LEUKEMIA & LYMPHOMA SOCIETY®
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Myeloma

Anne Grace, myeloma survivor

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Publication Update
Myeloma

The Leukemia & Lymphoma Society wants you to have the most up-to-date information about blood cancer treatment. See below for important new information that was not available at the time this publication was printed.

- In July 2015, the Food and Drug Administration (FDA) approved carfilzomib (Kyprolis®) in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy.

  Carfilzomib is also indicated as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

- In November 2015, the Food and Drug Administration (FDA) approved ixazomib (NINLARO®) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

For more information, contact an Information Specialist at (800) 955-4572 or infocenter@lls.org.

A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to finding cures for blood cancer patients. Our research grants have funded many of today's most promising advances; we are the leading source of free blood cancer information, education and support; and we advocate for blood cancer patients and their families, helping to ensure they have access to quality, affordable and coordinated care.

Since 1954, we have been a driving force behind almost every treatment breakthrough for blood cancer patients. We have invested more than $1 billion in research to advance therapies and save lives. Thanks to research and access to better treatments, survival rates for many blood cancer patients have doubled, tripled and even quadrupled.

Yet we are far from done.

Until there is a cure for cancer, we will continue to work hard—to fund new research, to create new patient programs and services, and to share information and resources about blood cancers.

This booklet has information that can help you understand myeloma, prepare your questions, find answers and resources, and communicate better with members of your healthcare team.

Our vision is that, one day, all people with myeloma will either be cured or will be able to manage their disease so that they can experience a great quality of life. Today, we hope our expertise, knowledge and resources will make a difference in your journey.

Louis J. DeGennaro, PhD
President and CEO

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Acknowledgement

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Introduction

Myeloma is a cancer of plasma cells. It is estimated that 24,050 new cases of myeloma will be diagnosed in 2014 in the United States alone.[1] Although myeloma is incurable in most cases, this is a very hopeful time for patients. Dramatic advancements in new treatments over the past decades are resulting in better overall survival, allowing many patients to maintain a good quality of life for years. An estimated 95,874 people in the United States are living with, or are in remission from, myeloma.[1]

This progress in disease management—with the ultimate goal of finding a cure—is expected to continue as a result of the concerted scientific research effort that is under way and because of patients' participation in clinical trials. This booklet provides information about myeloma; it covers diagnosis, staging and classification, treatment, and includes a brief description of normal blood and marrow and a list of medical terms.

[1]Source: *Facts 2014-2015*. The Leukemia & Lymphoma Society. January 2015.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet 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.

For Help and Information

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 (Monday through Friday, 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 booklets that can be either read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/publications.

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.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

Community Resources and Networking

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

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. For more information about these programs or to contact your chapter, please

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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, locating summer camps and other needs. For more information, please visit www.LLS.org/resourcedirectory.

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

- Call: (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials and click on TrialCheck®.

Advocacy. The LLS Office of Public Policy (OPP) 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.

Additional Help for Specific Populations

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

Language Services. Let your doctor know if you need a language interpreter or some other resource person, such as a sign language interpreter. Often, these services are free.

Information for Veterans. Veterans with myeloma who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes.

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html.

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-week period. For more information, please

- Call: National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov. Enter “depression” in the search box.

Feedback. To give suggestions about this booklet, visit www.LLS.org/publicationfeedback.

About Myeloma

Myeloma is a cancer of the plasma cells. The disease belongs to a spectrum of disorders referred to as "plasma cell dyscrasias."

Plasma cells are made from "B lymphocytes" (B cells), a type of white blood cell that is found in the bone marrow. Healthy plasma cells are part of the immune system and make proteins called "antibodies," which help fight infection. Myeloma develops when a plasma cell is changed (mutated). The change in the cell is caused by one or more acquired genetic mutations. The changed plasma cell (myeloma cell) multiplies, and, if untreated, these cells continue to grow in the marrow. They crowd out the healthy plasma cells and the normal stem cells in the bone marrow that form the white blood cells, red blood cells and platelets. At the time of diagnosis, most patients with myeloma already have disease that involves multiple sites; the name "multiple myeloma" is sometimes used to refer to the disease in its most common form.

In some cases, myeloma may also be described as "localized myeloma" (found in one site with exposure to neighboring sites) or "extramedullary myeloma" (when there is involvement of tissue other than the marrow, such as the skin, muscles or lungs).

The term "plasmacytoma" refers to a collection of malignant plasma cells in a single site, such as a tumor in the bone, skin, muscle, or lung. Plasmacytomas are only found in about 5 percent of all patients with a plasma cell dyscrasia. Patients with a plasmacytoma diagnosis need a thorough medical evaluation and screening to discover if there are signs that are suggestive of myeloma. A plasmacytoma can often be cured with radiation therapy alone. Some patients do have a recurrence of the plasmacytoma or progression to myeloma.

Incidence, Causes and Risk Factors

Myeloma is a relatively rare blood disease. It generally occurs in adults older than 50 years (see Figure 1). Myeloma affects slightly more men than women, and the incidence is twice as high in blacks as it is in whites. Asian Americans/Pacific Islanders and American Indians/Alaskan Natives are significantly less likely to be diagnosed with myeloma than other populations.

Myeloma: Age-Specific SEER Incidence Rates 2007-2011

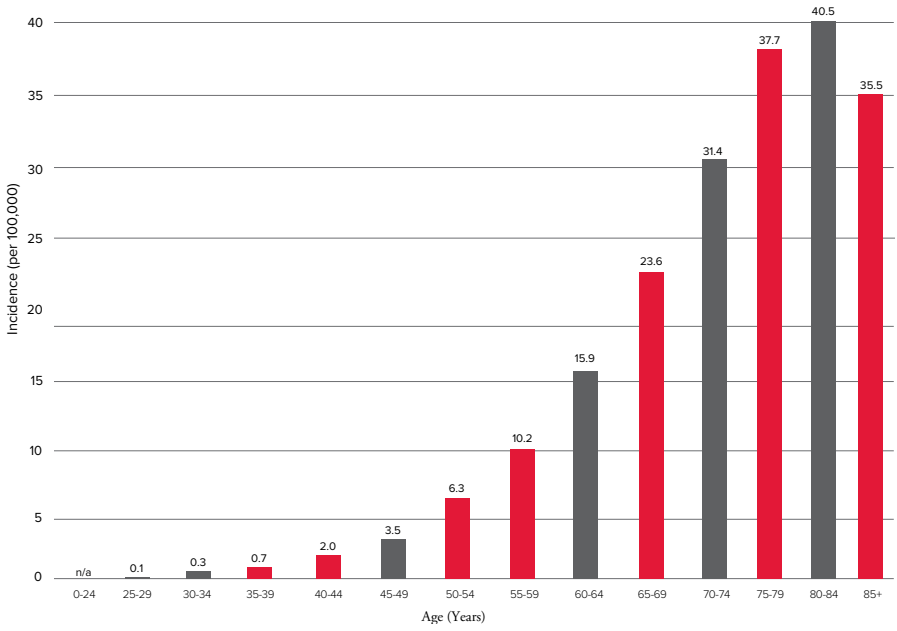

Figure 1. | The horizontal axis shows the age at diagnosis, in five-year increments, of people in the United States who develop myeloma. The vertical axis represents the number of new cases of myeloma per 100,000 people. Thus, the risk of myeloma is about 10 times greater in those aged 75 to 79 years (about 38 cases/100,000 people) compared to those aged 45 to 49 years (about 3 cases/100,000 people).
Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, www.seer.cancer.gov/csr/1975_20011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

Causes. Although the exact cause of myeloma is not known, doctors do know that myeloma starts when a change occurs to a single cell called a "B lymphocyte" (B cell). Normally, some B lymphocytes develop into plasma cells, which produce proteins called "antibodies." Antibodies help the body fight infection. With myeloma, the B lymphocyte becomes a myeloma cell instead of a normal plasma cell. Researchers are studying the DNA of plasma cells to determine what changes cause normal plasma cells to become cancer cells. The causes remain unknown,

but scientists have found that in almost all people with myeloma, plasma cells have developed new genetic abnormalities that likely contributed to the development of cancer in these cells.

Risk Factors. A risk factor is something that increases the chance of developing a disease. Some factors that may increase the risk of developing myeloma include

- Age—Most people who develop myeloma are older than 50 years. Fewer cases of myeloma occur in people younger than 40.
- Sex—More men than women develop myeloma.
- Race—Blacks are nearly twice as likely as whites to develop myeloma.
- Medical history—People with a history of MGUS (monoclonal gammopathy of unknown significance) (see page 32).
- Environment—Some studies are investigating a link between the development of myeloma and one or more of the following factors: radiation, or exposure to certain kinds of chemicals such as pesticides, fertilizers and Agent Orange.
- Obesity—New research suggests that obese people have a higher incidence of myeloma.

Signs and Symptoms

In the early stages of myeloma, some patients have no signs or symptoms of disease. In about a fifth of myeloma patients, the cancer is detected before symptoms appear, often when results of laboratory tests that were part of a routine medical examination show changes in blood and/or urine. Some symptoms of myeloma include

- Bone pain and/or skeletal fractures
- Fatigue and weakness as a result of low red blood cell counts (anemia)
- Frequent infections due to a weakened immune system.

Doctors sometimes refer to the acronym, **CRAB**, to describe symptoms of myeloma. The letters stand for

C—Calcium elevation (high levels of calcium in the blood; also known as "hypercalcemia")

R—Renal insufficiency (poor function of the kidneys that may be due to a reduction in blood-flow to the kidneys)

A—Anemia (low red blood cell counts)

B—Bone abnormalities (lesions)

Patients with one or more of these CRAB criteria are considered to have disease that requires therapy. Those who do not exhibit any of these criteria are said to have "smoldering" or "asymptomatic myeloma," and these patients may be followed with a watch-and-wait approach. Recently, other criteria that also probably indicate the need to start chemotherapy were added to the CRAB criteria. They include

- At least 60 percent concentration of bone marrow plasma cells
- A free light chain ratio (involved light chain /uninvolved light chain) of 100 or more
- More than one focal bone lesion on magnetic resonance imaging (MRI).

Effects on Bone. Bone pain is the most common early symptom of myeloma. Most patients feel pain in their back or ribs, but it can occur in any bone. The pain is usually constant and made worse by movement. Normally, bone is remodeled (broken down and replaced) continuously in the body to keep it strong. This remodeling is a coordinated effect of cells that dissolve bone (osteoclasts) and cells that lay down new bone (osteoblasts). Bone pain and destruction can be a part of myeloma because myeloma cells secrete a type of chemical called a "cytokine," which stimulates the cells that dissolve bone and inhibits cells that form bone. In other words, the chemicals secreted by myeloma cells stimulate the bone-dissolving cells into overactivity and inhibit the bone-forming cells, resulting in unopposed bone destruction. As a result of this imbalance in the normal bone remodeling process, holes (lytic lesions) develop in the bone. Bone is thinned (osteoporosis) and can be weakened enough to fracture during everyday activities such as walking, lifting or sneezing. Slightly increased activity, such as coughing and minor falls or injuries, can also result in broken bones and cause pain.

