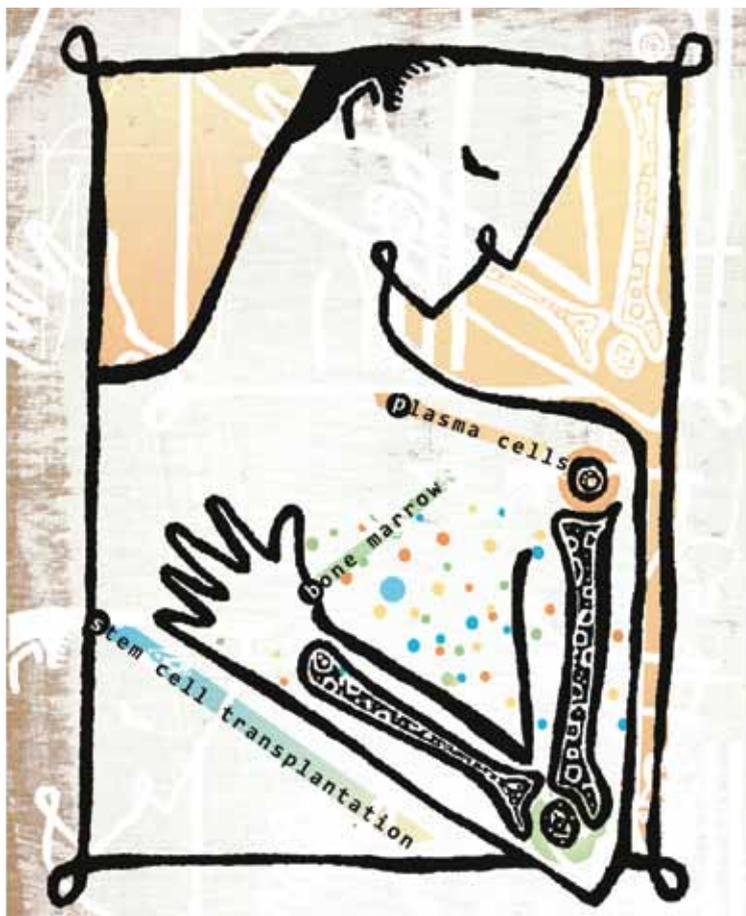


A Patient's Guide to **Multiple Myeloma**



Diagnosis ■ **Staging** ■ **Treatment Options** ■ **Side Effects and Complications** ■ **Patient Stories** ■ **Resources**

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A Patient's Guide to Multiple Myeloma

MYELOMA is a cancer of plasma cells that begins in the bone marrow. A single mass of myeloma cells is called a solitary plasmacytoma, which is most often found in the bones but can also be found in soft tissue (called an extramedullary plasmacytoma). Multiple plasmacytomas are referred to as multiple myeloma.

IN THE BONE MARROW, blood stem cells develop into three elements: red cells (which carry oxygen throughout the body), platelets (which help stop bleeding by causing the blood to clot) and white cells (which fight infection and perform other duties associated with the immune system). These cells are suspended in plasma, the liquid part of the blood, which also contains vitamins, minerals, proteins, hormones, antibodies and other chemicals. In response to bacteria or viruses entering the body, white blood cells, called plasma cells, produce antibodies that target particular bacteria and viruses for destruction. Multiple myeloma is a cancer characterized by plasma cells that multiply too fast and don't shut off reproduction when they should. Instead of producing antibodies that help fight infection, myeloma cells develop essentially useless antibodies called "monoclonal" or "M" protein.

It is unknown what causes plasma cells to become myeloma cells. It happens when a white blood cell hits a glitch in the genetic mechanism that programs its transition into a plasma cell. Instead of a normal plasma cell, a myeloma cell results. Eventually, these myeloma cells start crowding out other types

of blood cells in the bone marrow, including normal plasma cells. Like weeds in an untended garden, this overgrowth impedes the immune system and disrupts the continual process of bone remodeling.

