platelet counts. A mutation in the calreticulin (CALR) gene is found in 20-30% of PMF patients and associated with younger patients, lower hemoglobin and WBC counts with a higher platelet count.[12-14] The least frequent driver mutation, found in about 10% of PMF patients, is a mutation in the myeloproliferative leukemia (MPL) gene .[12-14] An estimated 10% of PMF patients do not have any of the three driver mutations and are known as "triple negative" cases .[12,13] Triple negative PMF patients can be difficult to distinguish from other myeloid diseases and have the poorest prognosis. In addition, there are several non-driver mutations associated with PMF patients that are believed to contribute to disease development and transformation to acute leukemia (Table 1).[4]

Table 1.
Frequent Non-driver Somatic Mutations in PMF

Mutation	Mutational Frequency
TET2 (TET oncogene family member 2)	~17%
SRSF2 (Serine/arginine-rich splicing factor 2)	~17%
U2AF1 (U2 Small Nuclear RNA Auxiliary Factor 1)	~16%
ASXL1 (Additional Sex Combs-Like 1)	~13%
EZH2 (Enhancer of zeste homolog 2)	~7%
DNMT3A (DNA cytosine methyltransferase 3a)	~7%
SF3B1 (Splicing factor 3B subunit 1)	~7%
IDH1/IDH2 (Isocitrate dehydrogenase 1 and 2)	~4%
TP53 (Tumor protein p53)	~4%

These non-driver mutations play a role in DNA methylation (TET2, DNMT3A, and IDH1/IDH2), RNA splicing (SF3B1), chromatin modifications (ASXL1, EZH2), and DNA repair (TP53).[1] In triple negative patients, the presence of one or more of these non-driver mutations may be useful in diagnosis and often indicate a poorer prognosis.[12]

The overexpression of hematopoietic cytokines and growth factors associated with the over-activation of the JAK2-STAT pathway lead to megakaryocyte hyperplasia ultimately resulting in the classic features of PMF – bone marrow fibrosis and abnormal megakaryocytes. Abnormal megakaryocytes and other bone marrow cells release cytokines promoting bone marrow fibrosis. Extramedullary hematopoiesis is associated with the extensive bone marrow fibrosis which contributes to the splenomegaly seen in PMF patients.[6]

Clinical and Diagnostic Findings

The clinical manifestations in PMF vary, however most patients present with anemia, constitutional symptoms (fatigue, fever, and night sweats), and splenomegaly. Splenomegaly is a hallmark finding in PMF patients

and it often seen in approximately 90% of patients.[1] Splenomegaly results from extramedullary hematopoiesis leading to abnormalities in splenic architecture and increased presence of megakaryocytes.[6] It is often a debilitating symptom and a contributing factor in morbidity. Other findings include changes in platelet counts, bleeding, bone pain, headache, hepatomegaly (40-70% of patients), thrombosis, and weight loss.[1-4] Symptoms are often due to the production of cytokines during disease progression. Clinical findings may vary and approximately 30% of patients are asymptomatic at diagnosis.[1]

Diagnosis of PMF is based upon the 2016 WHO criteria and includes a combination of clinical and laboratory findings (Table 2). Pre-PMF was integrated within the PMF category as a variant and was first mentioned in the 2001 WHO classification of tumors.[7,15] Patients with pre-PMF often present with thrombocytosis (increased platelet count) and a lack of bone marrow fibrosis, thus they were often misdiagnosed as having ET. In ET patients, the differentiating bone marrow findings include granulocytic and erythropoietic cells that are in regular ratio with normal megakaryocytes.[16] In pre-PMF, the most profound peripheral blood finding is thrombocytosis often resembling ET. Anemia may be present however tear-drop red blood cells (RBCs) are rare.[17] A slight leukocytosis is common, however an increase in peripheral blood blasts may or may not be present.[17,18]

In overt PMF (classical fibrotic stage), peripheral blood findings include leuko-erythroblastosis with tear-drop RBCs and abnormal platelets due to the release of abnormal cells from sites of extramedullary hematopoiesis. Leuko-erythroblastosis leads to the presence of nucleated RBCs and immature

Table 2. 2016 WHO Diagnostic Criteria for PMF (Diagnosis requires meeting all 3 major criteria and at least 1 minor criterion that is confirmed in 2 consecutive determinations.)

