

# Idiopathic Myelofibrosis

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

## Highlights

- Idiopathic myelofibrosis (IM) is one of a group of diseases known as myeloproliferative disorders.
- IM begins with one or more acquired changes (mutations) to the DNA of a single blood-forming cell. This results in abnormal blood cell development and scarring (the formation of fibrous tissue) within the bone marrow.
- Symptoms of IM may include fatigue, weakness, shortness of breath, weight loss, night sweats, bone pain and an enlarged spleen. However, individuals with IM may not have any symptoms.
- IM is a chronic disease. The goal of treatment is to relieve symptoms and reduce the risk of complications. Treatment may include blood transfusions, replacement of iron and folate and drug therapy.
- Patients who are symptom free are generally not treated. A very large proportion of symptom-free patients remain stable for years without requiring treatment.
- Approximately half of persons with IM have a mutation of the *JAK2* gene. Researchers are investigating the role that this mutation plays in IM's development and its implications for potential new therapies.

## About Idiopathic Myelofibrosis

IM is an uncommon disease that affects about two out of one million people. The disease is known by several other names, among them agnogenic myeloid metaplasia. It is one of several blood diseases that begin with an acquired, abnormal change in the DNA of a single hematopoietic (blood-forming) stem cell in the marrow. Abnormal cell production gradually overtakes normal cell production. Eventually, there are more abnormal cells in the marrow than normal cells. Fibrosis (scar tissue) is present in the marrow of most patients. This fibrosis gives the disease part of its name; the prefix *myelo-* in the word myelofibrosis denotes relationship to the marrow. "Idiopathic" is the medical term applied to diseases of unknown cause.

IM is one of a number of myeloproliferative disorders, a term used to describe a group of diseases in which specific types of blood cells are overproduced by the body. Other myeloproliferative disorders include essential thrombocythemia and polycythemia vera. About 10 percent to 15 percent of IM cases begin as either polycythemia vera or essential thrombocythemia.

IM is usually diagnosed in people between the ages of 50 and 80 years, but can occur at any age. It affects both men and women. Many patients with myeloproliferative disorders have a mutation in the *JAK2* gene. In patients diagnosed with IM, the *JAK2* gene mutation is present in about 50 percent of patients. By comparison, in polycythemia vera the mutation is present in most patients. Approximately 10 percent of patients with IM have an *MPL* gene mutation. The role that the *JAK2* and *MPL* mutations play in the development of the disease is being studied.

IM affects the production of red cells, white cells and platelets. Too few red cells are made, and usually too many white cells and platelets are made. An important constant feature of IM 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 (about one-tenth the volume of red cells) that stick to the site of 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 IM, extra megakaryocytes are made, causing too many platelets to be released into the blood and chemicals called “cytokines” to be released in the marrow. The cytokines stimulate the development of fibrous tissue in the marrow. The megakaryocytes can become so abnormal that platelet production decreases in some patients.

### Diagnosis of Idiopathic Myelofibrosis

A diagnosis of IM may be considered when a routine medical examination shows that the patient has an enlarged spleen and abnormal blood counts. There are variations in blood cell counts among patients diagnosed with IM. The results of a blood test (a complete blood count, or CBC) that suggest a diagnosis of IM often include

- A decrease below the normal range in red blood cells (called “anemia”)
- An increase above the normal range in 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)
- Abnormally shaped red cells and immature red cells and white cells in the blood (seen by microscopic examination of the blood cells).

A patient’s blood cell counts may vary during the course of the disease. Sometimes, patients have very little change in certain blood counts. For example, a patient may have no elevation in the white cell or platelet counts. In other patients, the numbers of white cells or platelets may be lower than normal, rather than the more common finding of higher than normal.

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

- Giant platelets, abnormal platelet formation and circulating dwarf megakaryocytes
- 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).

To complete the diagnostic workup, blood tests are followed by bone marrow aspiration and biopsy. A bone marrow aspiration and a bone marrow biopsy are tests to look at the cells in the marrow. These tests are usually done together. The marrow cells are looked at under a microscope to determine if they are normal and if they are not normal, what abnormality is present.

These tests can be performed as an outpatient procedure. Local anesthesia is used for the procedure. A special needle, inserted into the hip bone, is used to obtain a marrow aspirate and biopsy. Analysis of the marrow of a patient with IM shows either some, or a great deal of, fibrosis.

There are several other blood diseases that can occasionally cause marrow fibrosis, including leukemia and lymphoma. However, blood and marrow laboratory findings are used to distinguish IM from other causes of marrow fibrosis.

A blood or bone marrow sample may also be used for a test called a “karyotype.” In a karyotype, 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.

Analysis of blood cells for the *JAK2* mutation may help in making the diagnosis, but the mutation is not found in about 50 percent of patients.

