Cancer Association of South Africa (CANSA)

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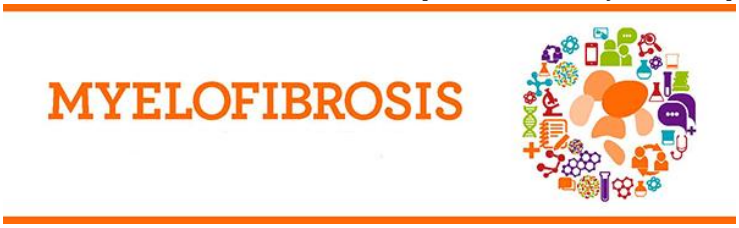
Fact Sheet
on
Myelofibrosis

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.
(Mayo Clinic; CallUSDoc).

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 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.

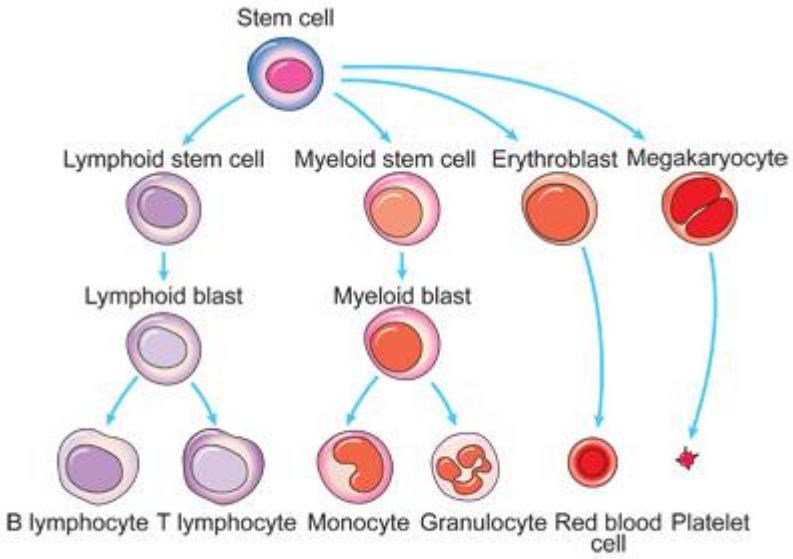


Diagram showing how blood cells are made
Copyright © Cancer Research UK

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 (2012) because it is an uncommon form of leukaemia.

Incidence of Leukaemia in South Africa
In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry does not make provision for the reporting of the different types of leukaemia – it also does not differentiate between acute and chronic leukaemia - neither does it provide for different statistics for cases of adult and childhood leukaemia.

According to the National Cancer Registry (2012) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	380	1:502	1,03%
Asian males	11	1:666	1,34%
Black males	201	1:762	1,73%
Coloured males	42	1:452	0,97%
White males	126	1:232	0,63%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	285	1:955	0,76%
Asian females	5	1:1 777	0,47%
Black females	160	1:1 409	0,97%
Coloured females	49	1:440	1,17%
White females	72	1:480	0,45%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	88	29	38	42	50	54	54	20
Asian males	3	1	0	0	1	2	2	2
Black males	67	21	25	20	20	23	13	3
Coloured males	6	2	5	1	8	6	8	4
White males	12	5	6	18	18	23	30	11

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	63	19	24	34	42	37	31	20
Asian females	0	1	1	2	1	0	0	0
Black females	40	18	27	16	22	11	12	6
Coloured females	10	4	3	3	5	13	5	5
White females	12	3	1	6	14	12	14	9

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Risk Factors for Myelofibrosis (MF)

Risk factors for Myelofibrosis 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.

(CallUSDoc).

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

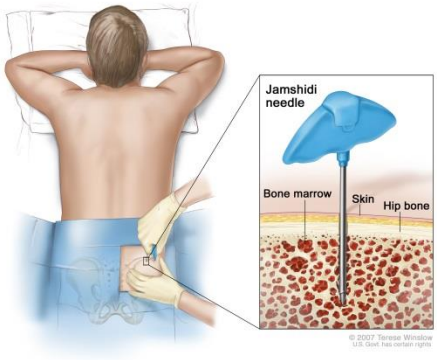
(MyelofibrosisAwareness.org).

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.
(MacMillan Cancer Support).

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.

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).

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.

Some systemic chemotherapies for symptoms of MF include:

Cladribine (Leustatin®) - this chemotherapy, given intravenously (IV), is a purine analogue that interferes with the cell's ability to process DNA. It helps diminish the symptoms of anemia in MF patients.

Hydroxyurea (Hydrea®) - this common chemotherapeutic agent, given by mouth, is used to reduce a number of MF symptoms, as well as high platelet and white blood cell counts; an enlarged spleen; night sweats and weight loss.

Immunomodulators (IMiDs) - the drugs in this class work against cancer cells by affecting the functions of the immune system. Two IMiDs, thalidomide (Thalomid®) and lenalidomide (Revlimid®), both given by mouth, are used to treat MF patients for anaemia.

Favourable responses to thalidomide have been reported in 20 to 60 percent of MF patients. Another IMiD, pomalidomide (Actimid®), also given by mouth, is showing positive results in clinical studies in the treatment of myelofibrosis-related anemia. Pomalidomide is also being studied in clinical trials to treat patients with myeloma. Interferon alfa (Intron®A, Roferon®-A), given by intramuscular or subcutaneous injection, is a synthetic version of a substance made by cells in the body to fight infection and tumours. It has been used to treat an enlarged spleen, bone pain and high platelet count in selected MF patients.