Multiple myeloma is relatively rare—the lifetime risk of getting multiple myeloma is 1 in 159, according to the American Cancer Society. The vast majority of patients are older than 65. For reasons that are unknown, myeloma occurs more frequently in some racial groups, such as African-Americans.

There is no cure for myeloma, but treatment advances over the past decade have enabled many patients to live longer, healthier lives with the disease. Less than a generation ago, the odds of someone surviving five years after diagnosis was about 1 in 10. Today, the odds of surviving five years are about 4 in 10, and doctors expect survival time to increase even more in the future. It's possible for patients to live many years with a disease on a slow simmer that does not pose an immediate threat to health. The longer survival means that about 100,000 Americans are currently living with multiple myeloma, according to the International Myeloma Foundation.



Diagnosis

WITHOUT KNOWING what causes myeloma, researchers have been unable to identify specific risk factors, only general characteristics such as being older, male and African-American (where disease rates are highest). In a small number of cases, past treatment with radiation can also increase the risk of developing multiple myeloma later in life. While myeloma is sometimes hereditary (someone with a parent or sibling with myeloma is four times more likely to develop the disease), the overwhelming majority of patients have no family history of the disease. Researchers are investigating whether exposure to certain chemicals, infections with viruses or obesity might be contributors to the condition.

To look for leads on the cause of myeloma, researchers are examining the genetics of malignant cells. For example, patients with myeloma show abnormalities in certain chromosomes. (Humans have 46 chromosomes, which are the bundles of genes that contain the operating instructions for every cell in the body.) Scientists have also found abnormalities in individual genes of cancer cells. By studying how these genetic mutations conspire to make cell growth run amok, researchers hope to find better ways to treat the cancer and offer insight into prevention. For now, however, there is no known way to prevent myeloma from occurring.

The odds of developing myeloma increase in those who have a condition known as monoclonal gammopathy of undetermined

significance, or MGUS. This is a state in which plasma cells produce the same M protein that is the hallmark of malignant cells but do not cause any of the health problems associated with myeloma. It's important that people with MGUS get regular checkups so doctors can look for signs that the condition may be advancing into multiple myeloma. About 1 percent of people with MGUS each year will be diagnosed with disease that has progressed to multiple myeloma, lymphoma or amyloidosis.

A TREATABLE DISEASE

Although there is no cure for multiple myeloma, it is a treatable disease. Many patients live full, productive lives after diagnosis. About 38 percent of patients with multiple myeloma live at least five years after their diagnosis, and around 19 percent live at least 10 years. Because new therapies have been developed to treat myeloma in recent years, patients who have been recently diagnosed are expected to live even longer.

COMMON SYMPTOMS

At the beginning, many symptoms of myeloma can be unspecific and vague—such as bone pain, repeated infections, loss of appetite and fatigue. Often, symptoms don't appear until the disease has advanced. Some patients have no outward symptoms at all. Because the first clues to the illness can be vague, patients are often treated for recurring symptoms before doctors perform blood tests and discover the true underlying cause.

While not always immediately apparent,

one of the more common early signs of myeloma is pain, which usually originates in the bones. This is because the myeloma cells interfere with the normal give-and-take between cells that form new bone and cells that dissolve the old. Once bones weaken, they can fracture more easily. In fact, doctors have often suspected myeloma after examining a broken bone or identifying other signs of bone distress.

Other times, patients complaining of feeling overly tired may actually be anemic. As myeloma cells edge out red blood cells, the body has trouble getting all of the oxygen it needs.

Other vague symptoms that occur with advanced disease include loss of appetite, nausea/vomiting and confusion caused by increased levels of calcium in the blood. This condition, referred to as hypercalcemia, results from the breakdown of bones.

Occasionally, kidney failure is the first sign that something is wrong. The kidneys can become damaged as they try to filter out high levels of abnormal protein and calcium. To evaluate kidney function, doctors will check the blood and urine for creatinine, a normal substance that is produced by breaking down and building up muscle cells and is filtered out of the bloodstream by the kidneys.

