Received : 2022-11-07 Revised : 2022-11-14 Accepted : 2022-12-12 Published : 2022-12-31

PRIMARY MYELOPHYBROSIS: RECOGNIZING ONCET TO COMPLICATIONS

Nimas Resti[1*], Mohammad Rizki [2] and Dita Kholida Nurlalwani[3]
[1]Medical education, Faculty of Medicine, University of Mataram, Mataram
[2]Department of Clinical Pathology, Faculty of Medicine, University of Mataram, Mataram
[3]Medical education, Faculty of Medicine, University of Mataram, Mataram
*Coresponding author: restinimas@gmail.com
Phone: +62 85955116018

Abstract: Myelofibrosis is the accumulation of scar tissue in the bone marrow so that blood cells cannot develop properly. Myeloproliferative disorders, myelofibrosis is classified into two, namely primary myelofibrosis and secondary myelofibrosis. In contrast to secondary myelofibrosis, primary myelofibrosis can occur without being preceded by myeloproliferative disorders or other diseases. In a 2013 meta-analysis study in Europe, the incidence of primary myelofibrosis (PMF) was around 0.3 per 100,000 per year. PMF may result from increased expression of inflammatory cytokines, lysyl oxidase, transforming growth factor-β, impaired megakaryocyte function, and aberrant JAK-STAT signaling. The most common clinical features found in patients with PMF are splenomegaly, hepatomegaly, fatigue, anemia, leukocytosis, and thrombocytosis. Currently the only treatment modality capable of prolonging survival or healing potential in MF is allogeneic hematopoietic stem cell transplantation (AHSCT) especially for high or very high risk patients.

Keywords: myeloproliferative disorders, primary myelofibrosis, scar tissue, bone marrow, JAK-STAT.

1. Introduction

Myelofibrosis, myelo means bone marrow and fibrosis is concerned with the development of fibrous tissue or scar tissue. So that it can be interpreted that myelofibrosis is the accumulation of scar tissue in the bone marrow so that blood cells cannot develop properly. Extensive scar tissue in the bone marrow due to myelofibrosis can cause impaired blood cell formation so that it can cause severe anemia that leads to weakness and fatigue. It can also cause a low number of blood clotting cells called platelets, which increases the risk of bleeding. In addition, myelofibrosis also often causes enlargement of the spleen (Johanis & Hajat, 2011).

Together with polycythemia vera and essential thrombocythemia, myelofibrosis is classified as a chronic hematological cancer (Grinfeld et al., 2018). Myeloproliferative disorders, myelofibrosis itself is also reclassified into two, namely primary myelofibrosis and secondary myelofibrosis (Johanis & Hajat, 2011).

Primary myelofibrosis is myelofibrosis that occurs without being preceded by myeloproliferative disorders or other diseases (Johanis & Hajat, 2011). In the pathogenesis of primary myelofibrosis, increased expression of inflammatory cytokines, lysyl oxidase, transforming growth factor-β, impaired megakaryocyte function, and aberrant JAK-STAT signaling are major factors in the pathogenesis of bone marrow fibrosis (Zahr et al., 2016). For the incidence of myelofibrosis cases, based on data from a meta-analysis of studies conducted on

populations in Europe, it was found that primary myelofibrosis cases were more common in males (range = 0.32 per 100,000 per year to 0.9 per 100,000 per year) than women (range = 0.32 per 100,000 per year to 0.9 per 100,000 per year) range = 0.2 per 100,000 per year to 0.7 per 100,000 per year (Moulard et al., 2013).Clinical manifestations found in patients with primary myelofibrosis include severe anemia, hepatosplenomegaly, constitutional symptoms (eg fatigue, night sweats). days, fever), cachexia, bone pain, splenic infarction, pruritus, thrombosis, and bleeding (Johanis & Hajat, 2011).

