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Myelofibrosis Facts

No. 14 in a series providing the latest information for patients, caregivers and healthcare professionals

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Highlights

- Myelofibrosis (MF) is a rare bone marrow cancer. It is one of a related group of blood cancers known as "myeloproliferative neoplasms (MPNs)" in which bone marrow cells that produce the blood cells develop and function abnormally.
- MF is a type of chronic leukemia and can occur on its own (primary myelofibrosis) or as a result of another bone marrow disorder: other MPNs that can progress to myelofibrosis include polycythemia vera and essential thrombocythemia.
- MF develops when a genetic mutation(s) occurs in bone marrow stem cells. Between 50 and 60 percent of people with MF have a mutation of the Janus kinase 2 gene (*JAK2*), and approximately 25 percent have a mutation of the calreticulin gene (*CALR*). A number of other mutations have been recently found in patients with MF. Researchers are investigating other possible gene mutations responsible for MF. The cause of the gene mutation(s), or cause of the disease, is unknown.
- MF usually develops slowly and some people may live symptom-free for years. Others, however, may get progressively worse, requiring treatment. In both cases, patients do need to be monitored regularly.
- The treatment goal for most patients with MF is to relieve symptoms, reduce an enlarged spleen, improve blood cell counts (eg, anemia), and reduce the risk of complications. Treatments include blood transfusions, chemotherapy, radiation or removal of the spleen (splenectomy), drugs to treat anemia, and allogeneic stem cell transplantation. Ruxolitinib (Jakafi®) is the first drug approved by the US Food and Drug Administration (FDA) to treat MF because it has been shown to reduce MF-related systemic symptoms and enlarged spleen. Other potential therapies for MF treatment are being studied in clinical trials.
- Allogeneic stem cell transplantation (ASCT) is the only potential cure for MF. This treatment has a considerable risk of life-threatening side effects. ASCT is not a good option for most people with MF because of age, the course of their disease or other health problems.

Introduction

Myelofibrosis (MF) belongs to a group of closely related blood cancers known as "myeloproliferative neoplasms (MPNs)" in which the bone marrow cells that produce the body's blood cells develop and function abnormally. The result is excessive fibrous (scar) tissue formation in the bone marrow, which can lead to severe anemia, weakness, fatigue, an enlarged spleen and liver, and body wasting (loss of body mass or size).

MF can occur on its own, called "primary myelofibrosis," or as a progression of other MPNs, notably polycythemia vera (PV) and essential thrombocythemia (ET). Between 15 and 20 percent of MF cases begin as either PV or ET. MF is also known by several other names, including agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, myelosclerosis with myeloid metaplasia and idiopathic myelofibrosis.

This fact sheet includes information about diagnosis, treatment and expected outcomes of MF, information about new treatments being investigated in clinical trials and support resources.

About Myelofibrosis

Myelofibrosis is a rare bone marrow cancer in which the marrow is replaced by fibrous (scar) tissue. Bone marrow is the soft, fatty tissue inside the bones. The cancer develops when a mutation(s) occurs in the DNA of a single hematopoietic (blood-forming) stem cell. Bone marrow stem cells have the ability to reproduce and divide into multiple specialized cells that make up the bone marrow and blood. As the mutated bone marrow cell replicates and divides, it passes along the mutation(s) to new cells. Eventually, this abnormal cell production overtakes the bone marrow's ability to produce enough normal blood cells, including

- Red blood cells, which carry oxygen to the tissues
- White blood cells, which fight infection
- Platelets, which help blood to clot.

When the bone marrow is unable to make enough healthy blood cells, the result can be severe anemia, weakness, bone pain, fatigue and increased risk of infection or bleeding. The abnormal growth of blood-forming cells can also take place outside of the bone marrow, called "extramedullary

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hematopoiesis," in such organs as the liver, spleen, lungs, lymph nodes and spinal cord, causing swelling.