Effects on Blood and Marrow. Myeloma patients may fatigue more easily and feel weak. They may have a pale complexion from anemia (the result of low hemoglobin concentration and/or a low red blood cell count). Anemia is a common problem for patients with myeloma, and may contribute to the fatigue. If the disease progresses, the concentration of other normal cells in the blood, for example the numbers of white blood cells and platelets, may also decrease. In normal marrow there are relatively few plasma cells (less than 5 percent). The number of plasma cells can slightly increase in the marrow because of the body's response to an infection, especially a virus, not to the presence of myeloma. However in patients with myeloma, plasma cells are often present in abnormally large numbers (see Figure 2, page 9). The myeloma cells accumulate in an uncontrolled manner and form tumors in the marrow.

While the bone marrow in adults is mainly concentrated in the iliac bone (low back and hip) and sternum (chest bone), there are pockets of bone marrow in all bones, therefore myeloma cells can generally grow and accumulate in most bones in the body, including the skull, vertebrae and ribs. Myeloma cells are not found in the joints and small bones of hands and feet because there is very little to no bone marrow in those areas.

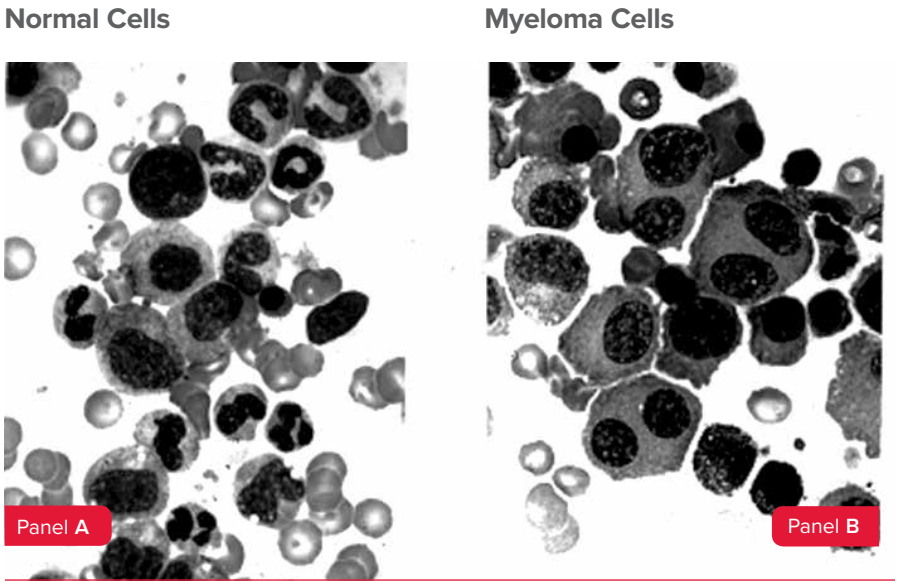

Figure 2. | **Panel A** is a photograph of normal marrow cells. The variations in the shape and appearance of the cells are characteristic of the developmental stages of normal cells. **Panel B** is a photograph of marrow cells from a patient with myeloma. The normal marrow cells are replaced by plasma cells. Several cells have two nuclei, which may be one sign of abnormal plasma cells (myeloma cells).

Patients may experience repeated infections because the antibodies they need to fight invading viruses, bacteria or other disease agents are not made efficiently and in adequate numbers. A urinary tract, bronchial, lung, skin or other type of infection may be the first sign of myeloma. In addition, recurrent infections may complicate the course of the disease.

Other Effects. Another early symptom can be numbness, tingling, burning, or pain in the hands and/or feet caused by a condition called "peripheral neuropathy." Some patients have high levels of calcium, which can cause increased thirst and urination, constipation and, in extreme cases, decreased alertness and kidney failure. Some patients can have amyloidosis, a condition in which the abnormal myeloma protein is deposited in various tissues in the body and can cause damage. In rare cases, patients may have "hyperviscosity syndrome," a condition that results from high concentrations of M protein in the blood. Symptoms of hyperviscosity syndrome are abnormal bleeding, headaches, chest pain, decreased alertness or shortness of breath. See *Myeloma Complications and Treatment Side Effects*, beginning on page 26, for more information about kidney impairment, hyperviscosity syndrome and peripheral neuropathy.

Diagnosis

Blood tests that accompany some periodic medical examinations include a measurement of blood proteins, for example albumin. A lab test result showing an elevated level of total protein may lead to further blood and marrow tests and to the diagnosis of myeloma.

The diagnosis of myeloma depends on three principal findings. They are

- Increased numbers of malignant plasma cells (myeloma cells) that are found when a bone marrow aspiration and biopsy (usually obtained from the hip bone) are performed. Bone marrow aspiration and biopsy findings indicate the percentage of myeloma cells in the marrow, as well as detecting any genetic abnormalities in the myeloma cells. Bone marrow that contains more than 10 percent plasma cells is suggestive of myeloma.
- Intact monoclonal immunoglobulins or immunoglobulin light chains (Bence Jones proteins) are found in the blood and/or urine. See *Monoclonal Immunoglobulins (Monoclonal Protein [M Protein] and Light Chains [Bence Jones Proteins])* below and Figure 3 on page 11).
- Imaging studies of the bones sometimes identify bone thinning, holes or fractures in the bones that characterize myeloma. Magnetic resonance imaging (MRI), especially of the spine, can detect bone changes earlier than conventional x-ray studies, and in some cases, so can positron emission tomography (PET) scanning.

Taken together, these findings make it possible for doctors to diagnose myeloma in patients.

Talk to your doctor about | Your diagnostic tests, what the results mean, and getting copies of the test results.

Monoclonal Immunoglobulins (Monoclonal Protein [M Protein] and Light Chains [Bence Jones Proteins]). The body's normal process is for plasma cells to produce proteins called "polyclonal immunoglobulins." These are antibodies that protect the body against all kinds of different invading viruses, bacteria or other infectious agents (antigens).

Most patients with untreated myeloma have large amounts of a single type of protein called "monoclonal immunoglobulin" (also called "M protein" or "M spike") in their blood. The term "monoclonal" indicates that the protein is derived from cancer cells that originally started as a single, malignant cell.

M protein can be measured in the blood and/or urine (See *Protein Electrophoresis Tests* on page 12). The amount generally correlates with the extent of the myeloma. Increasing M protein levels in the blood usually indicate progression of disease and decreasing levels usually reflect regression of disease. Decreasing levels are usually associated with successful therapy.

A small number of patients with myeloma have either "oligosecretory disease," in which the detectable level of monoclonal protein is low, or "nonsecretory disease," in which no monoclonal protein can be detected. Some of these patients can be followed with a newer blood test that measures serum free light chains, which are a small fragment of the larger intact M protein.

The intact immunoglobulin (Ig) molecule is composed of two larger pieces (heavy chains) and two smaller pieces (light chains) that are attached to each other.

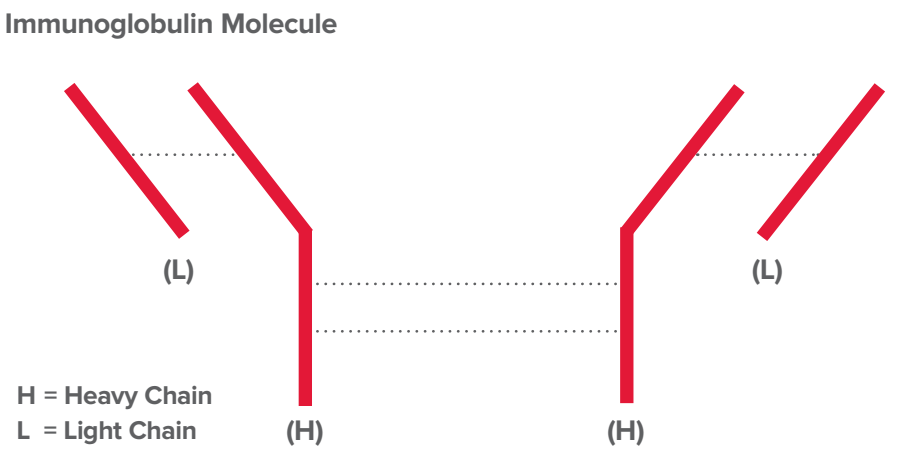

Figure 3. | The M protein in myeloma, like normal immunoglobulin, is made up of two heavy chains and two light chains attached to each other. In many cases, the coordination of making and attaching light chains and heavy chains in the malignant plasma cells is lost, and light chains leave the cell unattached. They are small enough to pass through the kidney and enter the urine, where they can be detected. Light chains in the urine are also referred to as "Bence Jones proteins."

This whole immunoglobulin, made of the four chains, is usually too large to pass through the kidney. Thus, it is most often present in the blood but not in the urine. When the whole immunoglobulin is present in the urine, it is usually at a low level. In many myeloma patients, the coordination of making and attaching light chains and heavy chains in the malignant plasma cells is lost. Unattached light chains enter the blood and are excreted rapidly in the urine. The light chain is also called the "Bence Jones protein," for the English doctor Henry Bence Jones, who studied its characteristics. When excreted in large amounts, the Bence Jones proteins (light chains) can sometimes make the urine appear foamy, and can cause injury to the kidneys and kidney failure (see *Blood and Urine Tests* on page 12).

There is a test available that detects the small light chains and there is also a test in development to measure the heavy chain portion of the M protein. See Figure 3, on page 11.

Normal plasma cells produce one of five types of antibodies (polyclonal immunoglobulins): IgG, IgA, IgM, IgE or IgD. Myeloma cells produce monoclonal immunoglobulins. The most common form of myeloma is "IgG myeloma," in which the monoclonal protein is composed of two long chains and two short chains as shown in Figure 3 on page 11. The next most common type is light chain myeloma, where an intact immunoglobulin is not made. Some patients have "IgA myeloma," and a small number of patients have "IgM," "IgD," or "IgE" myeloma.

Protein Electrophoresis Tests. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), both of which need to be performed with an immunofixation (IFX), are tests used to identify the presence of abnormal proteins, to identify the absence of normal proteins, and to determine increases and decreases of different groups of proteins in serum or urine. These tests are typically ordered to detect and identify excessive production of specific proteins (immunoglobulins). All five types of immunoglobulins (IgG, IgA, IgM, IgE, or IgD) are measured by these tests. If present, an excessive production of a monoclonal immunoglobulin may be shown on lab results as a spike on a graph (M protein or M spike). Most patients with untreated myeloma have a monoclonal immunoglobulin peak in serum, urine, or both.

These tests usually should be repeated at regular intervals to monitor the course of the patient's myeloma and the effectiveness of treatment.

Talk to your doctor about | Your test results and what the results mean.

Blood and Urine Tests. Light chains can often be detected in the blood and urine of patients with myeloma. In some patients, the myeloma cells do not make a complete monoclonal immunoglobulin molecule with two heavy and two light chains (see Figure 3 on page 11); their myeloma cells make only light chains. In these cases of myeloma, referred to as "light chain deposition disease" (see page 33), the examination of serum may not show the characteristic increase of M protein, but the urine will have large amounts of monoclonal light chains.

Blood Cell Counts. Doctors will also order a complete blood count, also called a "CBC," which measures the number of red blood cells, white blood cells and platelets in the blood. These measurements indicate the degree to which the myeloma cells in the marrow are affecting normal blood cell development. Sometimes a CBC with differential ("CBC with diff"), which examines the types of different white blood cells present in the blood, can be helpful as well.