PREFIBROTIC/EARY PMF	OVERT PMF
MAJOR CRITERIA	
1. BONE MARROW MORPHOLOGY: Megakaryocytosis with atypical features, lack of reticulin fibrosis > grade 1[a], accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis	1. BONE MARROW MORPHOLOGY: Megakaryocytosis with atypical features, accompanied by either reticulin and/or collagen fibrosis (grade 2 or 3)[a]
2. CLINICAL: Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, ET, myelodysplastic syndromes or other myeloid neoplasms	2. CLINICAL: Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, ET, myelodysplastic syndromes or other myeloid neoplasms
3. GENETIC: Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these 3 major clonal mutations, presence of another clonal marker or absence of minor reactive bone marrow reticulin fibrosis[b]	3. GENETIC: Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these 3 major clonal mutations, presence of another clonal marker or absence of reactive myelofibrosis[c]
MINOR CRITERIA	
• Anemia not attributed to a comorbid condition	• Anemia not attributed to a comorbid condition
• Leukocyte count ≥ 11 x 10^9/L	• Leukocyte count ≥ 11 x 10^9/L
• Palpable splenomegaly	• Palpable splenomegaly
• Serum LDH level above the upper limit of institutional reference range	• Serum LDH level above the upper limit of institutional reference range
	• Leuko-erythroblastosis

Table adapted from Passamonti and Maffioli 2016, and Abner et al. 2016.[9,10]

Key: WHO, World Health Organization; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; PV, polycythemia vera; ET, essential thrombocythemia; LDH, lactate dehydrogenase

[a]See Table 3.

[b]Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

[c]Bone marrow fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

myeloid cells. Often megathrombocytes and megakaryocyte fragments are seen. Anemia is common while the platelet and WBC count can be variable.[1,6]

In pre-PMF, the bone marrow is often hypercellular with an increase in the proliferation of megakaryocyte and granulocytic cells with a decrease in erythropoietic cells. There is usually no bone marrow fibrosis or minimal reticulin fibrosis at this stage but atypical megakaryocytes and micromegakaryocytes may be present. The bone marrow findings may resemble ET, yet in ET the megakaryocytes appear normal and mature.[1,19] Extramedullary hematopoiesis is minimal if present (Tables 2 and 3).

Table 3.
WHO 2008 Criteria for Grading Reticulin Fibers

Grade	Description
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of collagen and/or focal osteosclerosis
MF-3	Diffuse and dense reticulin with extensive intersections and coarse bundles of collagen, often associated with osteosclerosis

Table adapted from Abner et al. 2016.[10]
Key: WHO, World Health Organization

Due to the hallmark of bone marrow fibrosis in overt PMF, successful bone marrow aspiration is often not achieved resulting in a dry tap requiring a trephine bone marrow biopsy. Bone marrow findings include significant collagen and/or reticulin fibrosis, patches of hematopoietic cellularity, and an increased number of abnormal mega-karyocytes often found in clusters (Tables 2 and 3, and Figures 1-3).

Approximately 30%-50% of PMF cases demonstrate cytogenetic (karyotypic) abnor-malities at diagnosis.[1,6] Cytogenetic analysis is important in the diagnosis and prognosis but it can be challenging due to bone marrow fibrosis. Some of the more common chromo-somal abnormalities detected in PMF include deletions of the long arms of chromosomes 13 and 20, abnormalities of chromosomes 1, 7, and 9, and trisomy 8 and 9. Of these abnormalities, those associated with a favorable prognosis include deletions 13q and 20q, and trisomy 9. A normal karyotype is also associated with a favorable prognosis. Those associated with an unfavorable prognosis include deletions of 7q, trisomy 8, and complex karyotypes.[1,6] These abnormalities are not specific for PMF as they are found in the other Ph negative MPNs and other myeloid malignancies.

