Cancer Association of South Africa (CANSA)

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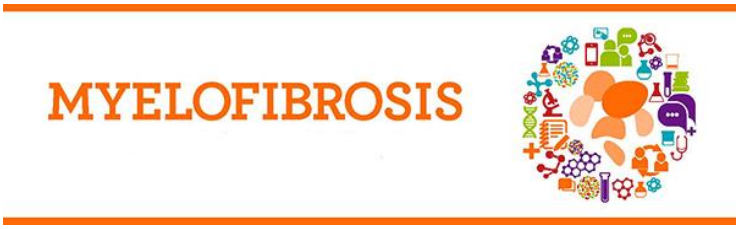
Fact Sheet
on
Myelofibrosis

Introduction

Myelofibrosis (MF) is a serious bone marrow disorder that disrupts one's body's normal production of blood cells. The result is extensive scarring in the bone marrow, leading to severe anaemia, weakness, fatigue, and often, an enlarged spleen and liver.

[Picture Credit: Myelofibrosis]



MF is an uncommon type of chronic leukaemia - a cancer that affects the blood-forming tissues in the body. MF belongs to a group of diseases called myeloproliferative disorders.

Many people with MF get progressively worse, and some may eventually develop a more serious form of leukaemia. Yet it is also possible to have MF and live symptom-free for years. Treatment for MF, which focuses on relieving symptoms, can involve a variety of options.

MF is also known as chronic idiopathic myelofibrosis, myeloid metaplasia, osteomyelofibrosis, agnogenic myeloid metaplasia and primary myelofibrosis.

Myelofibrosis (MF)

MF is a rare blood disorder. 'Myelo' means bone marrow and 'fibrosis' relates to the development of fibrous or scar tissue. So myelofibrosis is a condition that causes scarring of the bone marrow.

MF can develop without having had any other condition. This is called primary myelofibrosis (PMF) or chronic idiopathic myelofibrosis. It can also develop in people who have polycythaemia vera or thrombocythaemia. This is called secondary myelofibrosis.

The bone marrow is the soft inner part of one's bones that makes blood cells. All blood cells start from the same type of cell called a stem cell. The stem cell makes immature blood cells. The

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immature cells go through various stages of development before they become fully developed blood cells and are released into the blood as:

- Red blood cells to carry oxygen around the body
- White blood cells to fight infection
- Platelets to help the blood clot

The diagram below shows how the various different types of cells develop from a single blood stem cell.

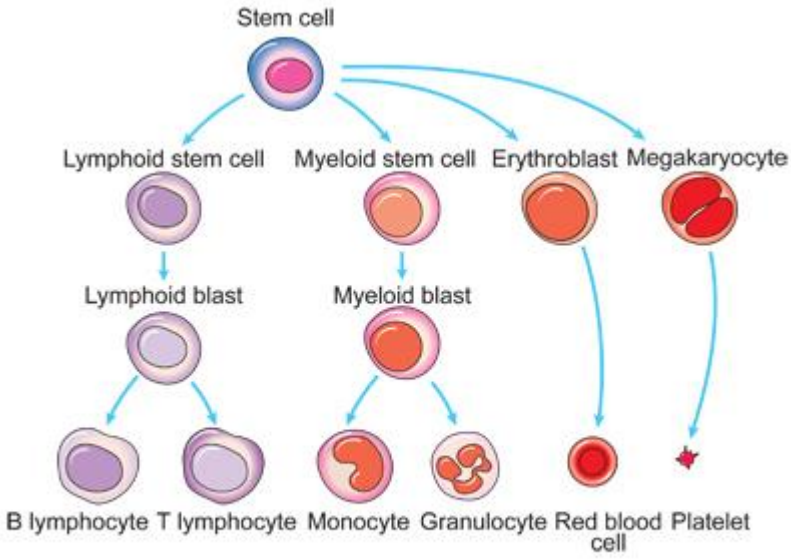


Diagram showing how blood cells are made
Copyright © Cancer Research UK

In people with myelofibrosis the stem cells make too many megakaryocytes. These cells usually develop into mega-karyoblasts and eventually into platelets.