An important constant feature of MF is the production of too many "megakaryocytes," the term for the giant cells in the marrow that break up into fragments and produce hundreds to thousands of platelets. Platelets are small blood cells (comprising about one-tenth the volume of red cells) that stick to the site of a blood vessel injury and form a plug to seal off the injured blood vessel to stop bleeding. Normally, new platelets are made to replace used platelets in the body. With MF, extra megakaryocytes are made, causing too many platelets to be released into the blood and chemicals called "cytokines" to be released into the marrow. The cytokines stimulate the development of fibrous tissue in the marrow. Paradoxically, the number of megakaryocytes can become so abnormal that platelet production decreases in some patients.

MF occurs in about 1.5 out of every 100,000 people in the United States annually. The disease affects both men and women and is usually diagnosed in people over the age of 60, however, MF can occur at any age.

About 90 percent of people with MF have a mutation (a change in their DNA) in one of three genes: Janus kinase 2 gene (*JAK2*), the calreticulin gene (*CALR*) or the myeloproliferative leukemia gene (*MPL*). All three of these gene mutations cause abnormal signaling in the JAK pathway, which regulates blood cell production. The JAK pathway is a cascade of proteins (enzymes) inside a cell that activate each other and ultimately lead to a change in cell activity, in this case, increased cell division and growth. About 50 percent of patients have the"V617F *JAK2*" mutation found in the *JAK2* gene, while about 25 percent have a mutation in the calreticulin (*CALR*) gene, and between 5 and 10 percent of MF patients have a myeloproliferative leukemia (*MPL*) gene mutation. In addition, over last several years, mutations in many other genes, such as *ASXL1, EZH2, IDH1/2, SRSF2* and *TET2* have been found in 5 to 20 percent of patients with MF; these mutations may occur in addition to *JAK2*, *CALR*, or *MPL* mutations, and one person may have several of them at the same time. Scientists are investigating the role these mutations and other gene mutations in other signaling pathways may have on MF onset and progression.

The reason genetic mutations occur in MF is unknown. Exposure to petrochemicals, such as benzene and toluene, and ionizing radiation may raise the risk of developing the cancer. But only a small proportion of people exposed to these chemicals develop MF. A theory about why MF develops in some people is that they have inherited genes that limit their ability to detoxify the causative agents. In most cases, MF is not an inherited disease, but there are some rare cases of familial clustering of the MPNs, including MF. There is no known prevention.

Signs and Symptoms

MF usually develops slowly. In its very early stages, many people—about one-third—do not have symptoms of the disease. However, as disruption of normal blood cell production increases, people may experience the following signs and symptoms:

- Tiredness, weakness, shortness of breath, usually due to a low red blood cell count (anemia)
- Pain or a feeling of fullness below the ribs on the left side, as a result of an enlarged spleen (splenomegaly)
- Enlarged liver (on the right side of the abdomen below ribs)
- Pale skin
- Easy bleeding or bruising, as a result of a low platelet count (thrombocytopenia)
- Excessive night sweats
- Fever
- Frequent infections, due to a low white blood cell count (neutropenia)
- Bone or joint pain
- Weight loss.

Supportive Care

There are supportive therapies that may be used to help manage a patient's anemia (and low blood cell count in general), enlarged spleen or other MF-related systemic symptoms. These therapies are described below.

Anemia. Replacing nutrients that stimulate red blood cell production, such as iron, folic acid and vitamin B_{12}, may help reduce anemia. The following treatments are used for myelofibrosis-related anemia; some of them may also help increase low platelet and white blood cell counts. Medications are described in more detail in the *Treatment* section on page 5. Some may have potentially serious side effects, so it is important to talk to your doctor about your options.

- Blood transfusions—Periodic blood transfusions can increase the red blood cell count and reduce symptoms of anemia, including fatigue and weakness.
- Androgen therapy—Includes drugs such as the anabolic steroid danazol, given by mouth. Taking a synthetic version of male hormones (androgens) may help build up red blood cell production, and therefore, reduce anemia.