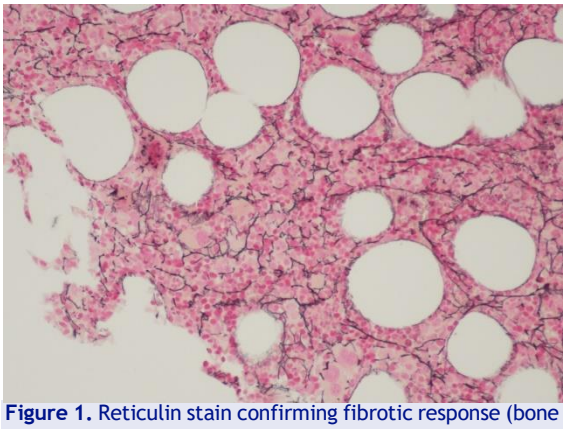

Figure 1. Reticulin stain confirming fibrotic response (bone marrow biopsy - magnification x100).

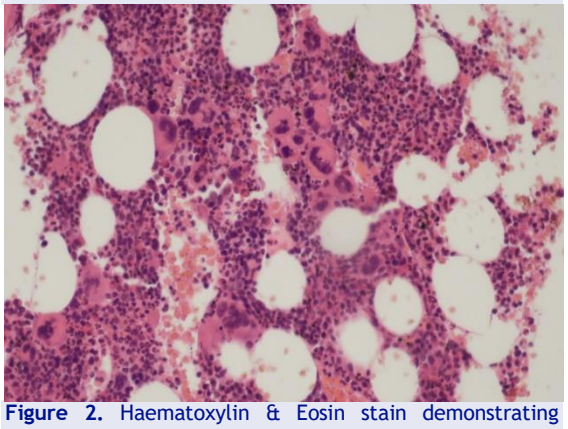

Figure 2. Haematoxylin & Eosin stain demonstrating clusters of abnormal megakaryocytes (bone marrow biopsy – magnification x200).

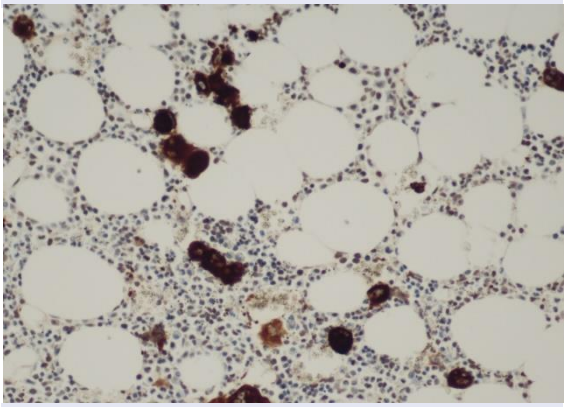

Figure 3. CD61 Immunohistochemical stain demonstrating clusters of megakaryocytes (bone marrow biopsy – magnification x200).

Since the discovery of the driver mutations in MPNs, genomic testing has become a critical component in diagnosis. Patients suspected of an MPN will have mutation analysis performed using next generation sequencing (NGS) methods. Myeloid gene sequencing panels can look for specific mutations in JAK2, CALR, and MPL genes.[13] Extended gene sequencing panels are used for identifying non-driver mutations assisting with prognostic information and therapeutic decisions. For example, PMF patients with mutations in serine and arginine rich splicing factor 2 (SRSF2), ASXL transcription regulator 1 (ASXL1), histone-lysine N-methyltransferase (EZH2), or isocitrate dehydrogenase 1/2 (IDH1/IDH2) have a shorter survival rate and increased risk of transformation to acute leukemia.[20] NGS allows for the identification of patients that are at high risk for disease progression and transformation, and factor into treatment decisions.[13,20]

Prognosis and Risk Stratification

Treatment decisions are often made based on overall survival and risk of transformation to acute leukemia. Thus, prognostic assessment of PMF (prognostic systems for pre-PMF have yet to be developed) has evolved over the years as scientific knowledge has advanced. Early prognostic scoring models were primarily based on clinical and hematology findings (Table 4).

One such system is the International Prognostic Scoring System (IPSS) developed in 2009 by the International Working Group for MPN Research and Treatment (IWG-MRT). The IPSS uses five risk factors (age > 65 years, hemoglobin < 10g/dl, WBC count > 25 x 10^9/L, percentage of circulating blasts ≥1%, and presence of constitutional symptoms), at diagnosis to predict survival.[4,5,14] The IPSS prognostic model places patients into one of four risk groups: low, intermediate-1, intermediate-2, and high based on the number of risk factors present.[5,14] The risk groups allow for better projections of median survival in years.