2. Definition

Primary myelofibrosis (PMF) is a haematological malignancy in the form of a hemopoitic clonal disorder of stem cells accompanied by excessive accumulation of collagen in the bone marrow (Johanis & Hajat, 2011). As a result of fibrosis that occurs in the bone marrow, it causes damage to healthy bone marrow (Garmezy, Schaefer, Mercer, & Talpaz, 2020). In contrast to secondary myelofibrosis that occurs due to the development or complications of other types of myeloproliferative disorders such as polycythemia vera or essential thrombocythemia, primary myelofibrosis can occur without myeloproliferative disorders or other diseases preceded (Johanis & Hajat, 2011).

3. Epidemiology

In a 2013 meta-analysis study with online participants in a European population, the incidence of myelofibrosis (MF) ranged from 0.1 per 100,000 per year to 1 per 100,000 per year. As for the incidence of primary myelofibrosis (PMF) itself, data obtained about 0.3 per 100,000 per year. This myeloproliferative disorder has a higher incidence in males (range = 0.32 per 100,000 per year to 0.9 per 100,000 per year) than in women (range = 0.2 per 100,000 per year to 0.7 per 100,000 per year). years) with a median age of diagnosis between 69 years (Moulard et al., 2013).

4. Pathogenesis

Primary myelofibrosis occurs through two processes. The first process is the development (expansion) of one or more myeloid strains in the bone marrow during the myeloproliferative process, this condition results in leukocytosis and/or thrombocytosis accompanied by an increase in immature myeloid in the blood circulation. The second process is a reactive bone marrow polyclonal process that stimulates fibroblast proliferation, accumulation of collagen and other connective tissues such as fibronectin and proteoglycans, neoangiogenesis, osteosclerosis, reticulin fibrosis, and decreased effectiveness of hematopoiesis (Johanis & Hajat, 2011).

The reactivity of polyclonal fibroplasia is stimulated by cytokines released by platelets, megakaryocytes, and monocytes, including transforming growth factor (TGF)-b, platelet-derived growth factor (PDGF), interleukin-1, and fibroblast growth factor (fibroblast growth factor). Johanis & Hajat, 2011).

The course of primary myelofibrosis (PMF) has two stages, the first is called the prefibrotic stage, which is characterized by bone marrow hypercellularity and the presence of large amounts of reticulin. The second stage is called the fibrotic stage with the characteristics of fibrotic reticulin or collagen (Johanis & Hajat, 2011).

Clone abnormalities in the form of transformation (transformation) of neoplastic cells play a role in the occurrence of myelofibrosis. Myeloproliferative hematopoiesis abnormalities most commonly occur in granulocyte and megakaryocyte strains and cause granulocytosis and thrombocytosis. Progenitor cells are hypersensitive to cytokines which results in an increase in the number of blood cells. Progenitor cells representing CD 34^{+} can increase up to 400 times (Johanis & Hajat, 2011).

The clonal abnormalities that play a role include mutations in the Janus kinase 2/JAK2 gene in the form of a G to T mutation in the nucleotide 1849, exon 14, causing the substitution of valine to phenylalanine at codon 617 ($JAK2V617F^{+}$). JAK2 is a cytoplasmic tyrosine kinase enzyme that plays a role in cell-induced signaling (signal transduction). These signal transduction proteins are called signal transducers and activators of transcription (STAT), which function as transcriptional activators of cytoplasmic cells. STAT is activated by phosphorylation (phosphorylation) of tyrosine in response to binding between cytokines and their receptors (receptors). In this case, the phosphorylated protein (phosphorylated) undergoes dimerization (dimerization) and enters the nucleus, then activates the transcription process by binding to specific DNA elements. JAK-STAT pathway (JAK-STAT pathway) affects the proliferation, activation, migration (migration), and cell death (apoptosis). In the $JAK2V617F^{+}$ mutation, there is continuous receptor activation due to self-inhibition (autoinhibition) of the JAK2 inhibitory enzyme and hypersensitivity to cytokines, for example excessive activation of the receptor signal (Johanis & Hajat, 2011).

