Cleveland Clinic Taussig Cancer Institute’s Multiple Myeloma Program

Our mission
The primary mission is to provide patients and physicians access to innovative treatment options, medical expertise, and dedicated support resulting in superior outcomes.

Understanding your diagnosis
Numerous challenges face the patient who has been recently diagnosed with a life-threatening illness. A diagnosis of multiple myeloma, as with any life-threatening disease, is often difficult to accept and understand. As one adjusts and develops the courage to move forward, it is critical to learn as much as one can about multiple myeloma, multidisciplinary care, and available treatment options.

Disease overview: What is multiple myeloma?
Multiple myeloma (MM) is a cancer of plasma cells, or specialized cells of the immune system. Normal plasma cells are located in the spongy tissue inside the bone (the bone marrow) and are responsible for producing proteins (also called antibodies) that help our bodies fight against infections. In MM, our bodies’ control over the growth of the plasma cells is lost, and these cells are present in much larger amounts in the bone marrow.

The plasma cells in a person with MM often continue to produce a large amount of a protein that can be measured in the blood or urine. The protein is called the M protein (or monoclonal gammopathy, monoclonal protein, bence jones protein, or paraprotein). The M protein can be used to monitor the status of the disease. It is thought that the amount of protein produced is proportional to the number of malignant plasma cells in the body.

Multiple myeloma usually causes symptoms that are due to two different factors: the excess number of plasma cells and the high concentration of the M protein produced. Because the bone marrow is also the location where blood is produced, the presence of too many plasma cells in the bone marrow often results in difficulty producing blood. This difficulty is
called anemia when it refers to a decreased number of oxygen carrying red blood cells and thrombocytopenia when the production of blood platelets—small corks in the blood that help stop bleeding—is decreased.

Anemia is usually manifested by fatigue and shortness of breath upon exertion. Thrombocytopenia often does not result in symptoms but occasionally, when severe, can result in easy bruising and bleeding. With the expansion of the bone marrow space that occurs in multiple myeloma, and the production of hormones by the plasma cells, loss of bone minerals follows. This results in bone lesions (the appearance of holes in the bones on X-rays of most patients with MM), as well as bone pains and bone fractures (or breaks).

In addition, the production of the monoclonal protein by the plasma cells can result in the following:

- kidney damage (renal dysfunction)
- nerve damage (neuropathy)
- heart dysfunction (when parts of the M protein cause deposits in the heart, a process called amyloidosis)
- thickening of the blood, called hyperviscosity, which results in decreased concentration ability and vision changes

It is worth noting that patients with multiple myeloma often have deficits in the immune system that result in frequent infections because part of the normal immune system is overwhelmed by the production of the myeloma proteins.

**Diagnosis**

Making a diagnosis of multiple myeloma is different than making a diagnosis of any other cancer. No single test can make such a diagnosis on its own. Instead, the diagnosis requires that a number of tests be performed and interpreted in the context of the individual patient. The following tests are considered necessary at baseline in any patients with multiple myeloma:

1. **Bone marrow biopsy and aspirate**: A biopsy of the bone marrow is usually performed from one of the hip bones. It is often an outpatient procedure.

2. **Skeletal survey**: This is a series of X-rays of the long bones of the body, including the spine, vertebrae, and the hips, as well as the skull.

3. **Laboratory tests for an M protein**: This test, called a protein electrophoresis, is performed on the blood and urine.

4. **Routine laboratory tests**: This group includes tests of kidney and liver function, calcium levels, and tests to grade the severity of the multiple myeloma (β2 microglobulin).

Additional testing may be warranted depending on the clinical presentation and the individual patient. The diagnosis of active MM relies on the identification of abnormal plasma cells in the bone marrow, an M protein in the blood or urine, as well as proof that the plasma cells or the protein being produced by them are resulting in harm to the patient. The last factor usually implies severe anemia, kidney problems, or bone problems.

Asymptomatic or smoldering multiple myeloma refers to the presence of the M protein in the blood or urine, as well as an increase in the plasma cells in the bone marrow; however, there is no evidence of harm to the patient (i.e., the patient has no attributable sign or symptom of MM).