- Erythropoietin—This therapy, a hormone that stimulates the production of red blood cells, given intravenously (IV) or by subcutaneous injection, may also be used to treat anemia.
- Glucocorticoids (also called "corticosteroids" or "steroids")—This therapy, given by mouth, may also be used to treat anemia.
- Immunomodulators (IMiDs)—Thalidomide (Thalomid®) and lenalidomide (Revlimid®), both given by mouth, are FDA approved in the treatment of the blood cancer myeloma, and are being used to treat anemia in MF patients.
- Interferon alfa (Intron® A [interferon alfa-2b], Roferon®-A [interferon alfa-2a], PEGASYS® [peginterferon alfa-2a])–A synthetic version of a substance made by cells in the body to fight infection and tumors, these drugs may be given by intramuscular or subcutaneous injection.

Enlarged spleen. There are several options for dealing with the painful effects of an enlarged spleen (splenomegaly) caused by MF. Medications are described in more detail in the *Treatment* section on page 5. Some may have potentially serious side effects, so it is important to talk to your doctor about your options.

- A JAK inhibitor—Ruxolitinib (Jakafi®), given by mouth, is the first drug that has been approved by the FDA to treat MF because it has been shown to reduce MF-related symptoms and control spleen enlargement.
- Chemotherapy—Hydroxyurea (Hydrea®) is given by mouth. Cladribine (Leustatin®) is given intravenously (IV).
- Immunomodulators (IMiDs)—Thalidomide (Thalomid) and lenalidomide (Revlimid)
- Interferon alfa (Intron A, Roferon-A, PEGASYS)–This therapy can also control spleen enlargement.
- Surgical removal of the spleen (splenectomy)—Removal of the spleen may be considered if other forms of therapy have not reduced the pain or complications associated with an enlarged spleen. However, the benefits and risks of this procedure need to be weighed before a decision is made. Benefits include a reduction of symptoms, decreased portal hypertension (see *Complications*) and less need for red blood cell transfusions. MF patients who will be undergoing splenectomy need to be evaluated prior to 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.
- Radiation therapy—Radiation therapy uses high-powered beams, such as x-rays, to kill cancer cells. When other treatment methods have failed and surgical removal of the spleen is not a viable option, radiation therapy can be used to help reduce the size of the spleen.

Systemic symptoms. In addition to anemia and an enlarged spleen, patients may also experience excessive night sweats, fever, bone or joint pain, itching, fatigue, weakness, and unintentional weight loss. The following treatment options may help patients who experience these effects.

- Ruxolitinib (Jakafi)
- Glucocorticoids

Complications

As MF progresses, complications may arise.

- Portal hypertension—Increased blood flow from an enlarged spleen can lead to high blood pressure within the portal vein, which carries blood from the spleen to the liver. This can force excess blood into smaller veins in the stomach and esophagus, potentially causing the veins to rupture and bleed.
- Extramedullary hematopoiesis—Formation of blood cells outside the bone marrow, called "extramedullary hematopoiesis," may create clumps (tumors) of developing blood cells in other areas of the body. These tumors may cause such problems as bleeding in the gastrointestinal system, coughing or spitting up blood, compression of the spinal cord or seizures.
- Hardening and inflammation of bone tissue—Myelofibrosis can cause hardening of the bone marrow and inflammation of the connective tissue that surrounds the bones, resulting in severe bone and joint pain and tenderness.
- Gout—Because MF increases the body's production of uric acid, which is a byproduct of the breakdown of purines (a substance found naturally in the body), needlelike deposits of uric acid can form in the joints, causing joint pain and inflammation (gout).
- Acute myeloid leukemia (AML)—In about 15 to 20 percent of patients with myelofibrosis, MF will transform to AML, a type of blood and bone marrow cancer that progresses rapidly.