Megakaryocytes also produce other cells called fibroblasts. Fibroblasts make a number of substances that help in wound healing and maintaining the body's supportive tissue (connective tissue). These substances make scar tissue form in the bone marrow. The scar tissue crowds out the bone marrow and stops it working normally. Gradually the bone marrow produces fewer blood cells. As the number of new blood cells falls, the liver and spleen try to make more blood cells. But they are not as good at making them as the bone marrow and they become enlarged.

MF usually affects red blood cells first. The bone marrow keeps trying to produce more of them but they are often immature and tear drop shaped, which is abnormal. This means they are not able to work normally which causes anaemia. As MF develops, the bone marrow also makes fewer white blood cells and platelets. MF can also cause an enlarged spleen (doctors call this splenomegaly). (Cancer Research UK).

Incidence of Myelofibrosis (MF) in South Africa

The incidence of MF in South Africa is not known. There is no available information about this condition in the National Cancer Registry (2017) because it is an uncommon form of leukaemia.

Risk Factors for Myelofibrosis (MF)

Risk factors for Myelofibrosis may include:

- Age - the disease usually develops slowly in people over age 50. Although it can occur at any age, it is most commonly diagnosed between the ages of 50 and 70
- Blood disorders - some people with leukaemia, lymphoma, essential thrombocythaemia (increased platelets) or polycythaemia vera (increased blood counts) develop MF
- Chemicals - MF has been linked to exposure to certain industrial chemicals such as benzene and toluene
- Radiation exposure - people exposed to high levels of radiations and radioactive contrast material like Thorotrast have an increased risk of developing MF.

Symptoms of Myelofibrosis (MF)

Living with myelofibrosis (MF) is different for every person. No matter how myelofibrosis affects the individual, it is important to monitor and keep track of any symptoms. This will help the health care team both treat and manage any symptoms the patient may experience.

Symptoms of MF might include:

- Abdominal pain
- Fatigue
- Fever
- Night sweats
- Bone/muscle pain
- Easy bruising or bleeding
- Pain under the left ribs
- Early feeling of fullness
- Itchiness
- Weight loss
- Shortness of breath

Diagnosis of Myelofibrosis (MF)

MF is usually diagnosed by a haematologist (a specialist in blood disorders). The diagnosis may be suspected from the results of a routine blood test called a full blood count. This test counts the number of red blood cells, white blood cells and platelets in the blood.

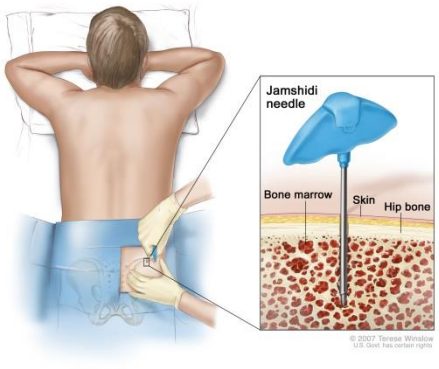
Tests and investigations that may be done to confirm a diagnosis of MF include:

JAK2 test - this blood test checks for a change (mutation) in a gene called JAK2. This gene helps control how many blood cells are made. A change (mutation) in the gene, which happens during the person's lifetime, can cause MF. It is not something one is born with and one cannot pass it on to one’s children.

CALR blood test - blood tests might also check for a change in another gene called calreticulin (CALR). As with the JAK2 gene change, it happens during the person's lifetime. It is not something one is born with and one cannot pass it on to one’s children.