Blood Calcium. Blood calcium levels are measured because bone destruction causes calcium to leave the bones and sometimes reach elevated levels in the blood. High calcium levels can damage the kidneys. In addition, an increase in the concentration of lactic dehydrogenase, beta$_2$-microglobulin or C-reactive protein in serum (blood) is an indirect measure of the size and growth rate of the myeloma tumors.

Kidney Function. Kidney function tests (measurements of blood urea nitrogen and creatinine) and a urine examination (urinalysis) are usually performed, since impaired kidney function can result from both the effects of the abnormal protein on the kidneys and metabolic changes such as elevated blood calcium levels. A 24-hour urine collection provides an accurate measurement of the level of kidney function and can indicate possible kidney damage from the myeloma. Also, the level of protein being excreted in the urine and the level of light chains can be measured; these measurements provide information about the extent of the disease.

Genetic or Chromosomal Abnormalities. Genetic or chromosomal abnormalities in the myeloma cells are identified by G-banding karyotyping and FISH (fluorescence in situ hybridization). Myeloma cell abnormalities may include deletion of chromosome 13, which is associated with disease that does not respond as well to chemotherapy, though some of the newer drugs seem to help in treating these patients. Other chromosome abnormalities, including translocations involving chromosome 14 (the site of a gene for the immunoglobulin heavy chain), are common findings, and can include translocations between chromosomes 11 and 14, 4 and 14, and 14 and 16. It is also not uncommon to see abnormalities of chromosome 1, with either a loss of material from the short arm (1p), or addition of extra copies (amplification) of material from the long arm (1q). A less common, but important, change is an abnormality or loss of the short arm of chromosome 17, where the important tumor suppressor p53 is located. These alterations can suggest how rapidly the disease may progress in the future, and predict the chances of a good, long-lasting response to therapy. This information may also play an important part in determining the best approach to treatment. Importantly, based on these alterations, myeloma can be classified as "high risk" or "standard risk." Speak to your doctor about your risk category.

Gene-expression profiling (GEP) is one newer technique that looks at which genes are expressed and at what levels in myeloma cells. Another method that is, for now, being done on a research basis, but that may soon be in routine practice, is called "next-generation sequencing (NGS)," and looks at what mutations are present in the genes of the myeloma cells. Since the expression levels of these genes and how (or if) they are mutated influences the behavior of the myeloma cells, these techniques may be helpful in better predicting outcomes. In the future, it may be possible to choose the best treatment based on this information as well.

In addition, doctors "stage" myeloma to help them decide on the best treatment plan. Staging is described in the next section.

Staging

Once a diagnosis of myeloma is made, the doctor will determine the stage or extent of the patient's myeloma to help in deciding which of several treatment approaches to take (see Figure 4, page 15). For decades, a system of myeloma staging called the "Durie-Salmon Staging System" has been used. The Durie-Salmon system measures the patient's hemoglobin concentration, the amount of the M protein in the blood and urine, the level of blood calcium, the level of kidney function and the presence of bone lesions on imaging studies to determine the extent of the myeloma. A newer method, called the "International Staging System for Multiple Myeloma," relies on the degree of increase in beta$_2$-microglobulin concentration and the degree of decrease in serum albumin levels—two serum measurements done on virtually all patients—to determine prognosis (outlook) at the time of diagnosis. These measurements allow the doctor to classify the patient's myeloma as stage I, stage II or stage III disease. In the future, it is likely that newer staging systems may be used that combine some of these measurements with either fluorescence in situ hybridization (FISH), gene-expression profiling (GEP), or next-generation sequencing (NGS) data, or two or three of these, to provide even more accurate staging.

Doctors also consider other factors in deciding whether to treat and what approach to take. The general health of the patient, the presence of other significant diseases such as heart disease or diabetes, the presence of kidney disease, and other findings that influence the patient's tolerance to treatment and the risk of treatment-induced difficulties are considered when deciding on a treatment approach. Your own input is important here as well, since patients have different considerations and goals for their therapy. Your plan needs to be individualized for you.

Myeloma Staging Systems

Stage	Durie-Salmon Staging System	International Staging System
I	**All of the following:** ○ Hemoglobin value >10.5 g/dL ○ Serum calcium value normal or ≤12 mg/dL ○ X-ray studies of bone, normal bone structure (scale 0) or solitary bone plasmacytoma only ○ Low M-component production rate—IgG value <5 g/dL; IgA value <3 g/dL ○ Urine light chains <4 g/24 hours	Serum $beta_2$-microglobulin <3.5 mg/L and albumin ≥3.5 g/dL
II	**Neither stage I nor stage III** ○ A = No renal failure (creatinine ≤2 mg/dL) ○ B = Renal failure (creatinine >2 mg/dL)	Serum $beta_2$-microglobulin <3.5 mg/L and albumin <3.5 g/dL or $beta_2$-microglobulin 3.5 to 5.5 mg/L
III	○ Hemoglobin value <8.5 g/dL ○ Serum calcium value >12 mg/dL ○ X-ray studies of bone, >3 lytic bone lesions ○ High M-component production rate—IgG value >7 g/dL; IgA value >5 g/dL ○ Urine light chains >12 g/24 hours	Serum $beta_2$-microglobulin ≥5.5 mg/L

Figure 4. | A doctor will consider many factors for each patient in conjunction with staging information to develop a treatment approach.

Treatment

The goals of treatment for myeloma patients are to reduce symptoms, to slow disease progression, to provide prolonged remissions, and to lengthen survival while preserving quality of life. There have been many significant treatment advances in recent years and treatment options continue to evolve. The goals of research for myeloma treatment are to develop curative therapies and to decrease the side effects of treatment. See page 24 for more about *Research and Clinical Trials*. The approach for treating each patient is customized, based on a number of factors that include

- Extent and characteristics of his or her disease, such as chromosome abnormalities
- Rate of disease progression
- Presence of other conditions, such as heart or kidney disease, diabetes or neuropathy
- Age (note that the patient's overall health is considered in determining his or her ability to tolerate intensive therapy, rather than age alone).

Talk to your doctor about | Your treatment options and the results you can expect from treatment. Ask about the results you might expect with standard therapy and the possibility of participating in a clinical trial.

People are advised to consult a doctor who specializes in treating patients with myeloma and to discuss the most appropriate treatment for their situation. Most treatment plans include a combination of therapies. Some patients only need supportive care to address symptoms of anemia, high blood calcium levels, infections and/or bone damage or osteoporosis (see *Supportive Care* on page 21). Other patients receive myeloma-specific therapies to treat disease progression and induce remission. Myeloma-specific therapies include

- Single or combination drug (standard-dose) therapy
- High-dose chemotherapy with one of three types of stem cell transplantation
  - Autologous
  - Allogeneic
  - Reduced-intensity allogeneic
- Radiation therapy for local disease
- New and emerging drug therapies (as part of clinical trials).

Some patients have minimal disease and little evidence of progression (asymptomatic or smoldering myeloma) at the time of diagnosis. In such cases, watchful waiting (observation with periodic examinations and imaging tests) may be preferable to early treatment. However, in most cases therapy will eventually be required. Patients with active myeloma need immediate treatment.

Getting a Second Opinion. People diagnosed with myeloma may want to consult a myeloma specialist or a second myeloma specialist before proceeding with a prescribed treatment plan to make sure they are getting the best therapy available. Many health insurance companies will authorize a second opinion.

When you go to the consulting myeloma specialist for a second opinion, make all medical records, including laboratory and imaging test results, and findings from your bone marrow aspirate and biopsy, available for examination. The second doctor's review of your medical records can confirm or suggest modifications to a proposed treatment plan and reassure you that you have explored all of your options.

Drug Therapy. Drug therapy to kill myeloma cells is the mainstay of treatment for myeloma. Before drug therapy begins, patients with symptomatic myeloma are assessed to determine if they are candidates for stem cell transplantation (see

Autologous Stem Cell Transplantation on page 20). For transplant candidates, drug treatment begins with a combination of induction agents that do not cause marrow damage—for example, bortezomib (Velcade®), thalidomide (Thalomid®) and dexamethasone; lenalidomide (Revlimid®) and dexamethasone; Velcade, liposomal doxorubicin (Doxil®) or standard doxorubicin (Adriamycin®) and dexamethasone; cyclophosphamide (Cytoxan®), Velcade and dexamethasone; or other combinations. Alkylating agents, such as melphalan (Alkeran®), will reduce the ability to easily harvest a patient's stem cells for a transplant; therefore, these drugs should be avoided in potential transplant candidates. After prolonged use, Revlimid can also adversely affect stem cell collection; therefore, if you are receiving a Revlimid-containing regimen upfront, you should discuss with your doctor the best time to mobilize and collect stem cells. Table 1 and Table 2 list the drugs and drug combinations most commonly used to treat transplant and nontransplant myeloma patients.

Table 1. Some Drugs Used for Myeloma Treatment*

- Bortezomib (Velcade®)
- Carfilzomib (Kyprolis®)
- Carmustine (BiCNU®)
- Cyclophosphamide (Cytoxan®)
- Dexamethasone
- Doxorubicin (Adriamycin®)
- Lenalidomide (Revlimid®)
- Melphalan (Alkeran®)
- Pamidronate (Aredia®)
- Panobinostat (Farydak®)
- Liposomal doxorubicin (Doxil®)
- Pomalidomide (Pomalyst®)
- Prednisone
- Thalidomide (Thalomid®)
- Vincristine (Oncovin®)
- Zoledronic acid (Zometa®)

*Some of these drugs are being studied in clinical trials.

Table 2. Some Drug Combinations Used for Myeloma Treatment*

- Revlimid, dexamethasone
- Revlimid, dexamethasone, Velcade
- Revlimid, melphalan and prednisone
- Revlimid, Velcade
- Thalomid, dexamethasone
- Thalomid, dexamethasone, melphalan, Velcade
- Thalomid, melphalan, prednisone
- Thalomid, Velcade
- Velcade, dexamethasone, Thalomid
- Velcade, Doxil
- Velcade, melphalan, prednisone
- Velcade, melphalan, prednisone, Thalomid

*Some of these drugs are being studied in clinical trials.

Some patients may not want a stem cell transplant, and for other patients—such as certain older patients or patients with other medical problems—the potential risks of transplantation may outweigh the benefits. For patients who are not transplant candidates, treatment may begin with a combination drug therapy, such as melphalan and prednisone, with thalidomide, Revlimid, or Velcade, or Revlimid with dexamethasone. Often, two or three drugs are used simultaneously. As many as six drugs are combined in some intensive treatment programs. Talk to your doctor about your entire treatment plan before beginning drug therapy.

Drug therapy for myeloma has led to sustained remissions in some patients. Temporary cessation or significant slowing of the disease may occur for a time. Long periods of complete remission are being seen more often as newer, more effective drugs are developed (see *Treatment Outcomes* on page 21), and some patients who have been treated with these drugs may be functionally cured of their disease. The following newer agents are being used to treat myeloma:

Thalidomide (Thalomid®). This drug, given by mouth, in combination with dexamethasone and another agent like bortezomib (Velcade), is indicated for the treatment of patients who have newly diagnosed myeloma. Its use in combination with several other drugs is under study in clinical trials.