Diagnosis

A diagnosis of MF is made based on the World Health Organization (WHO) criteria. There is no one test that can diagnose a person as having MF; the diagnosis is based on findings from a bone marrow biopsy exam, blood cell counts and chemistry, and physical exam. In people who have no symptoms, MF may be suspected when a routine medical checkup reveals an enlarged spleen and abnormal blood test

results. The results of a blood test (a complete blood count, or CBC) that suggest a diagnosis of MF often include

- A decrease below the normal range in the number of red blood cells (anemia)
- An increase in the normal range in the number of white blood cells
- An increase above the normal range in platelet counts (for about one-third of patients)
- A mild to moderate decrease below the normal range in platelet counts (for about one-third of patients).

In addition to blood cell counts, blood tests may also show

- Teardrop-shaped red cells and immature red cells and white cells in the blood (seen by microscopic examination of the blood cells)
- Giant platelets, abnormal platelet formation and circulating dwarf megakaryocytes (bone marrow cells responsible for the production of platelets)
- Elevated serum levels of uric acid, lactic dehydrogenase (LDH), alkaline phosphatase and bilirubin
- Decreased serum levels of albumin, total cholesterol and high-density lipoprotein (HDL).

Because there are several other blood diseases, such as leukemia and lymphoma that can cause marrow fibrosis, to confirm a diagnosis of MF, the following tests may also be performed:

- Bone marrow examination—Bone marrow biopsy and aspiration findings can confirm a diagnosis of MF. In these procedures (usually done together), a small amount of bone and marrow is removed and then examined under a microscope by a hematopathologist (a doctor specializing in evaluating cells, tissues and organs to diagnose disease). Studying genetic components of the bone marrow cells can show mutations in the cells that may help eliminate other types of bone marrow disorders. For example, the absence of the Philadelphia chromosome or the BCR/ABL translocation can rule out chronic myeloid leukemia (CML). A blood or bone marrow sample may also be used for a test called a "karyotype." In this test, a microscope is used to examine the size, shape and number of chromosomes in a sampling of cells. The results of the karyotype may be helpful in making certain treatment decisions.
- Gene tests—A sample of blood or bone marrow may be analyzed in a laboratory to look for gene mutations, such as the *JAK2*, *CALR*, or *MPL* mutations, present in 90 percent of MF patients.
- Imaging tests—Ultrasound tests may be used to determine the size of the spleen. Magnetic resonance imaging (MRI) tests may be used to identify changes in the bone marrow that indicate MF.

Treatment Planning

Some doctors use a prognostic scoring system to plan a risk-adapted treatment strategy for a patient, which might include

- Observation only
- Jakafi
- Investigational therapies (eg, other JAK inhibitors)
- Drug therapy
- Allogeneic stem cell transplantation or reduced-intensity allogeneic stem cell transplantation
- Splenectomy
- Radiation therapy.

One model is The Dynamic International Prognostic Scoring System (DIPSS), which classifies risk as low (no risk factors), intermediate-1 (1 or 2 risk factors), intermediate-2 (3 or 4 risk factors) and high (5 or 6 risk factors). The independent risk factors include

- Age above 65 years
- Anemia
- Leukocytosis (high white blood cell count)
- Circulating blast cells
- Constitutional symptoms (eg, weight loss greater than 10 percent in the previous year, unexplained fever or excessive sweating persisting for greater than one month).

Every patient's medical situation is different and should be evaluated individually by an oncologist or hematologist who specializes in treating blood cancers. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center.*

Treatment

There is no drug therapy that can cure MF. An allogeneic stem cell transplant (see *Stem Cell Transplantation* on page 6) 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 10 percent of patients with MF.

Patients who are symptom-free and do not have signs of anemia, 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 checkups and examinations to detect any signs and symptoms of disease progression.