[Picture Credit: Bone Marrow Biopsy]

Bone marrow sample (biopsy) - the doctor may want to take a sample of bone marrow (biopsy) to examine under a microscope. The sample is usually taken from the back of the hip bone (pelvis). The patient will be given an injection of local anaesthetic to numb the area. The doctor will then pass a needle through the skin into the bone, and draw a small sample of liquid marrow (bone marrow aspirate) into a syringe.



After this, the doctor will also take a small core (piece) of marrow from the bone (a trephine biopsy). Both samples will be looked at later under a microscope.

Tefferi, A. 2021.
Disease overview: Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation that is often but not always accompanied by JAK2, CALR, or MPL mutations. Additional disease features include bone marrow reticulin/collagen fibrosis, aberrant inflammatory cytokine expression, anemia, hepatosplenomegaly, extramedullary hematopoiesis (EMH), constitutional symptoms, cachexia, leukemic progression, and shortened survival.
Diagnosis: Bone marrow morphology is the primary basis for diagnosis. Presence of JAK2, CALR, or MPL mutation, expected in around 90% of the patients, is supportive but not essential for diagnosis; these mutations are also prevalent in the closely related MPNs, namely polycythemia vera (PV) and essential thrombocythemia (ET). The 2016 World Health Organization classification system distinguishes "prefibrotic" from "overtly fibrotic" PMF; the former might mimic ET in its presentation. Furthermore, approximately 15% of patients with ET or PV might progress into a PMF-like phenotype (post-ET/PV MF) during their clinical course.
Adverse mutations: SRSF2, ASXL1, and U2AF1-Q157 mutations predict inferior survival in PMF, independent of each other and other risk factors. RAS/CBL mutations predicted resistance to ruxolitinib therapy.
Adverse karyotype: Very high risk abnormalities include -7, inv (3), i(17q), +21, +19, 12p-, and 11q-.
Risk stratification: Two new prognostic systems for PMF have recently been introduced: GIPSS (genetically-inspired prognostic scoring system) and MIPSS70+ version 2.0 (MIPSSv2; mutation- and karyotype-enhanced international prognostic scoring system). GIPSS is based exclusively on mutations and karyotype. MIPSSv2 includes, in addition, clinical risk factors. GIPSS features four and MIPSSv2 five risk categories.
Risk-adapted therapy: Observation alone is advised for MIPSSv2 "low" and "very low" risk disease (estimated 10-year survival 56%-92%); allogeneic hematopoietic stem cell transplant (AHSCT) is the preferred treatment for "very high" and "high" risk disease (estimated 10-year survival 0%-13%); treatment-requiring patients with intermediate-risk disease (estimated 10-year survival 30%) are best served by participating in clinical trials. In non-transplant candidates, conventional treatment for anemia includes androgens, prednisone, thalidomide, and danazol; for symptomatic splenomegaly, hydroxyurea and ruxolitinib; and for constitutional symptoms, ruxolitinib. Fedratinib, another JAK2 inhibitor, has now been FDA-approved for use in ruxolitinib failures. Splenectomy is considered for drug-refractory splenomegaly and involved field radiotherapy for non-hepatosplenic EMH and extremity bone pain.

New directions: A number of new agents, alone or in combination with ruxolitinib, are currently under investigation for MF treatment (ClinicalTrials.gov); preliminary results from some of these clinical trials were presented at the 2020 ASH annual meeting and highlighted in the current document.

Treatment of Myelofibrosis (MF)

Currently, there is no drug therapy that can cure MF. An allogeneic stem cell transplant is the only potential cure for MF. The procedure is risky in older MF patients, who may also have other health problems, so allogeneic stem cell transplantation is usually appropriate only for a small subset of younger patients, typically less than 5 percent of patients with MF.

Patients who are symptom-free and do not have signs of anaemia, an enlarged spleen or other complications are generally not treated. Some people remain stable and symptom-free for many years. However, these patients need to be monitored closely through regular medical check-ups and examinations to detect any signs and symptoms of disease progression.