CRITERIA FOR DIAGNOSIS

Doctors diagnose myeloma in patients with some of the symptoms listed above by using different forms of imaging to examine bones for lesions and by analyzing samples

of blood, urine and bone marrow. Laboratory tests are used to find the telltale signs of myeloma cells and evidence of threats to organs and tissue.

An official diagnosis is based on three basic criteria:

- **A bone marrow aspiration and biopsy showing that at least 10 percent of the cells in the marrow are plasma cells.** In normal bone marrow, only about 5 percent or less of the cell population are plasma cells. For the aspiration and biopsy, doctors take a sample of bone marrow, usually from the hip, though they will also check other areas because the condition can affect some bones more than others. Pathologists will then use a microscope to check the tissue for myeloma cells.
- **The presence of M protein in the blood or urine over a certain level.** M protein is a substance manufactured by myeloma cells and is often the source of kidney damage. It can also cause bleeding problems and blood thickening. The lab will check the levels of many proteins in the blood, including M protein.
- **Evidence of health threats from excessive plasma cells, including kidney dysfunction, increased calcium levels, bone lesions and/or anemia.** The lab will conduct a complete blood count, check for high levels of calcium and monitor kidney function by testing for creatinine.



Staging

STAGING IS THE PROCESS of identifying how far a disease has progressed, and it is important both to prognosis (predicting the course of the disease) and treatment decisions. Although there are different staging systems for myeloma (which are sometimes used in combination), the disease is generally divided into stages that signify the severity of illness. However, predicting the course of the disease will also depend on other factors, such as age and other underlying health problems in addition to cancer. (Because myeloma usually strikes at an older age, patients often have other health issues, including heart problems or diabetes.) Generally speaking, the “stage” in myeloma reflects the number of cancerous plasma cells in the blood.

- **Smoldering or indolent myeloma** means that the disease is at a very early stage and has not caused any symptoms or damage to tissues in the body. About 15 percent of myeloma cases diagnosed each year are at this stage.
- **Stage 1 disease** is more advanced than smoldering myeloma, but it still means that few malignant cells are circulating. Patients with stage 1 disease often have relatively normal levels of red blood cells and calcium. M protein levels are also low, and bone structure is normal or has only a single area of bone damage. Smoldering and stage 1 myeloma can persist for years without progressing or causing any immediate danger.

- **Stage 2** means that more cancer cells are spreading throughout the body but that the level falls between stage 1 and stage 3.
- **Stage 3** is the most advanced stage. At stage 3, there are even more plasma cells, and a large amount of M protein is circulating in the blood. Patients with stage 3 disease also have other complications, including extreme anemia and multiple bone lesions.

About one in four patients with myeloma have “high-risk” disease. This type of myeloma is particularly aggressive and may call for more aggressive treatment, such as stem cell transplantation. Doctors determine whether the condition is high risk by looking at genetic abnormalities that signal the disease will advance more aggressively.

While staging myeloma is important to determine a patient’s prognosis and, therefore, decide how aggressively the disease should be treated, the factors used to determine stage are not the only factors that influence prognosis. For instance, it is well known that older patients with myeloma do not live as long as younger patients, even if they both have the same stage of disease. Certain laboratory tests can also help predict how well a patient will do. These include a test called a myeloma cell labeling index, which measures how fast cancer cells are growing (fast growth results in a worse prognosis), and chromosome analysis, which can identify certain chromosomal abnormalities that signal a poorer outlook.



Treatment Options

TREATMENT IS BASED on the stage of disease at diagnosis, underlying health conditions and other considerations. Often, very early-stage disease is monitored without active therapy since a person can live years before the disease escalates. When and how to treat myeloma is a complex decision. Because patients can live with the disease for years and treatment rarely offers a cure, patients may undergo several types of therapy as time passes.

In general, treatment options for myeloma can be divided into four categories: chemotherapy (including targeted agents, such as proteasome inhibitors), corticosteroids, immunomodulating agents and stem cell transplantation. If a patient might eventually be a candidate for a stem cell transplantation, certain drugs might be used for initial therapy, because some drugs affect stem cells more than others.