One year later the IWG-MRT developed the dynamic IPSS (DIPSS) that utilizes the same risk factors as the IPSS, however it is applicable throughout the course of the disease.[4] The DIPSS was further developed to include three additional risk factors (unfavorable karyotype, platelet count < 100 x 10^9/L, and the need for RBC transfusions) and is identified as the DIPSS-plus model.[5] Both the DIPSS and DIPSS-plus the

Table 4. Earlier Prognostic Models for PMF

	IPSS - estimates survival at time of diagnosis	**DIPSS** - can be applied anytime during clinical course	**DIPSS-plus** - can be applied anytime during clinical course
	RISK FACTORS		
	• Age >65 years (1 point)	• Age >65 years (1 point)	• Age >65 years (1 point)
	• Constitutional symptoms (1 point)	• Constitutional symptoms (1 point)	• Constitutional symptoms (1 point)
	• Hemoglobin <10 g/dL (1 point)	• Hemoglobin <10 g/dL (2 points)	• Hemoglobin <10 g/dL (2 points)
	• WBC Count >25 x 10^9/L (1 point)	• WBC Count >25 x 10^9/L (1 point)	• WBC Count >25 x 10^9/L (1 point)
	• Circulating (PB) blasts ≥ 1% (1 point)	• Circulating (PB) blasts ≥ 1% (1 point)	• Circulating (PB) blasts ≥ 1% (1 point)
			• RBC transfusion need (1 point)
			• Platelet count <100 x 10^9/L (1 point)
			• Unfavorable karyotype (1 point)
	RISK GROUPS		
Low	0 points (median survival 11.3 years)	0 points (median survival; not reached)	0 points (median survival 15.4 years)
Intermediate-1	1 point (7.9 years)	1-2 points (14.2 years)	1 point (6.5 years)
Intermediate-2	2 points (4.0 years)	3-4 points (4.0 years)	2-3 points (2.9 years)
High	≥3 points (2.3 years)	≥5 points (1.5 years)	≥4 points (1.3 years)

Key: IPSS, international prognostic scoring system; DIPSS, dynamic international prognostic scoring system; WBC, white blood cell count; PB, peripheral blood; RBC, red blood cell count; PMF, primary myelofibrosis.

model place patients into the same four risk groups as the IPSS.[5,14]

Newer prognostic scoring systems have further incorporated cytogenetic and molecular findings along with the hematological findings (Table 5). In 2018, the Mutation-Enhanced International Prognostic Score System (MIPSS-70) was developed to better select patients, less than 70 years old, as candidates for allogenic hematopoietic stem cell transplant (AHSCT).[9] MIPSS-70 included the classical hematology parameters but incorporated cytogenetic and molecular aberrations. The model places patients into one of three risk categories: low, intermediate or high. Building upon the MIPSS-70, the MIPSS-70 plus was developed and added a fourth risk category (very high) which allowed for better selection of patient candidates for AHSCT.[9] The MIPSS-70 plus version 2.0 incorporates more detailed anemia and cytogenetic information and added a fifth risk category (very low). Lastly, the Genetically-Inspired Scoring System (GIPSS) relies solely on cytogenetic and molecular findings and places patients into one of four risk categories.[5,14]

Any of the three Ph negative MPNs can transform into acute myeloid leukemia. However, the probability for leukemic transformation is the highest in PMF as estimates of incidence range from 11% to 30% with a poor prognosis.[3,21,22] This transformation is often termed blast-phase MPN or secondary acute myeloid leukemia. In PMF patients, the French-American-British (FAB) classification subtypes of M7 (acute megakaryocytic leukemia), M0 (acute myeloid leukemia, minimally differentiated), and M2 (acute myeloid leukemia with maturation) are common.[22] In general, risk factors useful in predicting transformation include: dependence on RBC transfusion, leukocytosis, thrombocytopenia, peripheral blood and bone marrow blasts, abnormal karyotypes, and triple negative mutational status.[22] Primary causes of death in PMF patients include leukemic transformation,