Drug Therapies

Janus-associated kinase (JAK) inhibitors—This drug class inhibits enzymes called 'JAK1' and 'JAK2', which are involved in the production of blood cells.

Gangat, N. & Tefferi, A. 2020.

"Myelofibrosis is an enigmatic myeloproliferative neoplasm, despite noteworthy strides in understanding its genetic underpinnings. Driver mutations involving JAK2, CALR or MPL in 90% of patients mediate constitutive JAK-STAT signaling which, in concert with epigenetic alterations (ASXL1, DNMT3A, SRSF2, EZH2, IDH1/2 mutations), play a fundamental role in disease pathogenesis. Aberrant immature megakaryocytes are a quintessential feature, exhibiting reduced GATA1 protein expression and secreting a plethora of pro-inflammatory cytokines (IL-1 ß, TGF-ß), growth factors (b-FGF, PDGF, VEGF) in addition to extra cellular matrix components (fibronectin, laminin, collagens). The ensuing disrupted interactions amongst the megakaryocytes, osteoblasts, endothelium, stromal cells and myofibroblasts within the bone marrow culminate in the development of fibrosis and osteosclerosis. Presently, prognostic assessment tools for primary myelofibrosis (PMF) are centered on genetics, with incorporation of cytogenetic and molecular information into the mutation-enhanced (MIPSS 70-plus version 2.0) and genetically-inspired (GIPSS) prognostic scoring systems. Both models illustrate substantial clinical heterogeneity in PMF and serve as the crux for risk-adapted therapeutic decisions. A major challenge remains the dearth of disease-modifying drugs, whereas allogeneic transplant offers the chance of long-term remission for some patients. Our review serves to synopsise current appreciation of the pathogenesis of myelofibrosis together with emerging management strategies."

Ruxolitinib (JakafiTM), given by mouth, is the first JAK inhibitor and currently the only drug approved by the FDA to treat symptoms and signs of MF, including an enlarged spleen, night sweats, itching and bone or muscle pain. It is indicated for treatment of patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post polycythaemia vera myelofibrosis and post essential thrombocythaemia myelofibrosis. The most common side effects affecting the blood cells

are thrombocytopenia (a decrease below the normal number of platelets) and anaemia. Other common side effects include bruising, dizziness and headache.

Patients should be aware that after discontinuation of Jakafi, myelofibrosis signs and symptoms are expected to return. There have been isolated cases of patients discontinuing Jakafi during acute intervening illnesses after which the patient's clinical course continued to worsen. It has not been established whether discontinuation of therapy contributed to the clinical course of these patients. When discontinuing Jakafi therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered.

Current data suggest that constitutively active JAK-STAT signalling plays a central role in the pathogenesis (disease process) of BCR-ABL1-negative myeloproliferative neoplasms (MPNs), regardless of the specific underlying molecular abnormality. This observation provides strong rationale for use of JAK inhibitors for MPN treatment, and these drugs were first tested in myelofibrosis (MF) patients. Ruxolitinib, a JAK-1/2 inhibitor, is effective at controlling splenomegaly and constitutional symptoms, but has limited benefit in reversing bone marrow fibrosis or inducing complete or partial remissions. Ruxolitinib is currently in Phase 3 testing for treatment of hydroxyurea resistant/intolerant polycythemia vera (PV). Preliminary data reveals response rates of 60% for haematocrit control and 38% for spleen volume reduction per protocol-defined criteria, in addition to improving disease-related symptoms. These endpoints, however, have limited value as surrogates for long-term clinically relevant outcomes such as freedom-from-cardiovascular/thrombohaemorrhagic events or time-to-haematological transformation, and the early crossover design of the aforementioned trial introduces limitations in terms of analysis of these latter endpoints. In contrast, other recent trials in PV have demonstrated the feasibility of using long-term clinically relevant outcomes as a primary endpoint.
(Pardanani & Tefferi, 2014a).