For example, if stem cell transplantation is not an option, a combination of drugs that includes Alkeran (melphalan), prednisone in combination with Thalomid (thalidomide), Revlimid (lenalidomide) or Velcade (bortezomib) may be prescribed. Alkeran is a chemotherapy drug that attacks rapidly dividing cells, including myeloma cells. Prednisone is a corticosteroid that is also thought to tame the growth of tumor cells. Thalomid is an immunomodulator (it affects white blood cells) that slows the growth of blood vessels into cancer lesions and also targets tumor cells. Revlimid, an immunomodulatory drug

that works similar to Thalomid, is typically prescribed when the disease progresses or the patient relapses on Thalomid.

Velcade is a proteasome inhibitor that works inside myeloma cells to block a process that myeloma cells need to grow.

Alkeran combinations are not advisable prior to transplantation because of the effects on healthy cells in the bone marrow. Instead, a combination of Revlimid/Decadron (dexamethasone) or Velcade/Decadron may be prescribed. Decadron is an anti-inflammatory corticosteroid.

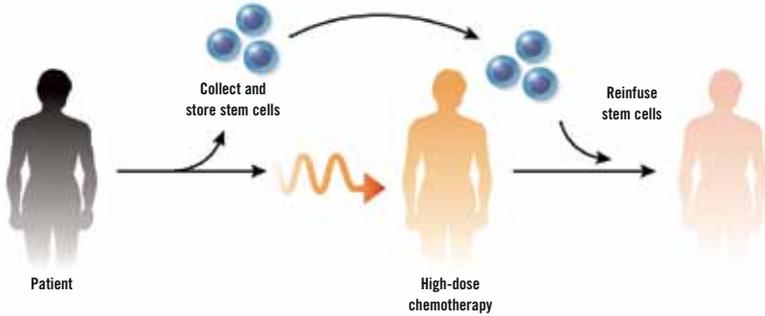
Another option may be to receive therapy by entering a clinical trial. Since new drugs and combinations are developed through clinical trials, this option may provide access to treatments that are not yet generally available. (For details, visit www.cancer.gov/clinicaltrials.)

STEM CELL TRANSPLANTATION

Many patients who are younger and healthier may be eligible for stem cell transplantation. During transplantation, doctors collect stem cells from the patient's bone marrow or from the circulating blood system and store them. The patient then receives high-dose chemotherapy to destroy the cancer cells. The previously collected stem cells are then reinfused into the patient so they can begin producing new blood cells.

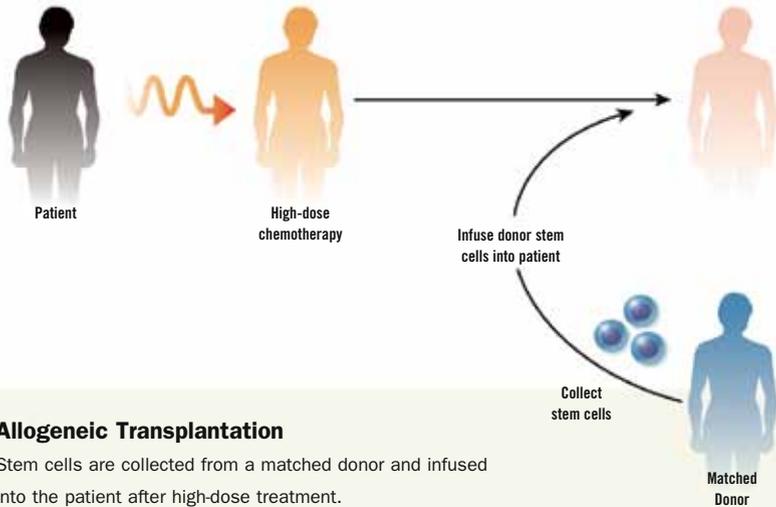
An autologous bone marrow transplantation means the cells come from a patient's own body. This is the most commonly recommended type of transplantation. Doctors may also use a tandem transplantation, giving two

TYPES OF STEM CELL TRANSPLANTATION



Autologous Transplantation

Stem cells are harvested from the patient, frozen and reinfused after high-dose treatment.