Lenalidomide (Revlimid®). This drug, given by mouth, is a more potent form of thalidomide and may have broader antimyeloma effects. Revlimid is approved in combination with dexamethasone for the treatment of myeloma patients who have received at least one prior therapy and to treat newly diagnosed patients. Combination therapy with other drugs, including carfilzomib is under clinical investigation.

Bortezomib (Velcade®). This drug, given intravenously (IV) or subcutaneously (Sub-Q, or SC), interferes with the growth of cancer cells and is approved by the FDA for the treatment of patients with myeloma. In a randomized, phase 3 international trial conducted in 222 patients with relapsed myeloma who were not previously treated with Velcade, differences were observed in the incidence of peripheral neuropathy (PN) in patients receiving Velcade Sub-Q when compared to the incidence of PN in patients receiving intravenous Velcade. In the subcutaneous arm of the trial, 6 percent of patients experienced PN of grade 3 or higher, compared with 16 percent in the intravenous arm. In the subcutaneous arm, 38 percent of patients experienced PN of all grades, compared with 53 percent of patients in the intravenous arm. Results from the trial also showed that patients receiving Velcade Sub-Q achieved a 4-cycle overall response rate of 43 percent and complete response rate of 7 percent. By comparison, patients receiving Velcade intravenously achieved an overall response rate of 42 percent and a complete response rate of 8 percent. In addition, the overall safety profile was similar between the two arms.

Other studies indicate that myeloma patients who are treated with Velcade- or Kyprolis®-based combinations benefit from an antiviral drug (acyclovir, valacyclovir or famciclovir) to prevent reactivation of the varicella (herpes zoster) virus, which can cause shingles.

Velcade, in combination with several other drugs, is also being studied in clinical trials.

Velcade and liposomal doxorubicin (Doxil®). Doxil, given intravenously, is a specially formulated version of the chemotherapy agent doxorubicin, and it is approved for use in other forms of cancer. The Velcade and Doxil combination is approved by the FDA to treat myeloma patients whose condition has relapsed or who have not responded to at least one other treatment. Study findings indicate that the combination of Velcade and Doxil improves the time-to-disease progression as compared to the time-to-disease progression for Velcade given alone.

Bisphosphonates. Treatment for some myeloma patients includes drugs such as pamidronate (Aredia®) and zoledronic acid (Zometa®), both given intravenously. These are examples of bisphosphonates, which are potent inhibitors of bone resorption. These drugs alleviate the effects of bone disease by decreasing pain, decreasing the likelihood of fracture and reducing the high blood calcium levels that are associated with bone destruction. Studies indicate that the inhibition of myeloma cell growth may be a possible secondary effect of bisphosphonates. Side effects of bisphosphonates can include kidney damage and a rare form of damage to the jaw bone called "osteonecrosis" (see *Osteonecrosis of the Jaw [ONJ]* on page 28).

Carfilzomib (Kyprolis®). This proteasome inhibitor is given intravenously and is FDA approved for the treatment of patients with multiple myeloma who have received at least two prior therapies including Velcade and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy (also called "refractory disease"). A recent large phase III trial showed that carfilzomib with Revlimid and dexamethasone was superior to just Revlimid and dexamethasone in patients with one to three prior lines of treatment.

Pomalidomide (Pomalyst®). This drug, given by mouth, is FDA approved to treat people with multiple myeloma who have received at least two prior therapies including Revlimid and Velcade and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Panobinostat (Farydak®). This drug, given by mouth, is FDA approved for the treatment of patients with myeloma who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent. Panobinostat is to be used in combination with bortezomib, a type of chemotherapy, and dexamethasone, an anti-inflammatory medication.

Talk to your doctor about | Whether treatment in a clinical trial is right for you.

Stem Cell Transplantation. High-dose chemotherapy and autologous stem cell transplantation are important therapies for many myeloma patients.

Autologous Stem Cell Transplantation. During this procedure stem cells are collected from the patient, the patient is then treated with high doses of chemotherapy, often using melphalan. The cells are then returned to the patient via an infusion into the bloodstream (like a blood transfusion) to rescue the bone marrow from the effects of the high doses of chemotherapy. This procedure is associated with good response rates. It is relatively safe for many patients, including older patients, as a result of improved transplantation techniques and supportive therapies. However, it is not appropriate for all patients, and it is not a cure for myeloma. Patients should discuss the benefits and risks of any procedure with their doctors. Response to the transplant is measured by the standard tests used to monitor myeloma treatment, such as blood and urine protein levels, marrow tests and imaging studies (see *Treatment Outcomes* on page 21). Myeloma patients who have had an autologous transplant may require maintenance therapy (see below).

Allogeneic Stem Cell Transplantation and Reduced-Intensity Allogeneic Stem Cell Transplantation. Allogeneic and reduced-intensity allogeneic transplantation are other types of stem cell transplants used to treat certain blood cancers; they are associated with higher rates of side effects and mortality than are likely with an autologous transplant. The main difference between autologous and allogeneic transplant is that in allogeneic transplant, the cells are obtained from a donor whose cells are compatible with those of the patient, usually a brother or sister. Selected patients may have an autologous transplant followed by an allogeneic transplant or a reduced-intensity allogeneic transplant. Talk to your doctor to find out if a stem cell transplant is a treatment option for you. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation.*

Maintenance Therapy. Two recent large randomized studies that compared post-transplant maintenance with low-dose Revlimid to placebo showed longer time before progression of myeloma for the patients who received Revlimid. Therefore, the use of Revlimid as post-transplant maintenance is emerging as the standard of care. More information is needed about the effects on overall survival as well as the risk of second cancers. There are several ongoing maintenance therapy trials evaluating the effectiveness of treatment with Revlimid, Velcade, and combinations based on these and other approved drugs, as well as newer drugs.

Talk to your doctor about | Whether maintenance therapy is an option for you.

Radiation Therapy. This treatment uses high-energy rays (x-rays) to kill malignant plasma (myeloma) cells and it may be used to treat myeloma patients in select circumstances. Radiation therapy is the main treatment for plasmacytoma. Carefully selected patients whose bone pain does not respond to chemotherapy may receive radiation therapy as well. Radiation therapy may be impractical if there are widely distributed sites of painful bone involvement. Other means of delivering

radiation therapy are under investigation, such as by attaching a radioactive isotope to a molecule that goes predominantly to the bones, where most myeloma is located.

Supportive Care. Treatments that reduce the symptoms of myeloma are described below.

Treating Anemia. In some patients with severe anemia due to the effects of chemotherapy, the administration of an engineered form of the red cell growth factor erythropoietin (EPO) may alleviate the anemia or decrease the need for blood transfusions. However, some studies suggest that correcting anemia too vigorously may increase the risk for blood clots. Also, in some forms of cancer, the use of EPO may be associated with a worse outcome, although this may not be the case in myeloma. Patients should discuss the risks and benefits of EPO therapy with their doctors.

Stabilizing Damaged Bones. Vertebroplasty and kyphoplasty are surgical techniques that may be used to help myeloma patients who have back pain. With vertebroplasty, a chemical cement is inserted into the damaged or broken vertebrae through a catheter. Kyphoplasty involves inflating a balloon before stabilizing the area with the chemical cement. These procedures relieve bone compression and may alleviate pain and reduce the amount of pain medication that the patient needs. In some cases, height lost through vertebral collapse is restored. The usefulness of either of these procedures for any individual patient is a matter that should be carefully discussed by patients and their doctors. These techniques tend to be more effective for recent fractures than for older ones. The use of bisphosphonates (pamidronate [Aredia] and zoledronic acid [Zometa]) can help reduce bone pain and the risk of bone fractures. These drugs also prevent the high levels of calcium in the blood that are the result of bone destruction.

Preventing Infections. Antibiotics and intravenous immunoglobulins may be given to some patients to treat or prevent infections that can develop when the immune system is compromised.

Maintaining Kidney Function. Drinking adequate amounts of water and other healthy fluids can flush the kidneys and help them filter impurities from the blood.

Treatment Outcomes. It is not unusual for myeloma patients to live 10 years or more. Outcomes are influenced by patient factors, such as stage of the disease, chromosome changes, age, and other medical problems. Patients should discuss individual potential outcomes with their doctors.

Table 3. Some Terms Used to Describe Myeloma Treatment Response

Remission
No sign of disease. The terms "complete remission" (or "complete response") and "partial remission" (or "partial response") are sometimes used (see *Remission* on page 45).

Complete response
No sign of M protein using standard tests; normal percentage of plasma cells or no sign of myeloma cells in the marrow

Near complete response
Above normal free light chains ratio and no myeloma cells detected in the marrow by very sensitive tests

Very good partial response
A 90 percent or greater decrease in M protein but not meeting the definition for a complete response

Partial response
More than a 50 percent decrease in M protein in the blood and a 90 percent reduction in M protein in 24-hour urine collection but not meeting the definition for a complete or very good partial response

Minimal response
Reduction between 25 percent and 50 percent in M protein in the blood

Stable disease
Less than a 25 percent decrease or less than a 25 percent increase in M protein in the blood

Progressive disease
At least a 25 percent increase in M protein in the blood and if associated with symptoms, usually indicates the need to start therapy or to change therapies if the patient is already receiving treatment

Measuring Treatment Response. Some of the terms used to describe patients' responses to treatment are defined in Table 3. Tests that may be used following therapy to monitor response to treatment include

- Bone imaging studies, such as x-ray studies, MRI and PET scans
- Blood tests to measure blood cell counts; M protein, calcium, and creatinine levels; and free light chains
- Urine tests, such as a 24-hour urine collection test for M protein or a free light chains test for patients with nonsecretory myeloma
- Bone marrow aspiration and biopsy.

Treatment response, as determined by these well-established methods, is often supplemented with measurements of minimal residual disease (MRD). A number of techniques can be used to identify MRD, including

- Immunophenotyping by flow cytometry of a bone marrow aspirate. Immunophenotyping uses antibodies to look for specific proteins on the surface of cells that are unique to each cell type, allowing for identification or fingerprinting of those cells. It can help, for example, in determining whether plasma cells in the marrow are from left over myeloma, or if they are normal plasma cells.
- Polymerase chain reaction (PCR) using allele-specific oligonucleotide probes (ASO-PCR), usually on bone marrow. This is a method to make many copies by PCR of the abnormal regions of plasma cells to be able to better detect even small amounts of remaining myeloma.
- Next-generation sequencing (NGS) of either the bone marrow or blood.

In general, clinical trials have shown that patients who are MRD-negative (no detectable disease by an MRD measurement) have better long-term outcomes than those who are MRD-positive (remaining detectable disease). Other terms that are sometimes used in this setting include "MRD-zero" ("MRD-negative" on several consecutive tests), "immunophenotypic complete response" (CR) (all of the criteria for CR are met and plasma cells are normal by flow), and "molecular CR" (all of the criteria for CR are met and no detectable disease by either ASO-PCR and/or NGS). These techniques, not yet in general use, will probably be used more in coming years. The information they provide informs decisions about whether treatment should be stopped or continued.

Treatment for Relapsed or Refractory Myeloma

Almost all myeloma patients will experience relapse (the cancer returns after a successful course of treatment) and/or the disease will become refractory (the cancer does not respond to treatment). In some instances, the drug or combination of drugs that the patient had a good response to initially, may be repeated. Another option is to try one or more of the other therapies typically used in initial treatment. Thalomid, once used routinely for newly diagnosed myeloma patients until the adoption of Revlimid and Velcade, is one of the drugs now often used for treating relapsed/refractory myeloma. This therapy is usually given in combination with either the corticosteroid dexamethasone or other drugs.