Ruxolitinib, a Janus kinase (JAK)-1 and JAK-2 inhibitor, is the first-in-class drug to be licensed in the United States for the treatment of high- and intermediate-risk myelofibrosis (MF). Several other JAK inhibitors are in development with some currently undergoing phase-3 clinical trial testing. None of the currently available JAK inhibitors are specific to mutant JAK2; their mechanism of action involves attenuation of JAK-STAT signalling with downregulation of proinflammatory cytokines, rather than selective suppression of the disease clone. Accordingly, while ruxolitinib and other JAK inhibitors are effective in controlling splenomegaly (enlargement of the spleen) and alleviating constitutional symptoms, their benefit in terms of reversing bone marrow fibrosis or inducing complete or partial remissions appears to be limited. The experience to date with ruxolitinib shows that despite its salutary effects on quality of life, over half of the patients discontinue treatment within 2-3 years.
(Pardanani & Tefferi, 2014b).

Harrison, C.N., Schaap, N. & Mesa, R.A. 2020.
"Myelofibrosis is a BCR-ABL1-negative myeloproliferative neoplasm characterized by anemia, progressive splenomegaly, extramedullary hematopoiesis, bone marrow fibrosis, constitutional symptoms, leukemic progression, and shortened survival. Constitutive activation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway, and other cellular pathways downstream, leads to myeloproliferation, proinflammatory cytokine expression, and bone marrow remodeling. Transplant is the only curative option for myelofibrosis, but high rates of morbidity and mortality limit eligibility. Several prognostic models have been developed to facilitate treatment decisions. Until the recent approval of fedratinib, a JAK2 inhibitor, ruxolitinib was the only available JAK inhibitor for treatment of intermediate- or high-risk myelofibrosis. Ruxolitinib reduces

splenomegaly to some degree in almost all treated patients; however, many patients cannot tolerate ruxolitinib due to dose-dependent drug-related cytopenias, and even patients with a good initial response often develop resistance to ruxolitinib after 2-3 years of therapy. Currently, there is no consensus definition of ruxolitinib failure. Until fedratinib approval, strategies to overcome ruxolitinib resistance or intolerance were mainly different approaches to continued ruxolitinib therapy, including dosing modifications and ruxolitinib rechallenge. Fedratinib and two other JAK2 inhibitors in later stages of clinical development, pacritinib and momelotinib, have been shown to induce clinical responses and improve symptoms in patients previously treated with ruxolitinib. Fedratinib induces robust spleen responses, and pacritinib and momelotinib may have preferential activity in patients with severe cytopenias. Reviewed here are strategies to ameliorate ruxolitinib resistance or intolerance, and outcomes of clinical trials in patients with myelofibrosis receiving second-line JAK inhibitors after ruxolitinib treatment."

Chemotherapy

Conventional chemotherapies kill cancer cells that divide rapidly. These treatments may also affect rapidly dividing healthy cells, such as cells that form nails and hair follicles, cells that line the gastrointestinal tract and stem cells that produce blood cells.

Radiation Therapy

Radiation may be useful for a small number of patients to treat an enlarged spleen, bone pain and tumours outside the marrow.

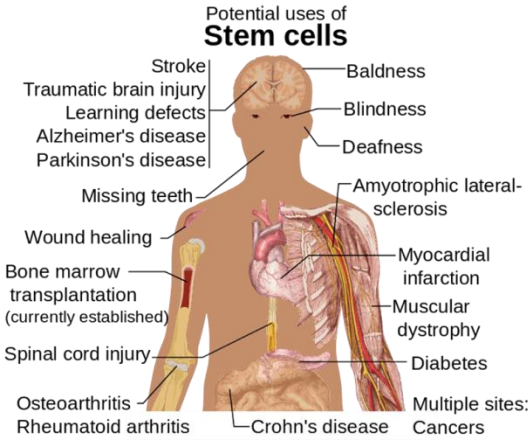
Splenectomy

The spleen can be surgically removed if it is very large and is causing a very low platelet count, severe anaemia or portal hypertension. The decision to do a splenectomy is based on weighing the benefits and the risks to an individual patient. MF patients who will be undergoing a splenectomy need to be evaluated before surgery and then monitored afterward for an increased risk of bleeding complications, including blood clot formation leading to a stroke or pulmonary embolism; infection; liver enlargement; and an increase in platelet count.