Allogeneic Transplantation

Stem cells are collected from a matched donor and infused into the patient after high-dose treatment.

consecutive transplantations within six to 12 months. Studies suggest that about half of patients who undergo a double autologous transplantation see their disease subside for an average of two or more years. An allogeneic transplantation means the cells come from a donor whose tissue type closely matches the recipient. It carries high risks of side effects and, thus, is used less often.

When it is successful, stem cell transplantation can prolong life or lead to disease remission. But it is a procedure with risks—about one or two out of every 100 patients will die from complications of the procedure.

RELAPSE

Because myeloma is not cured by available treatments, almost everyone with the disease will eventually relapse. In some instances, myeloma is resistant to initial treatment, and doctors must try other options. If the relapse is delayed—occurring more than six months after first treatment—patients may respond a second time to the same chemotherapy. Also, even if patients do not initially respond to treatment, they may still be eligible for a stem cell transplantation.

FUTURE OPTIONS

Treatment of multiple myeloma is evolving rapidly, with a lengthening list of drugs to treat the condition. New drugs are under investigation and may be available through clinical trials.

One experimental drug, carfilzomib, works similar to Velcade and is under consideration for approval among patients who have

already tried other therapies. In one study, about one in four patients responded to the drug (lowered M protein levels by at least 50 percent) for about eight months.

Pomalidomide, a new immunomodulator, is also in clinical trials. It may provide an option for patients who have developed resistance to Thalomid and Revlimid.

Another drug under investigation is elotuzumab, which works by trying to incite the immune system to find and destroy tumor cells.

Additional drugs, including subcutaneous Velcade and combinations of various agents, are also being studied.

BONE DAMAGE

To treat damaged bones, patients will commonly receive bisphosphonates—drugs that strengthen bones. Two intravenous bisphosphonates are Aredia (pamidronate) and Zometa (zoledronic acid).

A different class of drug under investigation to protect bones is Xgeva (denosumab), an intravenous therapy that is approved for use in other types of cancers that threaten bones, but it is not yet approved for myeloma or other blood cancers.

A rare but serious side effect of these drugs is osteonecrosis of the jaw, which happens when cells in the jaw bone die. The risk seems highest in patients who have oral surgery or tooth extraction immediately prior to or during therapy with these drugs. So before going on bisphosphonates, patients should have a dental checkup and avoid major dental procedures while taking them.



Side Effects and Complications

MULTIPLE MYELOMA symptoms can vary in intensity and scope, depending on how far the disease has advanced. Also, since myeloma tends to strike at older ages, many people have underlying health problems before the cancer shows itself. Here are some common complications of disease and side effects of treatment.

BONE PAIN AND WEAKNESS

The most common problems affecting myeloma patients are pain and weakness in the bones. The malignant plasma cells affect the remodeling of bone, causing overproduction of the natural substances that dissolve bone. When plasmacytomas form inside bones, the affected bones can develop soft spots or holes. Although these lesions can affect any bone, pain appears to be most common in the back, ribs and hips. Even seemingly slight movements, such as coughing or turning over in bed, can be painful. Sometimes bones can become so weak they easily fracture.

If the spinal bones become weak, they can collapse and press on nerves in the spine. Patients experiencing sudden and severe pain or numbness should contact their doctor immediately or seek emergency medical help.

When pain adversely affects quality of life, symptoms can be controlled with analgesics or radiation therapy. Drugs are commonly prescribed to delay the deterioration of bone. (See "Treatment Options.") Unlike medications that alleviate pain directly, drugs for bone loss may take a few weeks to bring

relief. Many patients also find that complementary techniques, such as relaxation therapy, acupuncture and massage, can alleviate pain.