A number of different chemotherapy agents may be used in combination with dexamethasone for relapsed/refractory myeloma. Some possibilities include

- Cyclophosphamide (Cytoxan), and doxorubicin hydrochloride (Adriamycin)
- Cisplatin (Platinol®), doxorubicin hydrochloride, cyclophosphamide, etoposide

(Toposar®, VePesid®), plus thalidomide (Thalomid)

- Cyclophosphamide, etoposide, cisplatin.

Treatments with novel agents include

- Panobinostat (Farydak®) in combination with bortezomib and dexamethasone
- The proteasome inhibitor bortezomib (Velcade), plus liposomal doxorubicin (Doxil)
- Velcade as a single agent or in combination with dexamethasone
- The immunomodulatory agent lenalidomide (Revlimid) plus dexamethasone
- The proteasome inhibitor carfilzomib (Krypolis)
- The immunomodulatory agent pomalidomide (Pomalyst).

The use of high-dose chemotherapy followed by autologous stem cell transplantation may also be an option for some relapsed/refractory myeloma patients, who have not been treated with a transplant before or who had a good durable response to a prior transplant.

Many new agents being studied in clinical trials are also showing promising results in the treatment of relapsed/refractory myeloma. Drugs that appear to be particularly effective are ixazomib and oprozomib, which are oral proteasome inhibitors, and daratumumab and elotuzumab, monoclonal antibodies that work either alone (daratumumab) or when given with Revlimid and dexamethasone (daratumumab and elotuzumab). (see *Research and Clinical Trials*, below).

Talk to your doctor about | Therapies under study in clinical trials for relapsed/refractory myeloma.

Research and Clinical Trials

New approaches under study in clinical trials for myeloma treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for myeloma.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and rigorously reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. This service is also available at www.LLS.org/clinicaltrials.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with myeloma.

Drugs and Drug Combinations. Recent advances in the treatment of myeloma have resulted in improved response rates and overall survival in newly diagnosed patients and patients with relapsed myeloma. Eventually, however, nearly all patients experience a relapse of their illness because myeloma cells become resistant with time to current drug therapies. This means there is a continuing role for the introduction of investigational agents that overcome drug resistance. Several new approaches, including combination therapies to counteract drug resistance, are being studied in clinical trials for initial treatment and for the treatment of relapsed or refractory myeloma. Some examples are

- **Elotuzumab (HuLuc63).** A monoclonal antibody that targets proteins on the surface of myeloma cells. It is being studied in combination with either Velcade or Revlimid, plus low-dose dexamethasone.
- **Daratumumab (HuMax®-CD38).** A monoclonal antibody that targets proteins on the surface of myeloma cells. It is being studied as a single agent, and in combination with either Velcade or Revlimid, plus low-dose dexamethasone.
- **Ixazomib (MLN9708).** An oral proteasome inhibitor being studied with Revlimid and dexamethasone versus placebo plus Revlimid and dexamethasone for relapsed/refractory and also newly diagnosed myeloma patients.

Stem Cell Transplantation. A number of approaches are under study, including allogeneic stem cell transplantation. A treatment for certain other types of blood cancers, it is being studied as a treatment for younger myeloma patients with high-risk disease. Allogeneic stem cell transplantation is associated with a higher risk for serious side effects and death compared to the risks associated with autologous transplantation. It may be considered for a patient who has an HLA [human leukocyte-associated antigen(s)]-matched donor, usually a brother or sister; other eligibility factors include patient age and the absence of certain medical conditions such as diabetes, kidney disease or heart disease. Two key potential advantages of this procedure are that using cells from a healthy donor rather than from the patient eliminates the chance that myeloma cells will be re-infused into the patient, and donor cells may also work as immunotherapy, providing an antimyeloma effect.

For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Immunotherapy. Various forms of immunotherapy are being studied, including

- Vaccines. Proteins on the surface of myeloma cells may be especially well-suited targets for attack by vaccines, which could help the patient's immune cells to attack his or her own myeloma cells.
- Antibodies. Drugs such as daratumumab and elotuzumab are immunotherapies because they work in part by making myeloma cells more visible to the patient's immune system for attack. Other antibodies are being studied as well, including some that target programmed death ligand 1 (PD-L1) or its receptor, programmed death 1 (PD-1). This approach may reduce the immune suppression caused by myeloma and free the immune system to be more effective.
- Chimeric antigen receptor (CAR) cells. These are either T cells from the patient or natural killer (NK) cells from the patient or another donor which are altered so that they can more easily find and attack myeloma cells.

See the free LLS publication *Immunotherapy Facts* for information about the development of blood cancer vaccines.

We encourage you to contact our Information Specialists and visit www.LLS.org/clinicaltrials for more information about specific treatments under study in clinical trials.

Myeloma Complications and Treatment Side Effects

Fatigue. One of the most troublesome complaints reported by myeloma patients is fatigue. Fatigue can be caused by many factors, including disease-related anemia, treatment and medication side effects, physical immobility, sleep disturbance, nutritional deficits, depression, stress and anxiety. Each individual's fatigue should be evaluated to identify other possible causes that are unrelated to myeloma, and management strategies that can be implemented to alleviate fatigue-causing or fatigue-related issues.

A helpful strategy to maintain a consistent energy level while dealing with fatigue may be to pace daily activities and take planned rest periods throughout the day. Support, compassion and understanding of self and from loved ones are key elements in managing fatigue successfully.

Infections. Infections are some of the most troublesome medical problems for patients with myeloma, and sometimes can contribute to the risk of dying from the disease. Patients with myeloma may not be able to fight infections effectively because their B lymphocytes do not make antibodies in response to microbes that

enter the body, and myeloma can also suppress other parts of the immune system. The effects of chemotherapy or radiation therapy on blood cell production can also cause a deficit in the number of white cells, which contributes further to the risk of infection. In some cases, antibiotics can be used to prevent infection—especially after high-dose chemotherapy. Rarely, the infusion of gamma globulin preparations on a regular basis may be helpful, though this treatment also carries risks of kidney damage, blood clots and fluid overload. Myeloma patients are advised to receive certain vaccinations, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or shingles vaccine, should not be administered. Your doctor can give you more information.

Pain. Bone pain may occur because of the growth of myeloma cells in the bone. Successful treatment may relieve bone pain. Patients may also experience pain that radiates from the back when the back bones (vertebrae) collapse and press on the nerves. Fractures of bones may also result in pain. In addition to treatment of the myeloma, many patients require pain medications, such as acetaminophen (Tylenol®) and, in some cases, narcotics. Narcotics can cause some sedation and constipation, but are often very effective and are not associated with a high risk of addiction or dependency in cancer patients. For more information see the free LLS publication *Pain Management Facts*.

Kidney Impairment. Myeloma patients may have serious problems with their kidney function for two principal reasons. One reason is the excretion of large amounts of Bence Jones proteins in the urine. This excess protein can damage the kidney filtration apparatus and the channels or tubules that are important in urine formation. Another reason is that patients with myeloma often have high levels of calcium (hypercalcemia) or uric acid (hyperuricemia) in the blood. When bones are damaged, calcium is released into the blood. High levels of calcium in the blood cause dehydration that can damage the kidneys. In rare cases, when patients present with very recent or acute kidney failure, a procedure known as "plasmapheresis and exchange" may be helpful in limiting kidney damage, though this approach is controversial. The most important and successful treatment for kidney failure secondary to myeloma is to treat the myeloma itself without delay. Timely, adequate treatment of myeloma can improve kidney function and, potentially, even return it to normal in most cases. When this is not the case, some patients may end up needing dialysis support.

Hyperviscosity Syndrome. Occasionally, the concentration of monoclonal proteins in the blood of some myeloma patients is so high that it makes the blood "viscous" or thick, thereby interfering with the blood flow and delivery of oxygen to the tissues. This condition is referred to as "hyperviscosity syndrome." The

circulation of the oxygen-carrying red cells slows, and the work of the heart is increased by the blood's resistance to being pumped through the body.

This complication can lead to headaches, dizziness, weakness, fatigue, sleepiness, oozing from cuts and other symptoms. Hyperviscosity syndrome is much less common in patients with myeloma than in those with Waldenström macroglobulinemia (see *Myeloma-Related Diagnoses* on page 32). This condition is considered a medical emergency, and it needs urgent treatment with plasmapheresis and exchange, which rapidly reduces the concentration of monoclonal proteins in the blood. Chemotherapy is needed also, since the plasmapheresis and exchange does not reduce the number of cells making these abnormal proteins. If the cells were not treated with chemotherapy, they would produce the proteins that, with time, would accumulate at high levels again.

Cryoglobulinemia. Rarely, monoclonal IgM may congeal in the blood and lead to poor circulation, especially if the body is exposed to cold temperatures. This condition is referred to as "cryoglobulinemia" and can cause joint pain, kidney problems, skin lesions and purpura (purplish or red-brown discoloration of the skin).

Acute Myeloid Leukemia. There is a heightened risk among myeloma patients of developing second cancers including acute myeloid leukemia, especially after treatment with certain cytotoxic drugs. This rare complication occurs in a small number of patients.

Osteonecrosis of the Jaw (ONJ). This is an uncommon but serious condition that has occurred in some patients receiving bisphosphonates such as pamidronate (Aredia) or zoledronic acid (Zometa). Although no cause-and-effect relationship between bisphosphonate therapy and osteonecrosis has been established, it is suspected.

ONJ may develop when the jaw fails to heal after a minor trauma, such as a tooth extraction, that results in bone exposure. Symptoms include pain, swelling, poor healing or infection of the gums, loosening of teeth or numbness (or a feeling of heaviness) in the jaw. Some factors that may increase the risk of osteonecrosis are radiation therapy to the head or neck, chemotherapy, corticosteroid therapy, anemia (low red blood cell count), infection, poor dental health, alcohol abuse or cigarette smoking, poor nutrition, poor blood circulation or clotting problems.

Treatment with bisphosphonates should be managed by an experienced oncologist, with close coordination between the oncologist and oral surgeon and/or dental specialist. It is important to have a dental examination performed by an experienced dentist who has seen and understands ONJ before patients begin therapy with intravenous bisphosphonates. Dental treatments and procedures that require

bone healing should be completed before intravenous bisphosphonate therapy is initiated. Patients should receive and follow instructions for maintaining good oral hygiene and should have regular dental checkups. For patients who are receiving bisphosphonates and who require dental procedures, there is no evidence to suggest that interrupting bisphosphonate therapy will either prevent or lower the risk of ONJ. Nonetheless, once patients have started bisphosphonate treatment, they should consult with their doctors before undergoing dental procedures. Frequent clinical assessments and conservative dental management are suggested for these patients. Treatment of patients who develop ONJ may include frequent clinical assessments, antibiotics, oral rinses and removable mouth prostheses. Minor dental work may be necessary to remove injured tissue and reduce sharp edges of bone. Typically, surgery is avoided because it may make the ONJ worse, but it is needed in some cases and can be helpful.