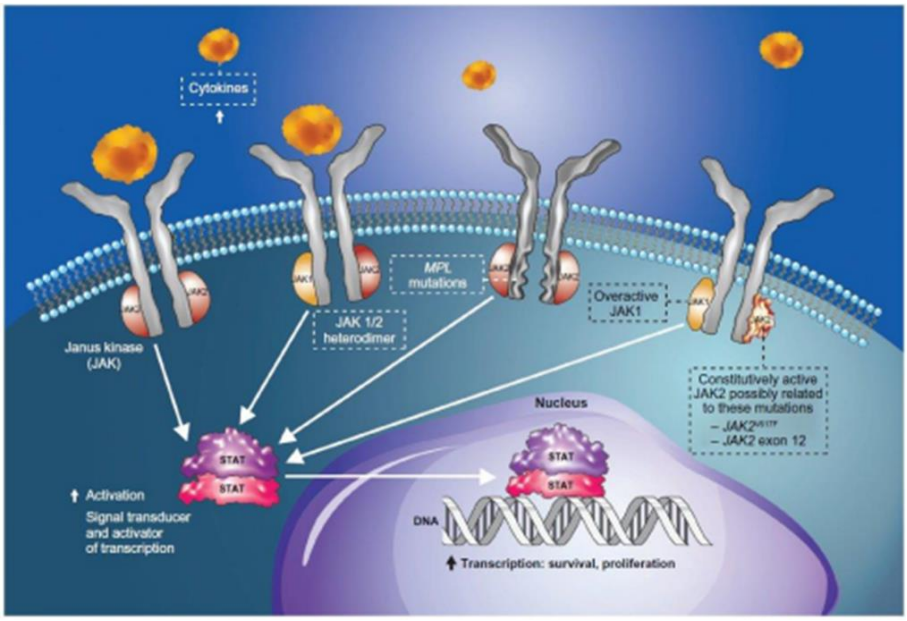

Figure 1. JAK-STAT pathway (JAK-STAT pathway) (Mughal, Vaddi, Sarlis, & Verstovsek, 2014).

In addition to mutations in JAK2, mutations in the thrombopoitin receptor (MPLW515L/K^+) are more typical in PMF and ET. MPLW515L/K^+ mutation in the form of G-to-T transition at nucleotide 1544, causing tryptophan substitution to leucine at codon 515, resulting from MPLW515L/K+ mutation hyperactivation of the JAK-STAT pathway (JAK-STAT pathway) (Johanis & Hajat, 2011).

Other factors that stimulate fibroblasts are tumor necrosis factor alpha (TNF-α), interleukin-1α (IL-1α) and IL-1b released by bone marrow cells. Platelet factor 4/platelet factor 4 (PF4) released by megakaryocytes will inhibit collagenase, resulting in a buildup of collagen (Johanis & Hajat, 2011).

5. Sign and Symptoms

Some people with PMF have no symptoms and are diagnosed during a medical examination. Symptoms usually include weakness, fatigue, shortness of breath, palpitations, weight loss, anorexia, fever, excessive night sweats, left upper abdominal pain caused by splenomegaly, severe pain in the left upper abdomen that radiates to the left arm due to tissue death. (infarction) of the spleen and surrounding inflammation of the spleen (perisplenitis), bleeding, thrombosis, bone pain, especially lower limbs (Johanis & Hajat, 2011).

Clinical signs found in patients with PMF are hepatomegaly, splenomegaly, muscle wasting, osteosclerosis, peripheral edema, lymphadenopathy, pleural effusion, ascites, nervous disorders, portal hypertension, purpura, neutrophilic dermatosis resembling Sweet's syndrome (Johanis & Hajat, 2011).

Table 1. Clinical features of PMF patients at diagnosis (Johanis & Hajat, 2011).