**Other plasma cells disorders**

Multiple myeloma is one of a spectrum of
disorders known as plasma cell dyscrasias which are characterized by levels of abnormal protein in blood or urine and by bone marrow involvement. The different forms of plasma cell dyscrasias include the following:

- **MGUS (monoclonal gammopathy of unknown significance):** Patients have only a small abnormal protein elevation, minimal or no bone marrow involvement with abnormal plasma cells, no bone involvement or “lytic lesions,” and normal blood counts. However, patients with MGUS have a 10 percent to 15 percent chance of developing multiple myeloma or another form of plasma cell dyscrasias over a 20-year period. The remainder will lead a normal life. There is no treatment necessary, outside of a clinical research trial, but the patient will need to be monitored with blood and urine studies at routine intervals.

- **SMM (smoldering/indolent or asymptomatic multiple myeloma):** Patients with SMM have the same characteristics as those with MGUS, but the amount of abnormal protein in the blood is greater, and there is a tendency to have more bone marrow involvement. Half of patients with SMM will progress to multiple myeloma. The other half will follow a more benign course similar to the course of patients with MGUS. There is no treatment necessary for SMM, outside of a clinical research trial, but the patient will need to be monitored with blood and urine studies at least every 3 months in most cases.

- **Plasmacytoma:** A collection of malignant (cancerous) plasma cells (myeloma cells) forms a mass somewhere in the body, typically in the upper respiratory tract or the bones. Such masses may be a part of multiple myeloma or may occur without the other characteristics of multiple myeloma (solitary plasmacytoma). Patients with solitary plasmacytoma are usually treated with radiotherapy alone with a curative intent.

- **Waldenstrom’s macroglobulinemia:** Waldenstrom’s macroglobulinemia is a rare cancer of plasma cell neoplasm that is often more closely related to non-Hodgkin’s lymphomas. Waldenstrom’s macroglobulinemia affects plasma cells, which develop from white blood cells called B-lymphocytes or B cells. While it shares some of the clinical features of multiple myeloma, it usually does not result in bone lesions and usually involves lymph glands and the spleen. While some of therapies used for multiple myeloma can be effective in Waldenstrom’s macroglobulinemia, the treatment overall is more closely related to the treatment of the other non-Hodgkin’s lymphomas.

- **Amyloidosis:** Amyloidosis is a disorder in which proteins are deposited in organs, an event that leads to improper function. Primary amyloidosis results from the deposition of light chains (parts of the antibodies produced by abnormal plasma cells). Primary amyloidosis can be part of multiple myeloma but can also occur outside of multiple myeloma. Treating primary amyloidosis involves stopping the production of the abnormal protein by administering therapy often effective for multiple myeloma. Other types of amyloidosis do not relate to abnormal plasma cells; some types occur in patients on dialysis or in patients with chronic inflammatory conditions (such as rheumatoid arthritis or inflammatory bowel disease). There are also hereditary types of amyloidosis.

**Staging**
The staging of multiple myeloma differs from the staging of any other cancer as well. The
older staging scheme (called Durie and Salmon staging system) relies on many clinical cues and is often difficult to interpret; hence, it has fallen out of favor. The more commonly used staging system is called the international staging system and relies on two simple blood tests (b2 microglobulin and albumin). Staging in multiple myeloma often does not predicate the treatment prescribed but can help in the prediction of survival outcomes.

What causes multiple myeloma?
The cause of multiple myeloma is not known. Exposure to a number of situations has been linked to the development of multiple myeloma. The most accepted of these is exposure to radiation. Also, individuals involved in the agricultural or chemical industries have occasionally been found to have a higher rate of multiple myeloma. However, most people with these risk factors never get the disease, and most individuals who have multiple myeloma had no risk factors for the disease.

The incidence of multiple myeloma in the United States is increasing, with approximately 19,000 new patients diagnosed each year (2007 SEER DATA). Some documented trends in the disease prevalence are indicated for multiple myeloma:

- The disease is more common in people over the age of 40; the average age is 71 years.
- The disease occurs in younger patients as well. Over the last several years, the occurrence of multiple myeloma in people under the age of 55 has increased.
- The disease occurs twice as often in African American men than Caucasian men.
- Caucasian women and those of Asian descent have been found to have the lowest rates of multiple myeloma.
- The northern two-thirds of the state of Ohio has one of the highest incidence rates of multiple myeloma in the United States.