Myelosuppression. The bone marrow is constantly producing red cells, white cells and platelets. Interruption or inhibition of this crucial function is called "myelosuppression." Chemotherapy agents, immunomodulatory drugs such as Revlimid, and proteasome inhibitors such as Velcade, can cause myelosuppression. If not managed effectively, myelosuppression can be life threatening and interfere with treatment planning and quality of life. A reduction in the number of red cells can result in anemia, which can make patients feel extremely tired and experience shortness of breath. When the number of neutrophils, the primary type of white cells, is lowered, the resulting condition is called "neutropenia," which can lead to serious infections that require patients to receive antibiotic therapy and possibly be hospitalized. Drugs such as filgrastim (Neupogen®), pegfilgrastim (Neulasta®) or sargramostim (Leukine®) may be prescribed to treat neutropenia. When myelosuppression causes the depletion of platelets in the blood, the resulting condition is called "thrombocytopenia." Patients who have low platelet counts may experience excessive bleeding from cuts or injuries and may need a platelet transfusion.

Peripheral Neuropathy. This is the term for damage to nerves of the peripheral nervous system, which transmits information from the brain and spinal cord to every other part of the body, and from the body back to the brain. There are several causes for this condition. It can be a result of the disease, or it can be a side effect of certain anticancer drugs, including Oncovin, Velcade, Kyprolis, Thalomid, Pomalyst, and, less commonly, Revlimid.

Other problems that can cause, or contribute to, neuropathy include diabetes, nerve compression caused by vertebral fractures, and vitamin deficiencies, particularly folate or vitamin B_{12}. Symptoms may include temporary or ongoing numbness, tingling, burning, coldness or weakness in the arms or legs. Patients who develop neuropathy as a result of chemotherapy should tell their healthcare providers as soon as these symptoms appear, because often reducing the dosage of

the drugs being used, or stopping them altogether, can reduce the symptoms or even allow them to resolve completely.

Thrombosis and Embolism. "Deep venous thrombosis" (DVT) is the term used to describe the condition caused by a blood clot that forms in the deep veins of the body, usually in the legs. Patients receiving myeloma treatment associated with DVT risk, especially newly diagnosed myeloma patients, are usually prescribed medication (such as aspirin, warfarin (Coumadin®), or low-molecular-weight heparin) to reduce the risk of DVT. It is important for patients to discuss with their doctors the risk of DVT and ask which of the options to reduce this risk is best for them. DVT can cause obstruction to blood flow and pain and swelling below the obstruction. Pulmonary embolism occurs when a blood clot in a deep vein breaks off, travels through the circulation and lodges in the pulmonary arteries. Depending on the size and number of clots that reach the pulmonary arteries, a patient may have chest pain, shortness of breath and other potentially severe or even life-threatening effects. Thalomid and Revlimid are associated with an increased incidence of DVT and pulmonary embolism when they are used in combination with corticosteroids like dexamethasone and, in particular, in combination with Doxil. Some doctors have observed that taking either Thalomid or Revlimid and dexamethasone in combination with red cell growth factors, for example Procrit or Aranesp, further increases a patient's risk for DVT. Other factors that can increase the risk of DVT include the presence of a central line (central venous catheter), decreased mobility, recent surgery, pregnancy, smoking, a prior history of DVT or a family history of blood-clotting problems.

See the free LLS publications *Blood Transfusion, Cancer-Related Fatigue Facts* and *Understanding Side Effects of Drug Therapy* for more information about managing side effects.

Talk to your doctor about | Possible side effects and how to manage them.

Follow-Up Care

Progress in myeloma treatment during the last decade, both in understanding how the genetic characteristics of myeloma influence patient outcomes and in the development of new myeloma drugs, is extending survival with good quality of life. Although myeloma remains incurable, the advent of less toxic, targeted therapies is making it possible for many patients to manage their cancer as a chronic disease.

A diagnosis of myeloma can feel like an emotional roller coaster because of the periods of remission and the periods of disease progression that may characterize the course of the disease. There is concern about the possibility of a shortened life span and about treatment side effects or disease-related symptoms, including pain. There may be concerns about finances. Patients are encouraged to find emotional, financial and psychological support by speaking to a social worker or therapist or participating in a local or an online support group.

To address their physical and other support needs, patients are encouraged to follow up with their doctors. It is important for myeloma patients to maintain regular follow-up appointments with their hematologists/oncologists to monitor a return of the cancer and detect any side effects from treatment or the development of other medical problems. Keeping a record of your cancer treatment is important so that your doctor can follow up on those effects. This record should include your diagnosis, the names of chemotherapy or other drugs taken, radiation treatment information, surgery information, transplantation information, information about any other treatments and the names and dates of any significant complications and the treatment received for those complications. This information can help your doctor develop a personalized follow-up schedule for you.

Patients can rebuild their strength and energy levels by following established guidelines for good health. Before embarking on any new health regimen, talk with your doctor or members of your medical team to develop a specific plan to meet your needs. Some general steps to consider include

- Maintaining a healthy weight
- Quitting smoking
- Eating a healthy diet
- Having recommended cancer screenings
- Staying physically active.

Learn about managing fatigue, anxiety, depression and pain through the experiences of two survivors, with insights from their healthcare professionals. View an insightful expert panel discussion for information about your finances, treatment and support needs. You can watch the free LLS program, *Paths to Recovery—Stories From Two Blood Cancer Survivors* at www.LLS.org/educationvideos.

Myeloma-Related Diagnoses

Monoclonal Gammopathy. This condition, also called "benign monoclonal gammopathy," "monoclonal gammopathy of unknown or undetermined significance" (MGUS) and other names, is commonly found in older persons, and it increases in frequency in the sixth through ninth decades of life. MGUS is associated with monoclonal protein in the blood. However, an increase in plasma cells is often not apparent in the marrow, and anemia, bone damage, recurrent infections and other features of myeloma are not present. The disorder usually does not affect the well-being of the patient, although occasionally the monoclonal protein may interact with normal tissues and lead to symptoms, depending on the tissue affected. MGUS evolves into a progressive B-lymphocyte malignancy such as myeloma or lymphoma in about 30 percent of patients affected over 20 years or more of observation. Patients are usually followed with blood tests once or twice a year to determine if there is any change in the level of monoclonal protein.

Waldenström Macroglobulinemia (WM). This disease has some features in common with myeloma. It is a malignancy of B lymphocytes that produce a monoclonal immunoglobulin that can be measured in the blood. The malignant B lymphocytes replace the normal marrow cells and may cause anemia and other blood cell deficiencies by preventing the normal marrow cells from making blood cells efficiently. The monoclonal immunoglobulin produced by the malignant B lymphocyte is a very large type of IgM, referred to as "macroglobulin" (large globulin). For more information see the free LLS publication *Waldenström Macroglobulinemia Facts.*

Primary Amyloidosis. This is an uncommon disease process associated with the accumulation of "amyloid" in tissue such as the heart, the gastrointestinal tract, the nerves, or the skin. Although there are several types of amyloid, one type is associated with a condition known as "AL amyloidosis," which is caused by the deposit of immunoglobulin light chains (see Figure 3 on page 11). In some patients with myeloma, the light chains made by their plasma cells can result in the formation and deposition of amyloid. This type of amyloidosis can occur either with or without overt myeloma and is called "primary amyloidosis." In patients with primary amyloidosis, the involvement of the heart, intestines or nerves can produce dysfunction in those organs, significantly complicating the management. In other patients, the numbers of plasma cells in marrow may not have increased, and the bones may not be affected, and these patients have primary amyloidosis without myeloma. In these cases, the malignant B lymphocytes that make the light chains that deposit themselves in the tissues and form the amyloid are too few to be identified by a marrow biopsy. Diagnosis of amyloidosis relies on some of the same tests used to diagnose myeloma, but occasionally biopsies of other sites are needed, such as the abdominal fat pad, gums, colon, heart or kidneys. Staging is done by the results of blood tests that reflect heart function, including the NT-proBNP and either a troponin T or troponin I level. Many of the drugs that work against myeloma are also effective against amyloidosis, including corticosteroids,

melphalan, Velcade, and Revlimid. In patients who are good candidates, autologous stem cell transplantation is the treatment of choice.

Heavy Chain Disease. This is a rare disease of B lymphocytes, so named because the protein made by the malignant lymphocytes is an incomplete immunoglobulin (the heavy chain of the immunoglobulin; see Figure 3 on page 11). Heavy chain disease is similar to myeloma in that it is a malignancy of B lymphocytes that secrete a characteristic immunoglobulin, but its clinical features are quite different. For example, there is no bone disease.

Light Chain Deposition Disease (LCDD). A systemic disorder that involves the immune system, LCDD is caused by an excess buildup of immunoglobulin light chains in the tissues and organs (see Figure 3 on page 11). Light chains are an important part of the body's immune system. However, if they become trapped in the tissues of the kidneys, lungs, skin, joints or blood vessels, the light chains can set off reactions leading to tissue or organ inflammation and damage. Early signs and symptoms of light chain deposition disease may include protein in the urine, high blood pressure, decreased kidney function and nephrotic syndrome (a kidney disorder that causes the body to lose too much protein in the urine). LCDD can occur in patients who have myeloma as well as in individuals who have monoclonal gammopathy of undetermined significance (MGUS) or lymph node disorders.

Plasma Cell Leukemia (PCL). A rare plasma cell disease that may be primary (de novo) or secondary (evolving from an existing diagnosis of myeloma). Most cases are primary; approximately 5 percent of cases are diagnosed in patients who have myeloma. In this disorder, patients have high numbers of plasma cells circulating in the blood. This disease is treated like myeloma but frequently requires more aggressive therapy as this disease is more aggressive than myeloma.

POEMS Syndrome. An uncommon marrow disorder related to myeloma, POEMS syndrome gets its name from its five most common features: P (peripheral neuropathy), O (organ enlargement), E (endocrine gland dysfunction), M (monoclonal plasma cell tumors and monoclonal immunoglobulin), S (skin changes). Peripheral neuropathy is often the most disabling feature of the syndrome and can include progressive weakness of the arms or legs. The bone alterations related to the accumulation of plasma cells in the marrow take on a different character from that in classic myeloma (the marrow looks more rather than less dense). Thyroid or sex hormone deficiencies caused by endocrine gland dysfunction may require hormone replacement therapy. Patients can benefit from radiation or chemotherapy treatment, and in some cases from autologous stem cell transplantation.

Normal Blood and Marrow

Blood and Marrow. Blood is composed of plasma and cells suspended in plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals include

- Proteins
  - Albumin, the most common protein in blood
  - Blood-clotting proteins, made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red cell production
  - Immunoglobulins, antibodies made by plasma cells in response to infections including those we develop from our vaccinations (such as poliovirus antibodies, which are made by normal plasma cells in the bone marrow)
- Hormones (such as thyroid hormone and cortisol)
- Minerals (such as iron and magnesium)
- Vitamins (such as folate and vitamin B_{12})
- Electrolytes (such as calcium, potassium and sodium).

The cells suspended in plasma include red cells, platelets and white cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes).

- The red cells make up a little less than half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers it to the cells all around the body; hemoglobin then picks up the waste product carbon dioxide from the body's cells and delivers it back to the lungs, where it is discharged when we exhale.
- The platelets are small cells (one-tenth the size of red cells) that help stop bleeding at the site of an injury in the body. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins such as fibrin and electrolytes such as calcium. Later, a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.
- The neutrophils and monocytes are white cells known as "phagocytes" (eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red cells and platelets, the monocytes can leave the blood and enter the tissues, where they can attack invading organisms and help combat infection. Eosinophils and basophils are white cells that respond to allergens or parasites.
- Lymphocytes, another type of white cell, are mostly found in the lymph nodes, the spleen and the lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. Each of these cells is a key part of the immune system.