The most common clinical features (>50% of cases)
Splenomegaly
Hepatomegaly
Tired
Anemia
Leukocytosis
Thrombocytosis
The clinical picture is quite common (10–50% of cases)
Asymptomatic (asymptomatic)
Weight loss
Excessive night sweat
Bleeding
Pain in the spleen
Leukopenia
Thrombocytopenia

Rare clinical features (<10% of cases)
- Peripheral edema
- Portal hypertension
- Lymphadenopathy
- Symptoms of yellowness (icteric)
- Gout

Laboratory Overview

In the laboratory description of myelofibrosis, anemia is generally found in the form of normochromic and mormocytic with hemoglobin levels of 9.0-12.0 g/dL, in addition, anisocytosis and poikilocytosis of red blood cells are also common. The morphology of erythrocytes that are often found are dacryocytes and nucleated erythrocytes (Johanis & Hajat, 2011).

In addition, the number of leukocytes also experienced a mild increase with predominantly granulocytes (granulocytosis). The range of leukocyte counts is very wide at the time of diagnosis, namely 0.4–237×103/µL with a mean of 10–14×103/µL found in several studies (Johanis & Hajat, 2011).

In the peripheral blood smear, there was a slight proportion of myelocytes and promyelocytes, but there was hypersegmentation, hyposegmentation (pseudo Pelger-Huët), neutrophil granulation abnormalities, and slightly increased basophils. The proportion of blast cells ranges from 0.5–2% (Johanis & Hajat, 2011).

Neutropenia occurs in 20% of cases at diagnosis. Neutrophil function is impaired in several cases, for example: decreased phagocytic ability which is known through the reaction to decreased nitroblue tetrazolium, decreased oxygen consumption, decreased formation of hydrogen peroxidase, glutathione reductase, and myeloperoxidase (Johanis & Hajat, 2011).

Platelet counts are elevated in 40% of patients with PMF and mild-moderate thrombocytopenia is found in one-third of patients. The number of platelets found ranged from 15–3215×103/µL with a mean of 175–580×103/µL at diagnosis. Typical features on peripheral blood smears are the presence of giant platelets, platelet granulation abnormalities, and megakaryocytes. Platelet function decreased on examination of bleeding and examination of platelet clots against epinephrine aggregators. The content of adenosine diphosphate in solid granules of platelets and lipoxygenase activity decreased (Johanis & Hajat, 2011).

Pancytopenia is found in 10% of patients, the cause is abnormal hematopoiesis and detachment of dead parts (sequestration) from splenomegaly. Associated pancytopenia with advanced bone marrow fibrosis. Lymphocytes experienced a slight decrease, including a decrease in T cells showing $CD3^+$, $CD4^+$, $CD8^+$, $CD3^-/CD56^+$ (Johanis & Hajat, 2011).

The number of progenitor cells of granulocytes, monocytes, erythroids, megakaryocytes has increased in the patient's blood through clonogenic examination in semisolid culture. An increase in cells showing $CD34^+$ is a hallmark of PMF. CD34+ count correlates with disease progression and severity. A $CD34^+$ count of more than 15 cells/µL leads to the diagnosis of PMF, more than 300 cells/µL leads to faster disease progression. Bone marrow biopsy showed

hyperplasia of granulocytes and megakaryocytes. The number of erythroid cells can be decreased, normal, or increased (Johanis & Hajat, 2011).

6. Diagnosis

To establish a diagnosis related to primary myelofibrosis (PMF), it is necessary to carry out several examinations such as (Mayo Clinic Staff, 2019):

1) Physical examination

   Physical examination includes examination of vital signs, such as pulse and blood pressure, as well as examination of lymph nodes, spleen/spleen, and abdomen.

2) Complete blood test

   In myelofibrosis, a complete blood count usually shows a very low level of red blood cells, a sign of anemia that is common in people with myelofibrosis. White blood cell and platelet counts are usually also abnormal. Often, white blood cell levels are higher than normal, although in some people they may be normal or even lower than normal. The platelet count may be higher or lower than normal.