What are the symptoms of multiple myeloma?
In the early stages of multiple myeloma, the symptoms may be vague:

- Low energy level, fatigue
- Flu-like symptoms
- Back pain (lower back pain is common)
- Bone fractures that occur without significant injury
- Abnormal bleeding such as from the gums or frequent nosebleeds

Other signs or symptoms that may develop include:

- weight loss
- decreased appetite
- shortness of breath
- bony pains
- constipation or diarrhea
- muscle weakness
- renal dysfunction
- anemia
- elevated calcium levels
- recurrent infections
The Multiple Myeloma Program at Cleveland Clinic offers all available testing including blood and urine analysis, biopsies, X-rays, bone evaluation, and bone marrow sampling. Our physicians’ judgment, gained over years of experience, is essential in developing optimal short- and long-term treatment plans. The best treatment for you is a choice that depends on your specific profile—the type of myeloma you have, the severity of symptoms, your age, and overall health. Careful staging is of the utmost importance and is the key to managing the disease.

A multidisciplinary approach
Since multiple myeloma may affect a number of organs, the Multiple Myeloma Program at Cleveland Clinic includes a multidisciplinary team of Cleveland Clinic specialists who treat all aspects of the disease. The specialists are from the fields of:

- medical oncology
- orthopedics
- cardiology
- neurology
- nephrology
- radiation oncology
- palliative medicine
- infectious disease
- social work
- physical medicine
- rehabilitation

These nurses and physicians have extensive experience specifically related to the treatment and complications of multiple myeloma and amyloidosis. Cutting-edge techniques and technologies are at their disposal.

Chemotherapy — These drugs are used to kill malignant cells. Since the 1960s, chemotherapy has been the main treatment for myeloma. In the past, a combination of several drugs and steroids (such as prednisone or dexamethasone) have been used. Currently, there are many more options available. Despite the major improvements in standard treatment, there is no cure. Thus, we encourage patients to enroll in clinical trials; the Multiple Myeloma Program offers many such opportunities.

Cardiac (heart) — Cardiologists assess heart involvement with selected tests and then prescribe appropriate treatment plans.

Renal (kidneys) — Nephrologists carefully analyze specific laboratory and urine test results in order to manage kidney involvement and prevent further deterioration.

Skeletal system/surgical intervention — In certain instances, bone fractures caused by multiple myeloma need to be treated surgically. Cleveland Clinic’s Orthopedic Surgery members are experts in assessing and evaluating bone involvement. This team of professionals determines surgical and nonsurgical therapeutic techniques that will assist in maintaining the patient’s quality of life. The Cleveland Clinic Spine Center works closely with patients, using physical therapy and supportive devices to help strengthen the bones. Our skilled physicians often recommend and perform new procedures, such as kyphoplasty and vertebroplasty.

Radiation therapy — Radiation treatments often are used to generate high-energy rays to destroy cancerous cells and stop them from growing. This is usually recommended to control pain as well as to prevent the cancer cell growth from causing damage to the spinal cord. The radiation oncologist works very closely with the medical oncologist and orthopedic surgeon to decide on the need, site, dose, and duration of radia-
tion treatments. Radiation Oncology at Cleveland Clinic is one of the leading academic centers in the world, in addition to being one of the busiest clinical departments in the country.

**Neuroradiology** – Cleveland Clinic neuro-radiologists offer innovative methods to help control pain and decrease the incidence of fractures of the spine.

**Pain control** – Palliative medicine experts at Cleveland Clinic are available to help manage patients' symptoms that result from cancer or its treatment, symptoms such as bone pain, nausea, and constipation. Also, palliative medicine assists in preserving the quality of life when active treatment is no longer an option.

In 1991, the World Health Organization (WHO) recognized the Palliative Medicine Program at the Cleveland Clinic as a "unique model of a much needed service." As a WHO Demonstration Project, the program serves as a model for other care institutions around the world. The Chronic Pain program in the Anesthesiology Institute provides assistance when pain is particularly difficult to control, using a variety of techniques that might include invasive procedures.