### **Symptoms and Complications of Idiopathic Myelofibrosis**

About 25 percent of individuals with IM have no symptoms at the time of diagnosis. Patients with symptoms may have

- Weakness, fatigue, shortness of breath, weight loss, night sweats and unexplained bruising
- An enlarged spleen, a finding in almost all patients, which may cause a feeling of fullness or a dragging sensation in the upper left abdomen
- An enlarged liver, detectable in two-thirds of patients
- Severe upper left shoulder pain (reflecting the referred pain from the spleen, sometimes as the result of impaired blood flow to part of the spleen)
- Bone pain, especially in the lower extremities; this symptom is uncommon.

IM may be complicated by

- Fibrohematopoietic tumors (masses containing developing blood cells), which may form outside the marrow in any tissue in the body. Untreated tumors may cause symptoms by compressing parts of the body.
- Portal hypertension, a condition that occurs when pressure in the portal vein (a major blood vessel that carries blood to the liver) is increased as a result of excess blood flow from the spleen and of fibrosis in the liver blocking blood flow.
- Esophageal and gastric varices, veins that have expanded and can rupture into the stomach or esophagus, causing bleeding. Varices are caused by heavy blood flow from an enlarged spleen to the liver. The liver cannot absorb this increased flow. Some of the extra blood is redirected through veins in the stomach and esophagus, causing these veins to expand.

About 10 percent of persons with IM are at risk of developing acute myelogenous leukemia (AML). The presence of abnormal chromosomal changes increases an IM patient's risk for developing AML.

### **Treatments for Idiopathic Myelofibrosis**

Treatment for IM is aimed at relieving symptoms and reducing the risk of complications.

Patients who are symptom free are generally not treated. A very large proportion of symptom-free patients remain stable for years without requiring treatment.

For patients needing treatment, blood transfusions, replacement of iron and folate and drug therapy are generally important aspects of care. For some patients, treatment may also include radiation therapy to shrink the spleen or fibrohematopoietic tumors or surgery to remove the spleen (splenectomy).

There is currently no drug therapy that can cure IM. However, allogeneic stem cell transplantation (see page 5) may be a cure for a small number of younger patients.

Specific treatments for the symptoms of IM include:

#### ***Drug therapy***

*Hydroxyurea (Hydrea®)* is a commonly used chemotherapeutic agent. The effects of hydroxyurea are to

- Decrease very high platelet counts
- Decrease size and associated complications of an enlarged spleen
- Decrease or eliminate night sweats and weight loss
- Improve hemoglobin levels
- Occasionally, decrease the degree of marrow fibrosis.

*Interferon alfa* (*Intron*<sup>®</sup>A, *Roferon-A*<sup>®</sup>) is a synthetic version of a substance made by cells in the body to fight infection and tumors. This drug has been used in the treatment of IM for an enlarged spleen, bone pain and high platelet counts.

*Androgens* are drugs that are synthetic versions (analogs) of male hormones. These agents can promote red cell production and are used to relieve the symptoms of severe anemia. *Oxymetholone* (*Anadrol*<sup>®</sup>) and *danazol* (*Danocrine*<sup>®</sup>) are two examples of androgens. About one in three patients has improvement of anemia or a low platelet count 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* has been used successfully to treat a small number of patients, as reported in recent studies. However, in general it has not been a successful treatment for IM-related anemia.

*Glucocorticoids*, such as prednisone, may benefit patients with significant anemia. Glucocorticoids are steroid compounds used to treat many conditions. About one in three patients has improvement of anemia with prednisone treatment.

*Bisphosphonates*—for example, *zoledronic acid* (*Zometa*<sup>®</sup>)—may relieve bone pain and improve blood counts.

*Anagrelide* (*Agrylin*<sup>®</sup>) is a drug that may be used to treat a very high platelet count. It may be used to lower an increased platelet count following splenectomy.

### ***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 removed by surgery if it is very large and is a cause of a very low platelet count, severe anemia, or portal hypertension. The decision to do a splenectomy is based on weighing the benefits to the individual versus the risks. IM patients who undergo surgery need to be evaluated prior to surgery and monitored after surgery for an increased risk of bleeding complications.

### ***Stem cell transplantation***

In certain circumstances, allogeneic stem cell transplantation, a treatment to restore blood and immune cells, is an accepted treatment for IM patients. A donor's stem cells are transfused into the patient's blood after high-dose chemotherapy and/or radiation therapy. The donor is usually a brother or sister, if one is available and is a "match" for the patient. An unrelated person with stem cells that match the patient's can be used if a brother or sister cannot be the donor. The transplanted stem cells go from the patient's blood

to his or her marrow. The new cells grow and provide a supply of red cells, white cells (including immune cells) and platelets.

For IM patients, stem cell transplantation can be difficult if fibrosis is extensive. However, if a well-matched donor is available, allogeneic stem cell transplantation has the potential to restore normal marrow function and may cure the disease. Ordinarily, only certain patients, such as those who do not have other good treatment options and who are generally younger than 55, are considered for this procedure.

Allogeneic stem cell transplantation can cause severe, potentially life-threatening problems:

- There is a high risk of toxicity from the high-dose chemotherapy and radiation given prior to this procedure.
- Donated stem cells sometimes attack healthy tissues in a reaction called “graft-versus-host disease (GVHD),” causing possibly fatal damage to the liver, intestines, skin and other organs.