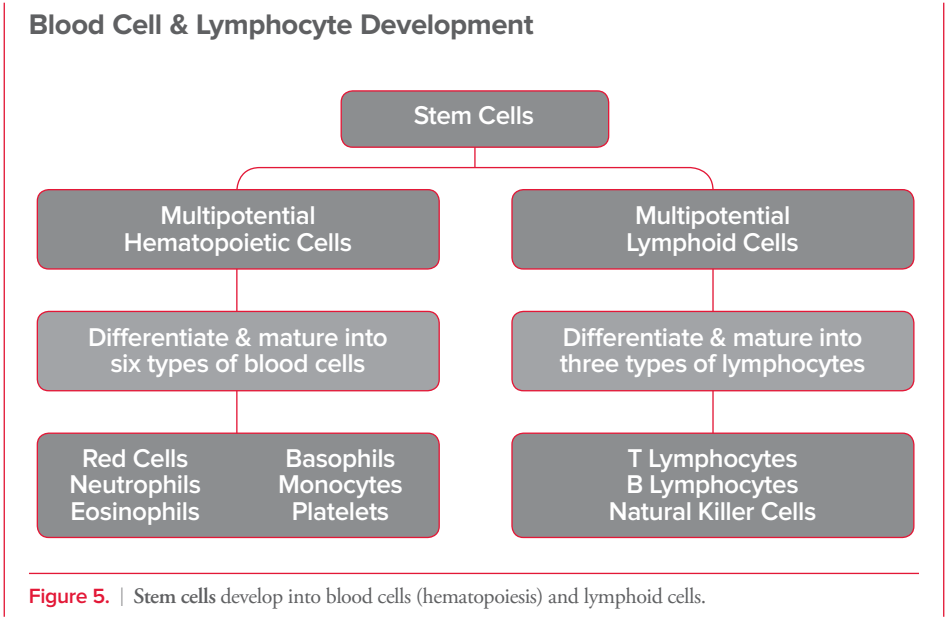

Figure 5. | **Stem cells** develop into blood cells (hematopoiesis) and lymphoid cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 5).

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow where it picks up the fully developed and functional red and white cells and platelets that will circulate in the bloodstream.

Some stem cells also enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique. There are also methods to induce more stem cells to leave their home in the marrow and circulate in the blood, allowing a greater number of stem cells to be collected. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

Health Terms

Albumin. A major protein in the blood that plays a role in fighting infections and building or repairing muscle tissue. The normal range for albumin is 3.5 to 5.5 g/dL (grams per deciliter). The optimal level is 4 g/dL. Test results can vary slightly between laboratories and may be affected by the method the lab uses to process the blood sample.

Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR). An approach to measure patient-specific (also referred to as allele-specific) minimal residual disease (MRD) using short stretches of DNA (oligonucleotides) and PCR.

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. First, the patient is given conditioning therapy (high-dose chemotherapy or high-dose chemotherapy with total body radiation) to treat the blood cancer and to "turn off" the patient's immune system so that the donor stem cells will not be rejected. A type of allogeneic transplant called a "reduced-intensity" or "nonmyeloablative" stem cell transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information see the free LLS publication *Blood and Marrow Stem Cell Transplantation*. See Reduced-Intensity Stem Cell Transplantation.

Amyloid. In myeloma, an abnormal protein made by malignant plasma cells. An amyloid deposit develops when parts of the immunoglobulin molecule, referred to as "light chains," accumulate in tissues. In the type of amyloid that occurs in myeloma or closely related diseases, organ failure can occur as a result of amyloid deposits in the heart, gastrointestinal tract, kidneys, nerves and other systems.

Anemia. A decrease in the number of red cells and, therefore, in the hemoglobin concentration of the blood. This results in a diminished ability of the blood to carry oxygen. If severe, anemia can cause a pale complexion, weakness, dizziness, fatigue and shortness of breath.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to the specific foreign substances called "antigens." Antibodies coat, mark for destruction, or inactivate foreign particles such as bacteria, viruses and harmful toxins. Antibodies can also be made in the laboratory in two ways. Material from one species is injected into a different species; the receiving species recognizes the material as foreign and makes antibodies to it. These antibodies are usually polyclonal antibodies; that is, they react to multiple targets (antigens). The second method involves creating monoclonal antibodies, which react to only one target (antigen) and these can be used in several important ways. They can be used to identify and classify types of blood cancers or they can be altered to make them useful in antibody-mediated immunotherapy.

Antigen. A foreign substance, usually a protein, that stimulates an immune response when it is ingested, inhaled or comes into contact with the skin or

mucous membranes. Examples of antigens are bacteria, viruses and allergens. Antigens stimulate plasma cells to produce antibodies.

Apheresis. The process of removing components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," circulates blood from a donor through a specialized machine and then back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white cells and plasma can be removed separately. This procedure is also used to remove circulating blood stem cells, which can be frozen, stored and later used for transplantation instead of marrow stem cells.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. In this treatment 1) the patient's stem cells are harvested, usually from the blood; 2) the stem cells are frozen for later use and the patient receives conditioning drug therapy; and 3) the stem cells are thawed and infused back into the patient through an indwelling catheter (central line). Patients receive supportive care to help prevent and/or manage the side effects. Generally, after 10 to 14 days, blood counts begin to normalize and the side effects of the conditioning therapy begin to resolve. For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Basophil. A type of white cell that participates in certain allergic reactions.

Bence Jones Protein. An abnormal protein (immunoglobulin) made by malignant plasma (myeloma) cells that enters the blood and is excreted rapidly in the urine. This protein can cause injury to the kidneys or kidney failure when excreted in large amounts. By contrast, normal immunoglobulin is too large to pass through the kidneys in large amounts, so it is present in the blood but usually not in the urine.

Beta$_2$-Microglobulin. A cell protein found in the blood. A high level of beta$_2$-microglobulin may be a sign of faster-growing disease. Levels of this protein together with levels of albumin are significant when staging myeloma.

Bisphosphonates. A class of drugs, including pamidronate and zoledronic acid, that has been helpful in preventing or minimizing bone loss. Bisphosphonates probably act by preventing cells called "osteoclasts" from dissolving bone. In myeloma, bone thinning (osteoporosis) and fracture are major problems.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. After puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms do not contain blood-forming marrow. In these sites the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A test to examine marrow cells for the presence of abnormalities. A marrow sample is usually taken from the patient's hip bone. After medication is given to numb the skin and the bone underneath, the liquid sample is removed using a special needle inserted through the bone into the marrow. The sample is looked at under a microscope and assessed not only for the presence of myeloma but also for how much of it there is. The cells obtained can also be used for cytogenetic analysis, flow cytometry and other tests.

Bone Marrow Biopsy. A test to examine marrow cells for the presence of abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a core of bone containing marrow. The marrow is examined under a microscope to determine if abnormal cells are present. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together. Both tests are also done after treatment to determine the proportion of blood cancer cells that has been killed by therapy. Because myeloma cells can stick tightly to bone marrow particles called "spicules," it is often important to perform both the aspirate and the biopsy, since the aspirate can sometimes underestimate the amount of disease present.

Chemotherapy. The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and some act to injure the DNA of the cancer cells. When the DNA is injured, the cells cannot grow or survive. Successful chemotherapy depends on the fact that malignant cells are somewhat more sensitive to the chemicals than normal cells. However, cells of the marrow are also sensitive to these chemicals, and injury to the gastrointestinal tract, skin and hair follicles causes the most common side effects of chemotherapy, such as mouth sores and hair loss. Other drugs work by blocking normal protein digestion in myeloma cells (Velcade and Kyprolis), or by helping the immune system function against myeloma (Thalomid, Revlimid, Pomalyst).

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest, abdomen or pelvis permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these and other structures before, during and after treatment, as well as of plasmacytomas. This type of scan is sometimes given with intravenous and/or oral contrast, and though the contrast can help to get a clearer picture of what is going on, intravenous contrast can rarely cause some kidney damage.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. Chromosome alterations can be detected, and in some cases it is possible to identify the actual genes that have been affected. These findings are very helpful in diagnosing specific types of blood cancers, in determining

treatment approaches and in following the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a "cytogeneticist."

Cytokine. Cell-derived chemicals that are secreted by various types of cells and act on other cells to stimulate or inhibit their function. (The prefix "cyto-" means "cell.") Chemicals derived from lymphocytes are called "lymphokines." Chemicals derived from lymphocytes that act on other white cells are called "interleukins"; that is, they interact between two types of leukocytes. See Growth Factor.

Differentiation. The process by which stem cells give rise to functional cells of a single blood cell line. Differentiation of stem cells forms red cells, platelets, neutrophils, monocytes, eosinophils, basophils and lymphocytes, as well as normal plasma cells. See Hematopoiesis.

Eosinophil. A type of white cell that participates in allergic reactions and helps fight certain parasitic infections.

Erythrocytes. See Red Cells.

Extramedullary Plasmacytoma. See Plasmacytoma.

Fluorescence In Situ Hybridization (FISH). A technique for studying chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different wavelengths (and different colors). The probes match to the chromosomes within the cells, and the chromosomes fluoresce in color. FISH can help to detect specific mutations in the chromosomes, but only those for which probes are used.

G-Banding Karyotyping. A testing method that makes a certain characteristic of chromosomes easier to see. A "karyotype" is the systematic arrangement, using images, of the 46 human chromosomes of a cell. Karyotypes are examined for deviations from the expected arrangement, number, size, shape or other characteristics of the chromosomes. Each chromosome pair has a characteristic banding pattern. To make the banding pattern easier to see, a dye called "Giemsa" may be used as a stain. This process is also referred to as "G-banding." Certain chromosomal abnormalities are associated with specific myeloma subtypes. G-banding karyotyping and other cytogenetic tests provide doctors with information that contributes to determining the best treatment approach for an individual patient. This test can take several weeks after samples are obtained from a bone marrow aspiration, since the cells have to be grown in a laboratory and then stained and examined individually. Thus, the test takes longer than the FISH test, but has the advantage of being able to detect any changes that are visible because it does not rely on specific probes. Usually, both tests are done on samples from the marrow, especially at the time of diagnosis. A common finding in myeloma is called "hyperdiploidy," in which myeloma cells have more than the normal number of 46 chromosomes, and this may have a better than average prognosis. In contrast, hypodiploidy, where there are fewer than the normal number of chromosomes, often has a worse than average prognosis.

Graft-Versus-Host Disease. See HLA.

Graft-Versus-Tumor Effect. See Reduced-Intensity Stem Cell Transplantation.

Growth Factor. A chemical used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) are examples of growth factors that are made commercially. GM-CSF can also stimulate monocytes.

Heavy Chains. Any of the large protein chains of five classes (IgA, IgD, IgE, IgG and IgM) that, paired with the light chains, make up the antibody molecule of an immunoglobulin. See Immunoglobulin; Light Chains.

Hemapheresis. See Apheresis.

Hematologist. A doctor who specializes in the treatment of blood diseases. This person is either an internist who treats adults or a pediatrician who treats children.