Drug Therapies

- Janus-associated kinase (JAK) inhibitors—This drug class inhibits enzymes called "JAK*1*" and "JAK*2*," which are involved in the production of blood cells. Ruxolitinib (Jakafi), given by mouth, is the first JAK inhibitor and 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 polycythemia vera myelofibrosis and post essential thrombocythemia myelofibrosis. The most common side effects affecting the blood cells are thrombocytopenia (a decrease below the normal number of platelets) and anemia. Other common side effects include bruising, dizziness and headache. Other side effects, like atypical infections (eg, herpes), are rare but need to be recognized. Jakafi is not recommended for a patient with a platelet count below 50×10^9/L.

Patients should be aware that after they stop taking 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.

For more details, please see the full prescribing information for Jakafi available at www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192s009lbl.pdf or contact an LLS Information Specialist.

- 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 and an enlarged spleen in MF patients. Because it reduces the number of all blood cells, cladribine can increase the risk of infections and bleeding.
  - 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. Patients with low blood cell counts or severe anemia should not take hydroxyurea. When taken over the long term, some patients may develop skin ulcers.
- Immunomodulators (IMiDs)—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 anemia. Favorable responses to thalidomide have been reported in 20 to 60 percent of MF patients. Thalidomide can cause peripheral neuropathy. Lenalidomide can lower neutrophil (a type of white blood cell that helps fight infection) counts, leading to an increased risk for infections. IMiDs should not be used by pregnant women or those considering pregnancy.
- Interferon alfa (Intron A, Roferon-A, PEGASYS), given by intramuscular or subcutaneous injection, is a synthetic version of a substance made by cells in the body to fight infection and tumors. It has been used to treat an enlarged spleen, bone pain and high platelet count in selected MF patients. Due to its effects on the immune system, interferon alfa may worsen thyroid abnormalities, diabetes mellitus, or autoimmune disorders. Interferon alfa may also cause or worsen depression.
- Androgen therapy (Oxymetholone [Anadrol-50®], danazol)—These drugs, both given by mouth, are synthetic versions (analogues) of male hormones and can promote red blood cell production. They are used to relieve the symptoms of severe anemia. About one in three patients with anemia who underwent androgen treatment experienced improved red blood cell counts. Due to the toxic effects of androgens on the liver, treatment with these drugs includes using blood tests to track liver functions. Androgens may cause facial hair growth or other masculinizing effects in women; they are contraindicated in men with history of prostate cancer.
- Recombinant erythropoietin (Epogen®, Procrit®)—This treatment, given intravenously (IV) or by subcutaneous injection, helps regulate red blood cell production. However, the response in anemia-related symptoms in MF patients has been limited. Erythropoietin may increase the risk of developing blood clots.

- 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 anemia. About one in three patients with anemia has improved red blood cell counts with prednisone treatment. Glucocorticoids can cause osteoporosis when taken over the long term. Glucocorticoids can also increase blood sugar and raise blood pressure.
- Anagrelide hydrochloride (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"). Frequent blood tests are necessary to ensure the correct dose. Anagrelide can cause headaches and a fast heart rate in some patients.

For more side effects information, please see the free LLS booklet, *Understanding Side Effects of Drug Therapy* and the FDA drug information Web page www.fda.gov/drugs/resourcesforyou/consumers/default.htm.

Radiation Therapy

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

Splenectomy

The spleen can be surgically removed if it is very large and is causing a very low platelet count, severe anemia 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.

Stem Cell Transplantation

Allogeneic stem cell transplantation (ASCT) is the only current treatment with the potential to cure myelofibrosis, 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 blood cells, white blood 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 generalizations. 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 cutoff for stem cell transplantation.

Reduced-intensity or "nonmyeloablative" allogeneic stem cell transplantation is a type of transplant that is being used to treat some patients with leukemia, 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-tumor 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.