3) Imaging tests (imaging)

   Imaging tests, such as X-rays, MRI, ultrasound tests may be done to check for an enlarged spleen.

4) Bone marrow examination

   A bone marrow biopsy and aspiration can confirm the diagnosis of myelofibrosis.

5) Gene test

   Blood or bone marrow samples may be analyzed in a laboratory to look for gene mutations in blood cells that are associated with myelofibrosis.

The current diagnosis of primary myelofibrosis (PMF) is based on the 2016 WHO criteria and involves a combined assessment of clinical and laboratory features.

Table 2. Revision of diagnostic criteria by the world health organization (WHO) for myelofibrosis prime (Tefferi, 2020).

Primary myelofibrosis (overtly fibrotic) (Diagnosis requires meeting all three major criteria and one minor criterion)	Primary myelofibrosis (pre-fibrotic) (Diagnosis requires meeting all three major criteria and one minor criterion)
Major criteria:	Major criteria:
1. Typical megakaryocyte changes,[a] accompanied by ≥grade 2 reticulin/collagen fibrosis[b]	1. Typical megakaryocyte changes,[a] accompanied by ≤grade 1 reticulin/collagen fibrosis
2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis	2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis
Not meeting WHO criteria for other myeloid neoplasms	3. Not meeting WHO criteria for other myeloid neoplasms
Minor criteria:	Minor criteria:
Anemia not otherwise explained	Anemia not otherwise explained
Leukocytosis ≥ 11×10^9/L	Leukocytosis ≥ 11×10^9/L
Palpable splenomegaly	Palpable splenomegaly
Increased serum lactate dehydrogenase	Increased serum lactate dehydrogenase
A leukoerythroblastic blood smear	