**Dentistry** — There are three ways in which cancers and/or their treatments can affect teeth. The first is when the cancer affects the maxillary or mandibular (jaw) bones. This can happen with any cancer that has a tendency to spread to bones, although it is more common in cancers of the head and neck area, or cancers, such as multiple myeloma, that could directly affect the bones or grow in the tissue of the sinuses or the upper respiratory tract. In these cases, the actual bone structure may not be able to support the teeth.

Often, doctors recommend that the teeth be removed prior to treating the bones. If treatment requires bone removal, the teeth would be removed as well. Reconstruction can replace the bone and dentures can be made to accommodate chewing.

In addition, dentists in the department of Dentistry at Cleveland Clinic are specialists in the diagnosis and management of osteonecrosis of the jaw, a rare condition related to the use of bone-building medications (bisphosphonates) for the prevention of bone fractures in multiple myeloma and other cancers. The department of Dentistry has undergone steady growth to become one of the largest hospital-based dental practices in the United States.

**Neurology** — Thoracic or lumbosacral radiculopathy may be a complaint related to multiple myeloma. A herniated intervertebral disk (nucleus pulposus) is one which has become displaced (prolapsed) from its normal position in between the vertebral bodies of the spine. A herniated disk is the most frequent neurologic complication of multiple myeloma.

Root pain results from compression of the nerve by the vertebral lesion or by the collapsed bone itself. Spinal cord or cord compression from an extradural plasma cell tumor (outside the spinal cord) results in back pain with radicular features, weakness, or paralysis, requiring immediate diagnosis and treatment.
In addition, neuropathy (damage to nerves) from multiple myeloma or its treatments (medications such as thalidomide and bortezomib) can be severe and disabling. Experts in Cleveland Clinic’s Neurological Institute help diagnose and manage these conditions. The Neuroscience Center has one of the largest and most diverse academic neurosurgical programs in the United States.

**Infectious disease** — Recurrent bacterial infections are a major cause of illness and are the most frequent cause of death in patients with advanced myeloma. Infections result primarily from the marked depression of production of normal immunoglobulins that occur in more than 75 percent of patients. In addition, infections are often a side effect of chemotherapy. Physicians in Infectious Disease at Cleveland Clinic work together with medical oncologists to help diagnose and treat infectious complications of multiple myeloma or its treatment.

**Bone marrow transplant: autologous stem cell transplant** — An autologous (derived from the bone marrow of the same individual) stem cell transplant is occasionally recommended in treating multiple myeloma. This often occurs after the patient has received some form of prior therapy (known as induction therapy, and usually consisting of four cycles of chemotherapy or biologic therapy).

The autologous stem cell transplant includes stem cell collection (harvest), high dose chemotherapy, and stem cell infusion. The latter two steps involve hospitalization on the bone marrow transplant ward at Cleveland Clinic. Peripheral blood stem cells (PBSC) are harvested from your own blood or directly from the bone marrow. This step is usually performed in the outpatient setting. Subsequently the patient is hospitalized and high dose chemotherapy delivered. This is followed by infusion of the stem cells, and supportive care with antibiotics and fluids is delivered while awaiting engraftment of the stem cells. The entire process requires an average hospitalization of three to four weeks.

The low morbidity and very low mortality associated with the procedure, and the improved results with selected patients, have resulted in the increased use of autologous stem cell transplant in the treatment of patients with multiple myeloma. Autologous stem cell transplantation, however, does not benefit all patients equally, and the decision to proceed to transplantation is often a complex one requiring individualized decision-making.

**Bone marrow transplant: allogeneic bone marrow transplantation** — An allogeneic (the bone marrow source is not from the same individual) stem cell transplant is occasionally performed for patients with multiple myeloma. Stem cells from a matched related donor (MRD), such as a relative or a sibling, or from a matched unrelated donor (MUD), are collected and preserved. After high doses of chemotherapy, these donor bone marrow cells are given back to the patient so that they reconstitute the patient’s bone marrow and immune system.
The major advantage to allogeneic bone marrow transplantation over autologous transplantation is that the source of the bone marrow is free of tumor cells and that the immune system of the donor which is engrafted in the recipient is intact and able to fight and destroy tumor cells.