Androgen therapy (Oxymetholone [Anadrol-50®], danazol) - these drugs, both given by mouth, are synthetic versions (analogues) of male hormones and can promote red cell production. They are used to relieve the symptoms of severe anaemia. About one in three patients has improvement of anaemia with androgen treatment. Due to the toxic effects of androgens on the liver, treatment with these drugs includes using blood tests and ultrasound imaging to track liver functions. Androgens may cause facial hair growth or other masculinizing effects in women.

Recombinant erythropoietin (Epogen®, Procrit®) - this treatment, given intravenously (IV) or by subcutaneous injection, helps regulate red cell production. However, the response in anaemia-related symptoms in MF patients has been limited.

Glucocorticoids (also called ‘corticosteroids’ or ‘steroids’) - glucocorticoids such as prednisone, given by mouth, are steroid compounds that are used to treat many conditions and may benefit MF patients who have significant anaemia. About one in three patients has improvement of anaemia with prednisone treatment.

Bisphosphonates (pamidronate disodium [Aredia®], zoledronic acid [Zometa®]) - bisphosphonates are a class of drugs that prevent bone loss in cancer patients and may relieve bone pain and improve blood counts in MF patients. Both of these drugs are given intravenously (IV).

Anagrelide hydrocholoride (Agrylin®) - this drug, given by mouth, may be used to treat patients who have a very high platelet count, especially following removal of the spleen (‘splenectomy’).

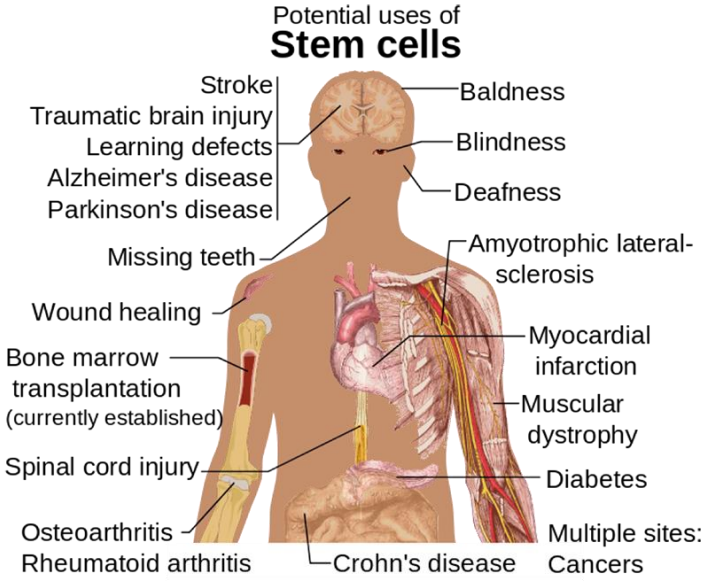
Radiation Therapy

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.

[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.
(Leukemia and Lymphoma Society).

Medical Disclaimer

Sources and References

Bone Marrow Biopsy
https://www.google.co.za/search?q=bone+marrow+biopsy&source=lnms&tbm=isch&sa=X&ei=gHW-U5-ODoOu7AaxsIHYCA&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=666&dpr=0.9#facrc=_&imgdii=_&imgrc=1zVFuhzexpFJwM%253A%3BMDlv_vCHRTTrdM%3Bhttp%253A%252F%252Fnationalcmlsocietyblog.org%252Fwp-content%252Fuploads%252F2013%252F03%252FCDR0000554337.jpg%3Bhttp%253A%252F%252Fnationalcmlsocietyblog.org%252Fanswering-questions-about-bone-marrow-aspirationsbiopsies%252F%3B3000%3B2400

Cancer Research UK
http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/myelofibrosis

CallUSDoc
http://callusdoc.com/DiseaseDetail/Myelofibrosis/What-is-myelofibrosis

Leukemia and Lymphoma Society
https://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/mpd/pdf/idiopathicmyelofibrosis.pdf

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Causesriskfactors/Pre-cancerous/Chronicidiopathicmyelofibrosis.aspx#DynamicJumpMenuManager_6_Anchor_4

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/myelofibrosis/basics/definition/con-20027210

Myelofibrosis
https://www.google.co.za/search?q=myelofibrosis&source=lnms&tbm=isch&sa=X&ei=RGa-U-DoM6yy7AaNj4D4CQ&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=Eo9MtIA9GXLGdM%253A%3BYl0pcXsXsWSAXM%3Bhttp%253A%252F%252Fwww.accc-cancer.org%252Fassets%252Fimages%252Fbanner-education-Myelofibrosis-600x180.png%3Bhttp%253A%252F%252Fwww.accc-cancer.org%252Fresources%252FMyelofibrosis-Overview.asp%3B600%3B180

MyelofibrosisAwareness.org
http://myelofibrosisawareness.org/symptoms-of-mf/

Pardanani, A. & Tefferi, A. 2014. Is there a role for JAK inhibitors in BCR-ABL1-negative myeloproliferative neoplasms other than myelofibrosis? *Leuk Lymphoma*. Dec: 55(12):2706-11. Doi: 10.3109/10428194.2014.985159.

Pardanani, A. & Tefferi, A. 2014. Definition and management of ruxolitinib treatment failure in myelofibrosis. *Blood Cancer J*. Dec 12:4:e268. Doi: 10.1038/bcj.2014.84.