7. Management

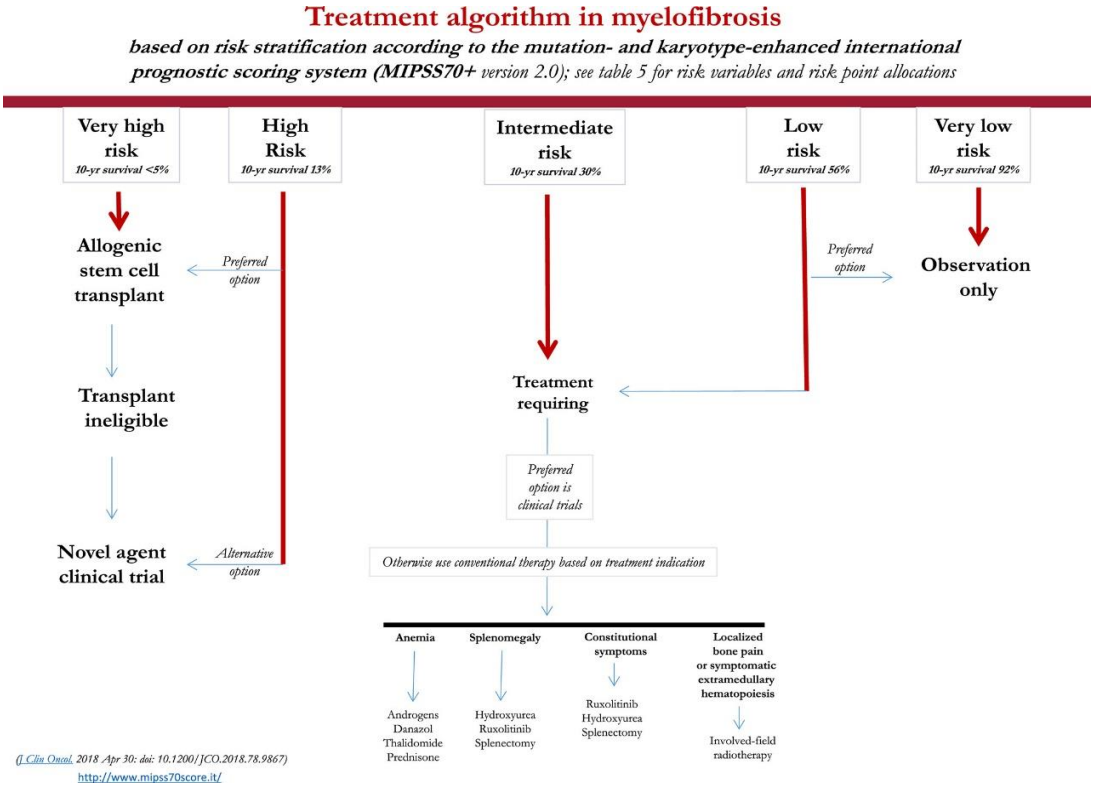

Figure 2. Treatment algorithm for myelofibrosis based on risk stratification according to the mutation –and karyotype-enhanced international prognostic scoring system (MIPSS70+ version 2.0) (Tefferi, 2020).

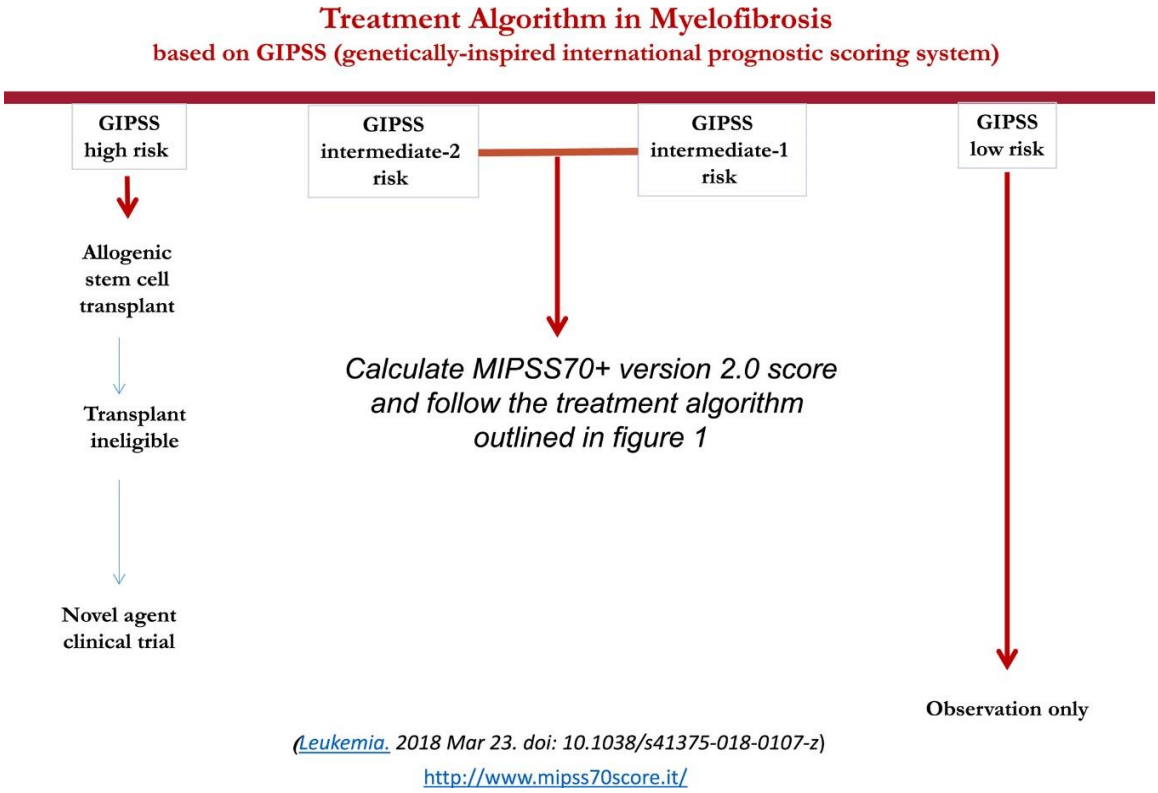

Figure 3. Treatment algorithm for myelofibrosis based on GIPSS (genetically-inspired international prognostic scoring system) (Tefferi, 2020).