Unfortunately, the allogeneic transplant is more risky and can result in much higher mortality than the autologous transplant. Accordingly, this method of transplantation is undergoing significant modification before its use becomes more common. One such modification is called a "mini" transplant or reduced intensity conditioning transplant. This procedure relies on the ability of the donor immune system to fight the cancer. Accordingly, it requires less chemotherapy and is a safer procedure than the full allogeneic transplant.

The Bone Marrow Transplantation Program at the Cleveland Clinic is one of the nation’s leading programs. The program’s staff has performed many autologous, allogeneic, and reduced intensity conditioning transplants for several conditions, including multiple myeloma.

Research
The Cleveland Clinic’s Multiple Myeloma Program performs both clinical research (with patients) and basic research (in the laboratory.)

Clinical research and drug development
Significant advances have occurred in the field of multiple myeloma. These include the approval of drugs with considerable activity against multiple myeloma, such as thalidomide, lenalidomide, pegylated liposomal doxorubicin, and bortezomib. Such advances would have been impossible without the tremendous dedication and courage of patients with multiple myeloma who enrolled in clinical trials.

While these advances have revolutionized the treatment of multiple myeloma, commitment to the identification of active drugs with improved side effect profiles continues. To this end, the Cleveland Clinic Multiple Myeloma Program persists its clinical trial development efforts.

These innovative therapies may involve biologic agents or immunotherapy, which stimulate the body’s immune system to defeat the disease. Examples are vaccines or combination therapies of novel agents and conventional chemotherapy.

Patients with multiple myeloma are often offered participation into clinical trials at the Cleveland Clinic. For further information, please go to: http://cms.clevelandclinic.org/body.cfm?id=148.

Initial therapy for multiple myeloma
The advent of effective novel agents has resulted in a significant change in the treatment paradigm for newly diagnosed multiple myeloma patients. While the combination of oral melphalan and prednisone represented standard of care therapy a decade ago, the combination of thalidomide and dexamethasone is the most frequently prescribed therapy in the United States now. It is likely, however, that the standard will change in the near future as the results of combination therapies with lenalidomide and bortezomib become known.

Because initial reports of high dose therapy and stem cell transplantation were restricted to patients younger than 65 years of age, many institutions and national organizations have dichotomized therapy for newly diagnosed multiple myeloma patients.
based on eligibility for stem cell transplantation. Advances in supportive care and transplantation techniques have resulted in more patients being eligible for this therapy, including older patients and those with greater comorbidities. Accordingly, the Cleveland Clinic multiple myeloma program recommends an individualized approach to therapy for newly diagnosed patients.

The goals of initial therapy for multiple myeloma are to reverse the signs and symptoms of multiple myeloma and decrease the tumor burden (or obtain a remission). At the same time, treatment seeks to avoid intolerable toxicities and jeopardizing subsequent therapy (such as stem cell transplantation). The choice of therapy also depends on the patient’s general well being (or performance status), medical comorbidities (such as existing neuropathy, heart disease, or diabetes), presenting features (such as kidney failure), and personal choices.

**Maintenance therapy for multiple myeloma**

Many studies have attempted to determine what forms of maintenance therapy can prolong progression-free survival in patients with multiple myeloma once plateau phase following therapy has occurred. This is when patients are no longer actively requiring therapy for disease, and their illness has stabilized. Long-term alternate-day treatment with oral prednisone has been shown to improve survival in certain patients with multiple myeloma. In addition, maintenance therapy with thalidomide after stem cell transplantation has shown the ability to improve the survival of patient.

**Skeletal complications/kyphoplasty**

Kyphoplasty is a promising technique that reduces pain and improves function in patients with fractured vertebrae due to osteoporosis and other osseous (composed of or containing bone) lesions, such as bone metastases, or multiple myeloma. Kyphoplasty is a new technique that involves the introduction of an inflatable bone tamp (IBT) into the vertebral body. The purpose of the IBT is to restore the vertebral body back toward its original height, while creating a cavity that can be filled with highly viscous bone cement. Studies have shown that this technique can restore height of the collapsed vertebrae in many cases. Mostly, it can improve pain control. Orthopedists at Cleveland Clinic have extensive experience in this procedure and others used to manage symptoms. Kyphoplasty is usually a procedure that does not require you to be hospitalized.