Talk to your doctor about whether stem cell transplantation is a treatment option for you. For additional information on stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Side Effects of Treatment for Patients with MF

The side effects of treatment will depend on many factors, including type of treatment and dosage, the age of the patient and coexisting medical conditions. Therapy may induce fatigue, nausea, fever, chills, dizziness, shortness of breath, peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet), temporary loss of hair and other side effects.

Side-effects management is important. If you are having any concerns about your side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed. For specific drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy* and the FDA drug information Web page www.fda.gov/drugs/resourcesforyou/consumers/default.htm.

Treatments Under Investigation

Patients are encouraged to explore, and enter, if they are eligible, clinical trials. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments. Clinical trials are designed to be accurate and very safe. Patient participation in clinical trials is important in the development of new and more effective treatments for MF and may provide patients with additional treatment options.

Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them.

For more information about clinical trials, see the free LLS booklet *Understanding Clinical Trials for Blood Cancers* at www.LLS.org/booklets or visit www.LLS.org/clinicaltrials.

The discovery of the *JAK2* gene mutation in 2005 has led to clinical trials of several JAK inhibitors in the treatment of MF. The *JAK2* mutation is one of several gene mutations believed to be involved in the development of MF. While a number of JAK inhibitors are being evaluated in clinical studies, none of them is specific for patients with the V617F *JAK2* mutation. These drugs inhibit the JAK pathway inside the bone marrow and blood cells, regardless whether patient has a *JAK2*, *CALR*, *MPL* or any other mutation. Combining JAK inhibitors with other agents, such as immunomodulatory drugs, androgens or inhibitors of pathways other than the JAK pathway, is also being tested. These combination therapies may provide additional benefits, such as improving anemia or providing better and/or longer responses. Medications meant to improve anemia or decrease bone marrow fibrosis are being developed as well.

Some of the classes of novel therapies and drugs under investigation include

- JAK inhibitors that target abnormal JAK pathway signaling, which is present in all MF patients, largely due to either *JAK2*, *CALR* or *MPL* mutations. Several JAK inhibitors are now in clinical trials and are showing effectiveness in reducing spleen size and symptoms such as night sweats and fatigue and possibly improving anemia. These new treatments include momelotinib (CYT387), pacritinib (SB1518) and NS-018.
- Histone deacetylase (HDAC) inhibitors play an important role in the regulation of gene expression. A clinical study of panobinostat (Farydak®), which is approved by the FDA for the treatment of multiple myeloma, in combination with ruxolitinib in patients with MF is ongoing. Pracinostat is another HDAC inhibitor that is being studied in combination with ruxolitinib.
- Antifibrotic agents interfere with the process of tissue repair and fibrosis. PRM-151 is an antifibrotic therapy that is being tested in MF. Lysyl oxidase-like 2 antibody is another antifibrotic medication that is being studied in a clinical trial.
- Therapies that target other pathways that may be abnormally activated in MF are also being tested. LCL-161 is an oral therapy that blocks the activity of inhibitor of apoptosis (IAP) proteins, which promote cell survival. SL-401 is a therapy that targets the IL-3 receptor, which is found on the surface of MF cells.
- Immune checkpoints inhibitors (nivolumab, ipilmumab) are a new class of drugs that harness the body's immune system to fight cancer. Nivolumab (Opdivo®), which is approved by the FDA for the treatment of melanoma and non-small cell lung cancer, is now being tested as a therapy for MF.
- Sotatercept (ACE-011) is a therapy that stimulates the production of red blood cells and is being tested to treat anemia in MF.
- Imetelstat is a telomerase inhibitor, which affects the ability of dividing cells to repair the loss of DNA that happens during cell division. It is being studied in MF to possibly improve bone marrow function and normalize blood cell count.

Treatment Outcomes

The prognosis (the likely outcome of a disease) varies widely in patients with MF. Each patient's prognostic risk factors are evaluated individually. While the median survival for people with MF is about 5 years, people younger than 55 and with good prognostic factors have a median survival of 11 years. However, some people may survive for decades following a diagnosis. It is important to know that outcome data can show how groups of people with MF responded to treatment, but cannot determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors.