Table 5. Newer Prognostic Models for PMF

	MIPSS-70	MIPSS-70 plus version 2.0	GIPSS
RISK FACTORS			
	• Constitutional symptoms (1 point) • Hemoglobin <10 g/dL (1 point) • WBC Count >25 x 10^9/L (2 points) • Circulating (PB) blasts ≥ 2% (1 point) • Platelet count <100 x 10^9/L (2 points) • Bone marrow fibrosis ≥2 (1 point) • Presence of one HMR mutation (1 point) • Presence of ≥2 HMR mutations (2 points) • Absence of CALR type-1 mutation (1 point)	• Constitutional symptoms (2 points) • Severe anemia (2 points) • Moderate anemia (1 point) • Circulating (PB) blasts ≥ 2% (1 point) • VHR karyotype (4 points) • Unfavorable karyotype (3 points) • ≥2 HMR mutations (3 points) • One HMR mutation (2 points) • Absence of CALR type-1 mutation (1 point)	• VHR karyotype (2 points) • Unfavorable karyotype (1 point) • Absence of CALR type-1 mutation (1 point) • ASXL1 mutation (1 point) • SRSF2 mutation (1 point) • U2AF1Q157 mutation (1 point)
RISK GROUPS			
Very Low		0 points (not reached)	
Low	0-1 point (median survival 27.7 years)	1-2 points (16.4 years)	0 points (26.4 years)
Intermediate-1	2-4 points (7.1 years)	3-4 points (7.7 years)	1 point (8 years)
Intermediate-2			2 points (4.2 years)
High	≥5 points (2.3 years)	5-8 points (4.1 years)	≥3 points (2 years)
Very High		≥9 points (1.8 years)	

Key: MIPSS-70, Mutation-Enhanced International Prognostic Score System for transplant age patients (≤70 years old); GIPSS, Genetically-Inspired Scoring System; WBC, white blood cell count; PB, peripheral blood; HMR, high molecular risk; VHR, very high risk; PMF, primary myelofibrosis.

bleeding, hepatic failure (due to extra-medullary hematopoiesis), pulmonary embolism, and complications from AHSCT.[6]

Treatment

In PMF, the primary goal of treatment is to alleviate symptoms, reduce the degree of splenomegaly, reduce risk of complications, and ultimately increase overall survival and quality of life.[23] Specific treatment options are based on clinical findings and prognosis (prognostic scoring system risk group). As the goal is to relieve symptoms and improve quality of life, asymptomatic patients (very low, low, and possibly intermediate-1 risk groups) may be observed initially with treatment following as symptoms develop.[19] Symptomatic PMF patients will receive treatment for anemia and splenomegaly. Currently, pre-PMF patients are often treated similarly to those with ET as specific treatment guidelines have yet to be developed.[15]

Anemia is managed with transfusion therapy and conventional drug therapy. Drug options include erythropoiesis stimulating drugs, corticosteroids (e.g., prednisone), and androgens (e.g., testosterone enanthate).[4,5] Newer drugs, such as Luspatercept, currently used for beta-thalassemia and myelodysplastic syndrome are being investigated as a therapeutic option for PMF patients.[5] Luspatercept binds to transforming growth factor beta (TGF-β) superfamily thereby reducing the Smad-2/3 (transforming growth factor-beta superfamily) signaling pathway in hematopoiesis and ultimately enhancing late-stage erythropoiesis.[24] Luspatercept has shown modest response rates in PMF patients.[24] Two additional drugs, Sotatercept and Galunisertib, are also being investigated and have potential to become treatment options for PMF patients.[24]

Historically the treatment of splenomegaly, and its negative outcomes, was chemotherapy. One of the longstanding chemotherapeutics used to relieve the symptoms and reduce spleen size is hydroxyurea (HU).[6] HU is a chemotherapeutic agent used to reduce the number of cells by inhibiting DNA synthesis.[1] With the discovery of JAK2 mutations in PMF, newer therapeutic drugs focused on inhibiting activity of janus kinase enzymes. Currently, the only JAK2 inhibitor to be approved in Canada, Europe, and the United States (US) is Ruxolitinib. Ruxolitinib was approved by the US Food and Drug Administration (FDA) in 2011 and works by inhibiting the JAK pathway resulting in the initiation of apoptosis and reduced cellular proliferation.[23] Both HU and Ruxolitinib improve the symptoms of splenomegaly with varying degrees of effectiveness.