BLOOD EFFECTS

Anemia: More than two-thirds of people with multiple myeloma experience anemia. In the blood, oxygen is carried throughout the body by hemoglobin, which is a protein nestled inside red blood cells. In addition to anemia from the disease, chemotherapy can also impede the production of red blood cells. When the body's tissues can't get the oxygen they need, the result is fatigue. The severity of anemia is measured by a patient's level of hemoglobin. If the hemoglobin is too low, doctors can help manage anemia with a blood transfusion or certain medications.

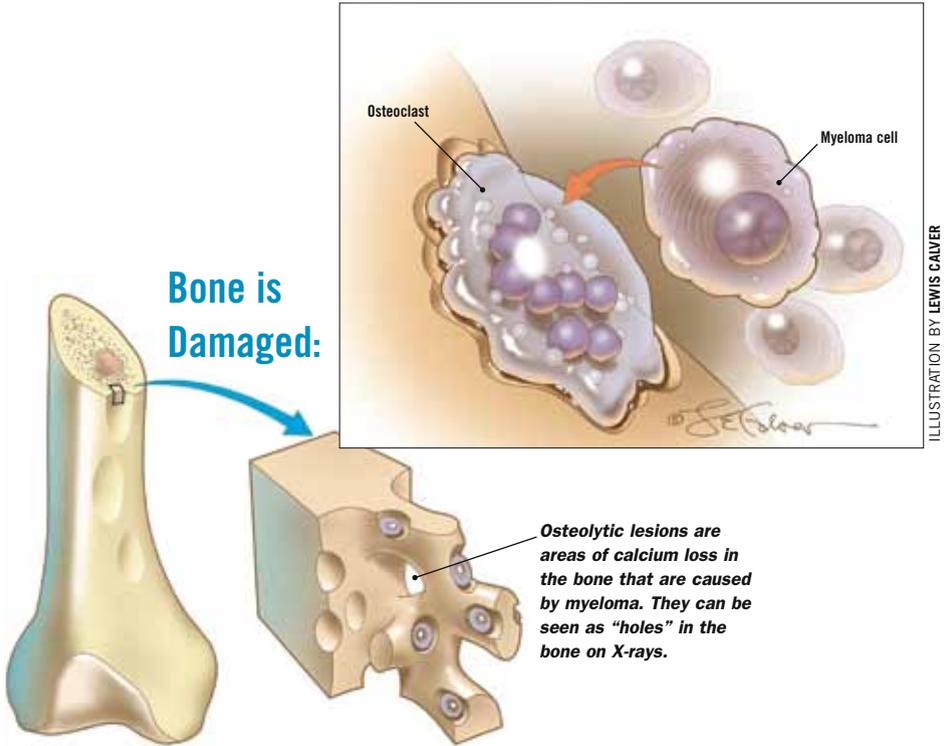
If a patient's condition warrants it, erythropoiesis-stimulating agents, or ESAs, may be prescribed to stimulate the production of red blood cells. However, although these drugs are well tolerated, they can be costly and introduce new risks (for example, some studies have suggested they increase the risk of blood clots and, if used inappropriately, may shorten survival time), so the potential benefits and risks must be carefully considered.

Although fatigue is associated with anemia, it can also be a side effect of some medications, stress and other underlying health conditions. Fatigue may be managed through diet (such as taking in more fluids and electrolytes), exercise and by treatment of anemia.

Repeated Infection: Myeloma cells disrupt

Bone Damage from Myeloma:

Myeloma cells stimulate osteoclasts, the body's normal bone-remodeling mechanism, resulting in excessive bone degradation and bone weakness.



the balance of the immune system, crowding out white blood cells that normally protect the body from invading viruses and bacteria. Myeloma cells do not produce antibodies to help fight infection, leaving patients vulnerable to serious infections—such as pneumonia—and at risk for bladder and kidney

infections, skin infections and shingles. The production of normal white blood cells that help fight infection, including normal plasma cells, is also impeded by chemotherapy. A lower than normal number of white blood cells is called leukopenia. Leukopenia usually resolves following treatment.