Although there is no staging system for MF, the International Prognostic Scoring System (IPSS), uses the following five risk factors for estimating survival from the time of diagnosis:

- Age—65 years or older
- Anemia—hemoglobin level lower than 10 grams per deciliter (g/dL)

- Symptoms—such as fever, night sweats or weight loss
- Leukocytosis—an elevated white blood cell count of above 25,000/µl
- Circulating blood blast cells—at least 1 percent.

According to the IPSS, patients without any of these adverse features, excluding age, have a median survival of more than 10 years. The presence of any three of the above adverse features reduces the median survival to 2 years. However, recent long-term studies of ruxolitinib (Jakafi) suggest that it can improve survival times in patients with MF for several years.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org.

LLS offers free information and services for patients and families touched by blood cancers. The following lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out to others in similar circumstances, and share information. For more information, please visit www.LLS.org/chat or www.LLS.org/discussionboard.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources.

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials.

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

The Leukemia & Lymphoma Society and the MPN Research Foundation are collaborating to advance therapies for patients with myelofibrosis through the MF Challenge, a partnership to fund concept grants to increase scientific understanding that will lead to new treatments for MF patients.

Other Resources

Cancer*Care*®

www.cancercare.org
(800) 813-4673

Cancer*Care*® provides free, professional support services to anyone affected by cancer. They provide counseling, support groups, education workshops, publications and financial assistance.

MPN Education Foundation

www.mpdinfo.org

The MPN Education Foundation provides information, education and support and looks to advance research and develop drugs to improve the quality of life and care of MPN patients. The Education Foundation provides patient and doctor conferences and facilitates patient participation and accrual in clinical studies and surveys.

MPN Research Foundation

www.mpnresearchfoundation.org

The MPN Research Foundation is a nonprofit organization whose primary mission is to promote, fund and support the most innovative and effective research into the causes, treatments and potentially the cure for essential thrombocythemia, polycythemia vera and MF. The organization also provides information and support to people who have myeloproliferative neoplasms.

The Myeloproliferative Disorders Research Consortium (MPD-RC)

www.mpdrc.org

The MPD-RC is an international, multi-institutional nonprofit consortium funded by the National Cancer Institute and set up to coordinate, facilitate, and perform basic and clinical research of the Philadelphia Chromosome-negative myeloproliferative neoplasms (Ph-MPNs).

National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute (NCI), part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including myeloproliferative neoplasms. The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trial Registry, at www.cancer.gov/clinicaltrials, where MF patients can look for clinical trials.

References

Lichtman MA, Tefferi A, Chapter 91. Primary myelofibrosis. Lichtman MA, Kipps TJ, Seligsohn U, et al, eds. *Williams Hematology*, 8th ed. Available from: AccessMedicine. Accessed on September 17, 2015.

Mayo Clinic, Myelofibrosis. www.mayoclinic.org/diseases-conditions/myelofibrosis/basics/definition/con-20027210. Accessed October 26, 2015.

National Cancer Institute. Chronic Myeloproliferative Disorders Treatment (PDQ®). Updated: August 12, 2015. Available at www.cancer.gov/types/myeloproliferative/patient/chronic-treatment-pdq. Accessed October 26, 2015.

Tefferi A. Primary myelofibrosis: 2014 update on diagnosis, risk stratification and management. *American Journal of Hematology*. 2014;89(9):915-925.

Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of oversurvival in COMFORT-I and COMFORT-II, 2 randomized phase 3 trials of ruxolitinib for the treatment of myelofibrosis. *Haematologica*. 2015;100(9):1139-1145.

Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. *Leukemia*. 2013;27(9):1861-1869.

Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. *Haematologica*. 2015;100(4):479-488.

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