The only treatment modality currently capable of prolonging survival or healing potential in MF is allogeneic hematopoietic stem cell transplantation (AHSCT). AHSCT is the treatment of choice for "high" or "very high" MIPSSv2 (Figure 2) (Tefferi, 2020).

Unfortunately, AHSCT in MF is currently associated with at least a 50% rate of transplant-related mortality or severe morbidity (eg, graft vs. host disease), regardless of the intensity of the conditioning regimen used. In previously published studies it was shown that these patients had more loss, in terms of survival, from AHSCT, compared to conventional treatment that did not include transplantation (Tefferi, 2020).

Conventional therapy is considered in MIPSS requiring intermediate risk v2 treatment and in high-risk patients who are not eligible for AHSCT or investigative drug therapy. Drugs to consider in MF-associated anemia include androgens (eg, testosterone enanthate 400-600 mg IM weekly, oral fluoxymesterone 10 mg TID), prednisone (0.5 mg/kg/day), danazol (600 mg/day), thalidomide (50 mg/day) ± prednisone, or lenalidomide (10 mg/day) ± prednisone (10 mg/day). In this case, the administration of an erythropoiesis-stimulating agent (ESA) is ineffective, especially in transfusion dependent patients because it can worsen splenomegaly (Tefferi, 2020).

The response rate for each of the drugs mentioned above is approximately 15% to 25%, and the median response duration is about 1 to 2 years. Lenalidomide works best in the presence of del (5q31). The side effects of using the drugs mentioned above include hepatotoxicity and

virilization effects for androgens, peripheral neuropathy for thalidomide, and myelosuppression for lenalidomide (Tefferi, 2020).

The first-line drug of choice for MF-associated splenomegaly is hydroxyurea, which is effective in reducing spleen size by half in approximately 40% of patients. The spleen's response to hydroxyurea lasts an average of 1 year, and side effects of treatment include myelosuppression and painful mucocutaneous ulcers (Tefferi, 2020).

In hydroxyurea-refractory MF patients presenting with splenomegaly, ruxolitinib offers an effective alternative, and also has the capacity to relieve constitutional symptoms and treat other disease-specific complications. Reports on long-term outcomes of ruxolitinib therapy in MF have revealed a high rate of discontinuation of treatment (92% after a median time of 9.2 months) and the occurrence of severe withdrawal symptoms during discontinuation of ruxolitinib treatment ("ruxolitinib withdrawal syndrome") characterized by symptoms acute relapsing disease, accelerated splenomegaly, worsening cytopenias, and occasional hemodynamic decompensation, including septic shock-like syndromes (Tefferi, 2020).

Indications for splenectomy in MF include splenic abdominal pain and discomfort, symptomatic portal hypertension, severe thrombocytopenia, and frequent red cell transfusions. In a report of 314 splenectomy patients with MF, 102 more than 75% benefited from this procedure and the benefit lasted for a median of 1 year. Specific benefits include being independent of transfusion (~approximately 50%) and resolution of severe thrombocytopenia (Tefferi, 2020).