At present, the number of reported studies and the number of study patients are too small to allow definitive comment regarding the role that stem cell transplantation plays in the treatment of IM. Research studies (clinical trials) are under way to investigate the safety and effectiveness of modified stem cell transplantation to reduce risks and extend the age limits for patients (see below, *Research and Clinical Trials for Idiopathic Myelofibrosis*).

### **Prognosis for Idiopathic Myelofibrosis**

About 20 percent of patients are still in treatment 10 years after diagnosis with IM. As mentioned earlier, a very large proportion of symptom-free patients remain stable for years without requiring treatment. The average survival time after a diagnosis of IM is about five years. Prognosis factors that may be indicative of better outcomes include absence of abnormal chromosomal changes, hemoglobin levels above 10 g/dL and younger age.

### **Research and Clinical Trials for Idiopathic Myelofibrosis**

Researchers are looking for more effective ways to treat IM. One method is to conduct clinical trials (research studies) of new therapies or combinations of therapies.

The Leukemia & Lymphoma Society is funding research for myeloproliferative disorders, including research to investigate

- The potential for developing new treatments to inhibit the activity of an enzyme linked to the *JAK2* mutation. Researchers believe this enzyme causes an overproduction of blood cells.
- The identification of oncogenes (cancer genes) for IM and other myeloproliferative disorders that may be suitable targets for new drug therapies.

Some treatments recently or currently under examination for IM in clinical trials include

*Thalidomide (Thalomid®)*. This is an immune modulator currently being used in the treatment of myeloma and other conditions. In studies with IM patients, thalidomide has been associated with improvements in anemia, platelet count, enlarged spleen, and constitutional symptoms such as night sweats, weakness, fatigue and shortness of breath.

Some patients treated with this drug have undesirable increases in their platelet and white cell counts. The use of low-dose thalidomide with a tapering dosage of prednisone has been reported to result in a higher response rate in anemia and fewer toxic side effects than higher-dose thalidomide alone.

*Lenalidomide (Revlimid®)*. This drug is similar to thalidomide but generally has fewer side effects and is more potent than thalidomide. Lenalidomide is being studied as a potential therapy for IM patients to treat anemia, thrombocytopenia, enlarged spleen and marrow fibrosis.

*Bortezomib (Velcade®)*. This drug is a proteasome inhibitor used to treat myeloma. Research is under way to determine whether bortezomib can prevent marrow fibrosis in IM patients.

*Nonmyeloablative stem cell transplantation*. This type of stem cell transplant is being used to treat some patients with leukemia, lymphoma or myeloma. The intention is to achieve the benefits of allogeneic stem cell transplantation while reducing the risks of the procedure. The use of nonmyeloablative transplantation has shown promise in a small number of patients. Additional investigation is needed to compare long-term outcomes of this treatment to outcomes of other types of therapy for IM patients.

## Resources

### **The Leukemia & Lymphoma Society**

The Leukemia & Lymphoma Society is a national voluntary health agency with chapters throughout the United States and Canada. The Society provides education and support services for the public and for cancer treatment professionals. To find the Society chapter nearest you, visit our online chapter finder or contact

The Leukemia & Lymphoma Society  
1311 Mamaroneck Avenue  
White Plains, NY 10605

#### **Information Resource Center**

(800) 955-4572 or [www.LLS.org](http://www.LLS.org)

Through the Society's Information Resource Center, callers may speak directly with an Information Specialist, Monday-Friday, 9 AM-6 PM, ET, (800) 955-4572. To contact an Information Specialist online, go to the Society's Web site and click on Live Help (10 AM-5 PM), or email us at [infocenter@LLS.org](mailto:infocenter@LLS.org). Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support, and assist with clinical trial searches for leukemia, lymphoma and myeloma.

The Society's Web site features a link to the clinical trial search service of the National Cancer Institute. Clinical trial listings for blood cancers, including abstracts of clinical trial protocols and contact information, are available.

The Society provides fact sheets and booklets that can be ordered via the 800 (toll-free) number or through the Free Materials section on the Web site, [www.LLS.org](http://www.LLS.org).

### **The Association of Cancer Online Resources (ACOR)**

[www.acor.org](http://www.acor.org)

An Internet-based public charity dedicated to improving the quality of care for cancer patients and the quality of life of patients, survivors and caregivers. ACOR provides support and information through its unique online community, which includes mailing lists, information on specific forms of cancer and links to additional resources.

### **The MPD Foundation**

[www.mpdfoundation.org](http://www.mpdfoundation.org)

The MPD (Myeloproliferative Disorders) Foundation is a nonprofit organization dedicated to funding research into new treatments for myeloproliferative diseases and eventually to find a cure. The organization also provides information and support to people who have myeloproliferative diseases.

### **The National Cancer Institute (NCI)**

www.cancer.gov

(800) 422-6237 or (800) 4-CANCER

Part of the National Institutes of Health, NCI functions as a national resource center for information and education about all forms of cancer including myeloproliferative diseases.

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