Thrombocytopenia and Blood Clots:

Some drugs, notably Velcade, might temporarily result in a higher risk of bleeding due to its effects on platelet formation in some patients—particularly those who are taking medications or supplements that interfere with blood clotting. This side effect, known as thrombocytopenia, is temporary in the majority of patients. Conversely, Revlimid and Thalomid treatments increase the risk of venous thromboembolism (the formation of a clot or thrombus in a vein). The chances of venous thromboembolism can be reduced or prevented by adding aspirin to the treatment regimen.

PERIPHERAL NEUROPATHY

Patients experiencing tingling, numbness or pain in the extremities may have peripheral neuropathy—nerve damage that can be related to the myeloma itself or can occur as a side effect of treatment with Thalomid or Velcade. In the case of Thalomid, some of the damage can be irreversible, so patients should alert their doctor if they start having symptoms while taking the drug. Neuropathy is usually reversible and appears to occur less often in patients who are taking Velcade. If neuropathy develops while taking these drugs, the dosage may be lowered or the treatment discontinued.

Certain medications can help with symptoms, but there are also practical steps that can be taken, such as massaging the feet and exercising regularly.

KIDNEY PROBLEMS

Some patients develop kidney problems

even before receiving a diagnosis of multiple myeloma. The kidneys remove waste and excess fluid from the body. Multiple myeloma can damage kidneys, leading to a buildup of salt, fluid and potentially harmful waste products. Sometimes the damage comes from the calcium released as bone tissue dissolves. (High calcium can also cause other symptoms, such as excessive thirst, constipation and even weakness and drowsiness.) Kidneys can also become damaged by the abnormal proteins produced by myeloma cells. As blood filters through the kidneys, the abnormal protein from myeloma cells can latch onto normal protein in urine. The two locked proteins are then too bulky to pass through the kidney's filtration system. Like clogged pipes, the tubes in the kidneys that filter the blood become more blocked over time.

Early damage often has no symptoms and is generally discovered only through a blood or urine test. Symptoms of advanced kidney disease include itching, swelling in the legs, loss of appetite, fatigue and confusion. Renal problems can become so serious that they are often the cause of death for patients with multiple myeloma, which is why the kidney function is closely monitored during the course of the disease.

Treatment of multiple myeloma will reduce the amount of abnormal protein in the blood and allow the kidneys a chance to heal. It's also important for patients to stay hydrated and avoid medicines (such as ibuprofen) that can tax the kidneys. If damage to the kidneys is severe, patients may require dialysis or transplantation.



Patient Stories

Fear of Recurrence

By Camille Fuller

I RECEIVED a diagnosis of multiple myeloma in 2004. The disease had progressed from being a plasmacytoma, or plasma tumor, that was mistaken for breast cancer. The myeloma diagnosis was confirmed by a bone marrow biopsy.

Every day, I worry that the myeloma will return, even though I have been receiving chemotherapy since my diagnosis. I have had induction chemotherapy, tandem stem cell transplants, consolidation chemotherapy and maintenance chemotherapy. And although I have been in remission since the first transplant, I still fear a recurrence. I return to my oncologist every six months for tests to determine whether I am still in remission.

I have three pieces of advice for newly diagnosed patients: First, listen to your gut. If you feel like something is wrong, keep pushing your doctor for proof that there isn't something wrong. If I had pushed my OB-GYN to take that lump in my breast seriously instead of dismissing it as something related to breastfeeding, maybe the plasmacytoma could have been treated and it wouldn't have developed into myeloma.

Second, find a treatment center that knows how to deal with myeloma. I'm grateful that my local doctor is being guided by my doctor in Arkansas. She is so kind and compassionate, and I truly am a person to her, as opposed to "just another patient."

Third, have faith in God. Many long nights are more tolerable because I pray to God when my anxiety won't let me sleep.

Living with Multiple Myeloma

By Cindy Chmielewski

TWO YEARS PRIOR to my cancer diagnosis, an orthopedist diagnosed me with degenerative disc disease when I went to him to help figure out what was causing excruciating lower back pain.

I was treated with pain medication and physical therapy, but my pain grew worse. After two years of treatment, an X-ray revealed several compression fractures, which ultimately led to my diagnosis of stage 3A multiple myeloma.