**Bisphosphonates**

Bisphosphonates (pronounced biss-FOSS-fuh-nates) are drugs that work by reducing the activity of osteoclasts (cells that help break down bone). In theory, when osteoclast activity is reduced, people should experience less bone pain, fewer fractures, and slower loss of bone mass. Bisphosphonates are already used to treat hypercalcemia in people with cancer, Paget’s disease of the bone, and osteoporosis in postmenopausal women. Bisphosphonates are indicated and considered standard of care for patients who have bone lesions due to myeloma. The drugs strengthen the bone and prevent fracture risk.
**National collaboration**

How do you know you are receiving the best possible treatment? If a breakthrough occurs, can you be assured you will know of it?

Our collaboration with national and international multiple myeloma research efforts ensures that you will receive the best possible treatment and that we stay abreast of all developments in multiple myeloma. Should we not have available a particular treatment plan that we deem best for you, we know where it is offered and will refer you there.

As members of the Southwest Oncology Group (SWOG), we can provide new treatments from more than 30 major institutions in the United States. When a new treatment is developed, this association ensures that the clinical trials will obtain the large numbers of enrollees necessary to demonstrate the treatment’s efficacy in a timely manner.

**Basic research:**

**understanding multiple myeloma**

In the laboratory, we are actively investigating the causes of multiple myeloma on a cellular and molecular level. Improved scientific understanding of the disease ultimately will help us to develop more effective new treatments. Our ongoing basic research projects involve examining various controls of the immune system and plasma cells (the master immune cell or the T cell). We also are looking into how myeloma cells obtain nutrition for their rapid growth. In bone pathophysiology, we are trying to understand the mechanisms of bone destruction. We are trying to develop medications to prevent bony destruction and possibly restore structure.

**Resources**

The International Myeloma Foundation (IMF), based in Los Angeles, California, can be contacted at: 800.452.CURE(2873) in the United States and Canada; 818.487.7455 (outside of the U.S. and Canada); or by e-mail: TheIMF@myeloma.org. The IMF’s Web address is: www.myeloma.org.

The Multiple Myeloma Research Foundation (MMRF) based in New Canaan, Connecticut, can be contacted at: 203-972-1250 or by e-mail: info@themmrf.org. The MMRF’s Web address is: www.multiple-myeloma.org

**Patient education and support**

The Cleveland Clinic Multiple Myeloma Program Support/Education Group—A diagnosis of multiple myeloma elicits a profound emotional response in patients and family members. Many feelings arise, such as denial, depression, hopelessness, and fear. Questions about the disease and treatments contribute to the emotional distress. Our support program can provide answers to many of your questions and in turn can help you cope. The main objective is to educate patients and families; we believe that a better educated patient will have a better quality of life and be able to make informed decisions. At meetings, expert speakers discuss a variety of issues: exercise and physical therapy, managing fatigue, nutrition, and much more. The group also aims to increase the community’s awareness of the disease and the importance of early detection.
Working with you
and your community physician
We serve patients in a variety of ways. Some patients seek a second or third opinion here. They then return to their community oncologist to begin or continue their treatment. Some begin treatment with their local physician and then come to us to enter a clinical trial or protocol for new, experimental therapies. Other patients are diagnosed and receive all of their treatment here. Our goal is to work with you and your referring physician in whatever way serves you best.

For more information
For more information about our program or research protocols, please contact us. Our business hours are 8:30 a.m. to 5 p.m. weekdays.

In case of emergency, please call 800.223.2273 and ask to have the operator page the hematology/oncology physician on call.

The Cleveland Clinic Cancer Answer Program also can provide you with information, and can be reached at 216.444.7923 or 800.862.7798. We also offer a myeloma Web page, part of the Cleveland Clinic’s Web site. Here you will find information on myeloma and related diseases as well as the most up-to-date listing of open clinical trials. Please visit us at:
http://www.clevelandclinic.org/myeloma/.

To inquire about our clinical trials, call 216.445.5008.

For appointments, call 216.444.6833, in the Cleveland area. Call 800.223.2273, ext. 46833, toll-free from outside the Cleveland area.

This information is not intended to replace the medical advice of your health care provider. Please consult your health care provider for advice about a specific medical condition.