Symptomatic low risk patients are often treated with HU or Ruxolitinib. Whereas, intermediate-2 and high-risk patients are traditionally treated with Ruxolitinib if AHSCT is not an option (discussed in more detail below). A significant number of PMF patients, in the intermediate-2 or high-risk categories, may experience Ruxolitinib failure due to intolerance or resistance to the drug.[25,26] Regardless of the cause, these patients discontinue using Ruxolitinib and had limited treatment options until 2019. In 2019, a second-line JAK2 inhibitor Fedratinib, was approved by the US FDA.[25,27] Fedratinib is an option for initial therapy in intermediate-2 or high-risk patients, or an alternative for those who experience Ruxolitinib failure.[27] Fedratinib is a more selective inhibitor of JAK2 than Ruxolitinib (a dual inhibitor JAK1/JAK2 inhibitor).[25]

Other options for splenomegaly include splenectomy or splenic irradiation.[23] Splenectomy aids in controlling persistent anemia and thrombocytopenia while reducing constitutional symptoms and pain. Splenic irradiation also reduces spleen size and provides symptom relief, however response to this treatment is usually short-lived.[23]

For PMF patients that transition to secondary acute myeloid leukemia, treatment options are limited. Transformation to acute leukemia is associated with a poor response to therapy and shortened survival. Cytotoxic chemotherapy regimens are often used yet have limited efficacy.[28] Often supportive care, including RBC transfusions and HU, is used in conjunction with chemotherapy. Survival rates vary with 1-

3 months if supportive care is given and extended (6-9 months) if combined with chemotherapy.[28] If AHSCT is an option, survival improves with rates of 2-3 years.[28]

The only treatment that is potentially a cure for PMF patients is an AHSCT.[1,23] Deciding to pursue AHSCT depends on numerous factors: age, medical comorbidities, clinical and genetic risk factors (high molecular risk mutations such as ASXL1 and SRSF2), and donor availability.[23] When successful, transplantation results in normalization of bone marrow and reduction in splenomegaly. This treatment option has a high rate of mortality and morbidity due to disease relapse and graft-versus-host disease. (Long-term survival occurring in roughly one third of patients.)[4] Therefore AHSCT is only recommended for those in high risk groups based on prognostic models such as the DIPPS and DIPSS-plus. [1,19]

NGS can significantly aid in therapeutic decision-making for PMF patients. Long-term use of HU can result in additional mutations and detection of SRSF2 at diagnosis. This is associated with a higher risk of developing additional mutations.[20] The efficacy of Ruxolitinib is another example, as mutations in ASXL1 often have a shorter time to treatment failure.[20] NGS is useful in determining candidates for AHSCT as those with adverse mutations (high-molecular risk) are ideal candidates for transplantation. However, those with multiple mutations have a higher incidence of post-AHSCT relapse.[20]

Several other JAK inhibitors are currently in clinical trials and include Pacritinib, Momelotinib, and Itacitinib. Pacritinib is a JAK2 inhibitor that shows promising results in reducing spleen size and reduction in symptoms, yet it was placed on clinical hold in 2016 due to concerns of hemorrhagic risk.[29] Momelotinib is a JAK1/JAK2 inhibitor that decreases transfusion dependency.[29] Itacitinib is a JAK1 inhibitor that reduces symptoms but is less effective at reducing spleen size than Ruxolitinib.[29] Most patients with PMF will be treated with a JAK inhibitor. As more inhibitors are approved, combinations of inhibitors might prove to be beneficial as a treatment option.[21,29]

Conclusion

Recent advances in molecular and genomic studies have contributed to the understanding of the pathogenesis and pathophysiology of PMF. Due to these advances, the diagnosis of, and prognostic models and therapeutic options for PMF have evolved to incorporate molecular and genetic findings. Despite the progress, the pathophysiology is complex, and diagnosis can be challenging especially in differentiating pre-fibrotic PMF from ET. In addition, multiple scoring systems have resulted in a variety of risk stratification groups to consider, and an AHSCT is the only curative option for a limited number of patients. As researchers continue to discover additional mutations associated with PMF and novel therapeutic agents are developed, the next decade will hopefully lead to better outcomes for PMF patients.

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