I have been on several chemotherapy protocols and have had a stem cell transplantation. Although I never achieved more than a partial response to my treatments, I am confident that with continued therapy, I will someday be able to say I am cancer-free. It is also reassuring to know that there are many drugs in the pipeline for when my myeloma becomes resistant to my current therapy.

To strengthen my bones, I receive a monthly intravenous bisphosphonate; I take calcium and vitamin D supplements daily; I spend at least 15 minutes a day in the sun; I include dark leafy vegetables in my diet; and I exercise. Since my bones are fragile, I need to be careful when exercising, so I participate in an aquatics program and walk daily with my dog. My goal is to walk a half-marathon next year. I am gradually adding gentle yoga and core-strengthening exercises to my routine.

I am living a full, active life while I am in treatment. I have learned to take things one day at a time, appreciate every day and be my own health advocate.



Questions to Ask

BEFORE TREATMENT

- What stage of myeloma do I have?
- Is the disease affecting my kidneys?
- How do I get a copy of the report from the pathologist?
- What are my treatment choices? Which do you recommend for me? Why?
- Will I have more than one kind of treatment? How will my treatment change over time?
- What are the expected benefits of each kind of treatment?
- What are the risks and possible side effects of each treatment? What can I do to control the side effects?
- What can I do to prepare for treatment?
- Will I need to stay in the hospital? If so, for how long?
- What is the treatment likely to cost? Will my insurance cover the cost?
- How will treatment affect my normal activities?
- Would a clinical trial be right for me? Can you help me find one?
- How often should I have checkups?

PEOPLE WITH STAGE 1 OR SMOLDERING MYELOMA

- If I choose watchful waiting, can I change my mind later on?
- Will the cancer be harder to treat later?
- How often will I have checkups?
- Between checkups, what problems should I tell you about?

BEFORE STARTING INITIAL THERAPY

- Which drugs will I get? What will the treatment do?
- When will treatment start? When will it end? How often will I have treatments?
- Where will I go for treatment? Will I have to stay in the hospital?
- Will I have side effects during treatment? What side effects should I tell you about? Can I prevent or treat these side effects?
- Will there be lasting side effects? How long will they last? What can I do about them?
- How often will I need checkups?

BEFORE RECEIVING STEM CELL TRANSPLANTATION

- What kind of stem cell transplantation will I have? If I need a donor, how will I find one?
- How long will I be in the hospital? Will I need special care? How will I be protected from germs?
- What care will I need when I leave the hospital?
- How will I know if the treatment is working?
- What are the risks and the side effects? What can I do about them?
- What changes in normal activities will be necessary?
- What is my chance of a full recovery? How long will that take?



Resources

International Myeloma Foundation

800-452-CURE (800-452-2873)

myeloma.org

Supports education, treatment and research for multiple myeloma. The organization also provides a toll-free hotline, seminars and educational materials for patients and their families.

Multiple Myeloma Research Foundation

203-229-0464

themmrf.org

Supports research grants and professional and patient symposia on multiple myeloma and related blood cancers. The MMRF publishes a quarterly newsletter and provides referrals and information packets free of charge to patients and family members.

The Myeloma Beacon

myelomabeacon.com

An online service provided by Light Knowledge Resources, an independent Internet publishing company based in Princeton, N.J. Provides news, information articles and online forums related to multiple myeloma.

The Leukemia and Lymphoma Society

800-955-4572

lls.org

Supports research and provides education and patient services. The organization seeks to improve the quality of life of multiple myeloma patients and their families. The organization also provides patient financial aid for specified treatment expenses and

transportation, family support groups, a professionally supervised peer support program and referrals to healthcare professionals with the latest information on multiple myeloma.

Multiple Myeloma Opportunities for Research & Education

888-486-4240

mmore.org

Supports moving life-prolonging treatments in development through the research stage and making them available to myeloma patients. The organization also seeks to improve quality of life for patients and raise awareness of the disease through community events.

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