8. Complications

Extramedullary hematopoiesis occurs when progenitor cells are released from the bone marrow and decreased splenic filtration function is accompanied by abnormal cytokine stimulation. Extramedullary hematopoiesis in primary myelofibrosis (PMF) can develop into fibrohematopoitic tumors in the organs concerned, for example: adrenal glands, renal parenchyma (renal), lymph nodes (lymph), digestive tract, breast, liver, lung, mediastinum, pleura, mesenteric , skin, synovium, thymus, thyroid (thyroid), chest (thorax), prostate, spleen, and urinary tract. Hematopoiesis outside the marrow (extramedullary) in the skull (intracranial) can cause severe neurologic complications, including: subdural hemorrhage, increased intracranial pressure, large brain tumor (cerebral), paralysis, coma. Hemopoitik on the serous surface causes effusions, for example in the chest, abdomen, and pericardial cavity (Johanis & Hajat, 2011).

Other complications of PMF are portal hypertension, ascites, esophageal varices, gastrointestinal bleeding, and hepatic-associated encephalopathy, which results from increased splenoportal outflow and decreased hepatic vascular flexibility or hepatic thrombosis. The causes of death in patients with PMF are infection (26–29%), bleeding (11–22%), heart failure (7–15%), liver failure (3–8%), tumors (3%), respiratory failure (3%)), and portal hypertension (6%) (Johanis & Hajat, 2011).

9. Conclusion

Primary myelofibrosis is a hematological malignancy in the form of a hemopoitic clone of stem cells accompanied by excessive accumulation of collagen in the bone marrow. In contrast to secondary myelofibrosis, primary myelofibrosis can occur without being preceded by myeloproliferative disorders or other diseases. In the pathogenesis of primary myelofibrosis, increased expression of inflammatory cytokines, lysyl oxidase, transforming growth factor-β, impaired megakaryocyte function, and aberrant JAK-STAT signaling are major factors in the pathogenesis of bone marrow fibrosis. The most common clinical features found in patients with PMF are splenomegaly, hepatomegaly, fatigue, anemia, leukocytosis, and thrombocytosis. To diagnose primary myelofibrosis, physical examination, imaging tests, bone marrow examinations, and gene tests can also be performed.

References

Garmezy, B., Schaefer, J. K., Mercer, J., & Talpaz, M. (2020). A Provider's Guide to Primary Myelofibrosis: Pathophysiology, Diagnosis, and Management. *Blood Reviews*, 100691. https://doi.org/10.1016/j.blre.2020.100691

Grinfeld, J., Nangalia, J., Baxter, E. J., Wedge, D. C., Angelopoulos, N., Cantrill, R., … Campbell, P. J. (2018). Classification and Personalized Prognosis in Myeloproliferative Neoplasms. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa1716614

Johanis, & Hajat, A. (2011). Patogenesis Dan Pemeriksaan Laboratorium Mielofibrosis Primer. *Indonesia Journal Of Clinical Pathology and Medical Laboratory*, *Vol 17*.

Moulard, O., Mehta, J., Fryzek, J., Olivares, R., Iqbal, U., & Mesa, R. A. (2013). Epidemiology of myelofibrosis , essential thrombocythemia , and polycythemia vera in the European Union. *European Journal of Haematology*, *92*(2), 289–297. https://doi.org/10.1111/ejh.12256

Mughal, T. I., Vaddi, K., Sarlis, N. J., & Verstovsek, S. (2014). Myelofibrosis-associated complications : pathogenesis , clinical manifestations , and effects on outcomes. *International Journal of General Medicine*, 89–101.

Staff Mayo Clinic. (2019). Myelofibrosis.URL: https://www.mayoclinic.org/diseases-conditions/myelofibrosis/symptoms-causes/syc-20355057

Tefferi, A. (2020). Primary myelofibrosis : 2021 update on diagnosis , risk-stratification and management. *WILEY AJH*. https://doi.org/10.1002/ajh.26050

Zahr, A. A., Salama, M. E., Carreau, N., Tremblay, D., Verstovsek, S., Mesa, R., … Mascarenhas, J. (2016). Bone marrow fibrosis in myelofibrosis: pathogenesis, prognosis and targeted strategies. *Haematologica*, *Volume 101*. https://doi.org/10.3324/haematol.2015.141283