Helbig, G., Wieczorkiewicz-Kabut, A., Markiewicz, M., Krzemień, H., Wójciak, M., Białas, K., Kopera, M., Rzenno, E., Woźniczka, K., Kopińska, A., Grygoruk-Wiśniowska, I. & Koclęga, A. 2019.
"Splenectomy before allogeneic stem cell transplantation (ASCT) for patients with myelofibrosis (MF) remains a matter of debate, and conflicting results have been reported to date. The procedure seems to fasten post-transplant hematological recovery, but it does not have an impact on survival. The role of pre-transplant splenic irradiation (SI) is much more difficult to evaluate. Forty-four patients (25 males and 19 females) with MF at median age of 49 years at diagnosis (range 14-67) underwent ASCT. The post-transplant outcome was compared between irradiated and non-irradiated patients. Eleven patients received irradiation before transplantation. Median dose of radiation was 1000 cGy (range 600-2400). There was no difference in median time to engraftment between patients with and without previous radiotherapy. Acute and chronic graft versus host disease (GVHD) occurred in 47% and 36% of patients, respectively. There was no difference in GVHD incidence between groups. Eight patients relapsed/progressed in irradiated group versus 17 in non-irradiated (70% vs. 51%; $p = 0.3$). Transformation to acute myeloid leukemia was observed in 3 patients: 2 in irradiated and 1 in non-irradiated group. In total, 22 patients died with no statistical difference in death rate between irradiated and non-irradiated subjects. The probability of overall

survival after transplant for the entire cohort at 2 years was 54% (72% for irradiated and 48% for non-irradiated patients; p = 0.25). Splenic irradiation prior to ASCT for myelofibrosis has not beneficial effect on post-transplant outcome."

[Picture Credit: Stem Cells]



Stem Cell Transplantation

Allogeneic stem cell transplantation (ASCT) is the only current treatment with the potential to cure MF, but it also carries a high risk of life-threatening side effects for most MF patients. In this procedure, the patient receives high doses of chemotherapy or radiation therapy to destroy the diseased bone marrow. Then, healthy hematopoietic (blood-forming) stem cells from a compatible donor (a sibling or unrelated person whose stem cells 'match' the patient's) are infused into the MF patient.

The transplanted healthy cells travel to the patient's bone marrow, replacing the defective stem cells. The new cells grow and provide a supply of red cells, white cells (including immune cells) and platelets. Most patients with MF are older and often have other health conditions that may impair organ function. Older individuals are also more likely to have other medical problems, develop complications from the treatment and have decreased tolerance for the cumulative effects of the intensive chemotherapy and for radiation treatments needed before the transplant.

However, these are generalisations. Allogeneic stem cell transplantation can be used in older people when medically appropriate. Whether or not a patient is a candidate for transplantation is determined by medical indications and the availability of a donor. There is no specific age cut-off for stem cell transplantation.

Reduced-intensity or 'non-myeloblative' allogeneic stem cell transplantation is a type of transplant that uses lower doses of chemotherapy or radiation, and it is being used to treat some patients with leukaemia, lymphoma or myeloma. Compared to a standard ASCT, a reduced-intensity transplant delivers lower doses of chemotherapy drugs and/or radiation to the patient in preparation for the transplant.

The success of reduced-intensity transplantation is a result of the graft-versus-tumour effect of the donor stem cells, rather than of high doses of chemotherapy. This approach may benefit older and sicker patients and other selected patients. Reduced-intensity transplants are now done with results that are increasingly encouraging for MF patients.

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