Hematopathologist. See Pathologist.

Hematopoiesis. The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells such as red cells or white cells of various types. This process is called "differentiation." The young or immature blood cells then further develop into fully functional blood cells. This process is called "maturation."

The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is that most blood cells live for short periods and must be steadily replaced. Red cells die in four months, platelets in 10 days and most neutrophils in one to three days. About 100 billion blood cells are made each day. When cancer cells invade the marrow, the constant demand for new blood cells cannot be met, resulting in a severe deficiency in blood cell counts.

HLA. The abbreviation for "human leukocyte-associated antigen(s)." These antigens are proteins on the surface of most tissue cells, and they give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of any individuals having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA factors is referred to as "tissue typing." There are six major groups of HLA: A, B, C, D, Dr, and Dq. These proteins on the cell surface act as antigens when donated (transplanted) to another individual, the recipient. If the antigens on the donor cells are identical (as in identical twins) or very similar (as in HLA-matched siblings), the transplant (donated stem cells) is more likely to survive (engraft) in the recipient. In addition, the recipient's body cells are less likely to be attacked by the donated immune cells (a result called "graft-versus-host disease").

Hypercalcemia. An abnormally high concentration of calcium in the blood. In myeloma, the breakdown of bone, which is rich in calcium, is the main cause of high levels of blood and urine calcium. Hypercalcemia can contribute to weakness, loss of appetite, nausea, confusion, constipation, lethargy and other symptoms, as well as to kidney damage.

Immunoglobulin. A protein that helps the body fight infection; it is also called "gamma globulin" and abbreviated as "Ig." Normal plasma cells produce one of five types of antibodies (polyclonal immunoglobulins): IgG, IgA, IgM, IgE or IgD. Low levels of immunoglobulin may be a cause of repeated infections in some patients.

Immunophenotyping. Use of flow cytometry to identify each individual cell in a sample, such as of a bone marrow aspirate. This is done using antibodies that recognize different cell surface proteins that are characteristic for each cell type, and therefore are different for B cells, T cells, and plasma cells, among others, similar to the process of fingerprinting.

Immunotherapy. Any of several treatment approaches that harness the body's immune system to treat diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy.

Karyotype. See G-Banding Karyotyping.

Light Chains. Either of the two small protein chains that, when linked to heavy chains, make up the antibody molecule of an immunoglobulin. The two types are kappa and lambda, which are unrelated to the immunoglobulin class (IgA, IgD, IgE, IgG and IgM). An example of a light chain is a Bence Jones protein. See Bence Jones Protein; Heavy Chains; Immunoglobulin.

Lymphocyte. A type of white cell that is the essential cell type in the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer cells, which can attack virus-infected cells or tumor cells.

Lytic Lesions. Holes in the bones where the tissue has been destroyed as a result of myeloma. These lesions are visible on x-ray images.

Macrophage. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A test that provides detailed images of body structures. It differs from the CT scan in that the patient is not exposed to x-rays. Signals generated in the tissues in response to a magnetic field produced by a specialized instrument are converted by computer into images of body structures. Thus, the size, or a change in size, of organs such as the lymph nodes, liver and spleen or of tumor masses can be measured. MRI is often done with an intravenous contrast agent that, while different than the one used with

CT scanning, can also, in rare cases, cause kidney damage. All patients scheduled for a CT scan or an MRI should let the radiology technicians know that they have myeloma and drink lots of fluids before (if allowed by the test procedure) and afterwards.

Maturation. See Hematopoiesis.

Minimal Residual Disease (MRD). Detection of the level of remaining myeloma cells using techniques that are more sensitive than just electrophoresis and immunofixation studies of the blood and/or urine, and testing of the bone marrow just by routine pathology. Examples include flow immunophenotyping, allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), and next-generation sequencing (NGS).

Monoclonal Antibody Therapy. Therapy using proteins (antibodies) made in the laboratory that either react with or attach to antigens on the cancer cells to which they are targeted. The antibodies are used therapeutically in three ways: as "naked" antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapies) and as antibodies to which toxins are attached (immunotoxins).

Monocyte/Macrophage. A type of white cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte in action: It can combat infection in the tissue, ingest dead cells (in this function it is called a "scavenger cell") and assist lymphocytes in their immune functions.

M Protein. A short name for "monoclonal immunoglobulin," a type of protein made in large amounts by malignant plasma cells and secreted into the blood. The term "monoclonal" indicates that the protein is derived from a single-cell population. Normal plasma cells produce many types of proteins (antibodies), called "polyclonal immunoglobulins," to protect the body against infection caused by invading viruses, bacteria or other agents. The production of M protein does not take place in response to an antigen, such as an infectious agent. M protein can be measured in the blood, and the amount generally correlates with the extent of the myeloma's progression. Increases in the amount of the protein in the body usually parallel increasing M-protein concentration in the blood; decreasing M-protein concentration in the blood usually reflects regression of the myeloma. In rare cases, myeloma can stop making M protein; thus, based on laboratory tests, the condition can appear to be improving but is actually progressing, and the patient usually feels worse. This situation can often be detected by bone marrow aspiration and biopsy, which will usually show increasing numbers of plasma cells. M protein is also referred to as "M spike."

Mutation. An alteration in a gene that results from a change to a part of the stretch of DNA that represents the gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent to offspring. A

"somatic mutation" arises in a specific tissue cell and can result in the growth of that cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes a somatic mutation (or mutations) that leads to the formation of a tumor. If a mutation results from a major abnormality of chromosomes, such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the original mutated cell (oncogene).

Myeloma Cells. Malignant plasma cells that are the hallmark of myeloma. Their appearance may be similar to normal plasma cells, but they are present in increased numbers.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main cell that combats infections. Patients with certain blood cancers or patients who have undergone chemotherapy often do not have sufficient quantities of neutrophils circulating in their bloodstream. A severe deficiency of neutrophils increases the patient's susceptibility to infection. A neutrophil may be called a "poly" (polymorphonuclear neutrophil) or "seg" (segmented neutrophil) because its nucleus has several lobes.

Nonmyeloablative Stem Cell Transplantation. See Reduced-Intensity Stem Cell Transplantation.

Nonsecretory Disease. A form of myeloma seen in a small percentage of patients. In nonsecretory disease, abnormal proteins cannot be detected through urine protein electrophoresis (UPEP), serum protein electrophoresis (SPEP) or serum immunofixation electrophoresis (SIFE). However, most of these patients will have free kappa or lambda light chains in the serum detected through a serum free light chain assay. See Serum Free Light Chain Test; Serum Immunofixation Electrophoresis (SIFE), Serum Protein Electrophoresis (SPEP); Urine Protein Electrophoresis (UPEP); Urine Immunofixation Electrophoresis (UIFE).

Oligosecretory Disease. A form of myeloma seen in a small percentage of patients. In oligosecretory disease the level of abnormal protein that is detected is low.

Oncogene. See Mutation.

Pathologist. A doctor who identifies disease by studying tissues under a microscope. A hematopathologist is a pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues and uses his or her expertise to identify diseases such as myeloma. In addition to the microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic test results to make the most accurate diagnosis. The hematopathologist works closely with the hematologist or oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

PET Scan. See Positron Emission Tomography (PET) Scan.

Phagocytes. Cells that readily eat (ingest) microorganisms, such as bacteria and fungi, and kill them as a means of protecting the body against infection. The two principal phagocytes are neutrophils and monocytes. They leave the blood and enter tissues in which an infection has developed. A severe decrease in the concentrations of these cells is the principal cause of susceptibility to infection in patients treated with intensive radiation therapy and/or chemotherapy. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

Plasma Cell. A cell derived from the antigen-induced activation and maturation of B lymphocytes. It is the principal antibody-producing form of B cells. In myeloma, tumor cells have the appearance of plasma cells; that is, they are malignant plasma cells, described collectively as "myeloma."

Plasmacytoma. A localized tumor of malignant plasma cells either in a bone or in another tissue of the body. A tumorous area outside of the bones may be referred to as "extramedullary plasmacytoma."

Platelets. Small blood cells (about one-tenth the volume of red cells) that stick to the site of blood vessel injury, aggregate and then seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet, and a form of this word is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia (too few) or thrombocythemia or thrombocytosis (too many).

Polymerase Chain Reaction (PCR). A method to make many copies of a target DNA sequence which makes it easier to detect when it is at a very low level. This is sometimes used as part of minimal residual disease (MRD) studies.

Positron Emission Tomography (PET) Scan. A test used to detect cancer sites, in which glucose, a type of sugar, is labeled with a positron particle emitting a radioisotope such as fluorine 18. The utilization of sugar is greater in cancer cells than in normal tissue, and the isotope thus becomes concentrated in areas of cancer. PET is combined with CT to establish the precise location of cancer cells; this is called "PET-CT." A PET scan can provide complementary information to that obtained by MRI or other radiology tests, but each has its limitations. For example, a very small collection of myeloma cells may be missed by all of these tests.

Red Cells. Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation, now in clinical trials. In reduced-intensity transplantation (also called "nonmyeloablative stem cell transplantation") patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft (donor tissue).

The engraftment of donor immune cells may allow these cells to attack the disease (graft-versus-tumor effect), but sometimes the donor cells can also attack and damage host tissues (graft-versus-host disease). More study is needed to determine the effectiveness of this treatment for myeloma patients. Studies to determine the usefulness of reduced-intensity stem cell transplantation in older patients are also under way. For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Refractory Disease. Disease that is either progressing on treatment, did not respond at all to treatment, or started to grow significantly within 60 days of stopping treatment.

Relapsed Disease. Disease that initially responded to therapy but has begun to progress. Usually this progression must have occurred 60 days or more after stopping treatment for it to be considered relapsed.

Remission. The disappearance of evidence of a disease, usually as a result of treatment. The terms "complete remission" (or "complete response") and "partial remission" (or "partial response") are also used. Complete remission means all evidence of the disease is gone. Indicators would include no M protein in the blood and/or urine and a normal number of plasma cells in the bone marrow. Partial remission means the disease is greatly improved by treatment, usually by at least 50 percent, but residual evidence of the disease is present. Sometimes the term "very good partial response" is used, which means showing a 90 percent or greater reduction in disease burden but not meeting all of the criteria for a complete response. Lesser degrees of response include "minimal response," in which there is a reduction between 25 percent and 50 percent in disease burden, or "stable disease," in which there is less than a 25 percent decrease or less than a 25 percent increase in myeloma. "Progressive disease" usually means at least a 25 percent increase in myeloma burden and, if associated with symptoms, usually indicates the need to start therapy, or to change therapies if the patient was already receiving treatment.

Serum. The liquid portion of the blood, in which no cells are present.

Serum Free Light Chain Test. A diagnostic test that measures free light chains (protein components) in the blood. This test is best performed on serum rather than urine due to the filtering effects of the kidneys.

Serum Immunofixation Electrophoresis (SIFE). A laboratory test that can identify the subtype of M protein (myeloma protein) being produced by the myeloma cells.

Serum Protein Electrophoresis (SPEP). A laboratory test that can identify the subtype of M protein (myeloma protein) in the blood.

Skeletal Bone Survey. Head-to-toe x-ray studies of the body undertaken in order to detect the lytic bone lesions, bone/compression fractures and osteoporosis (thinning of the bones) that can be a result of myeloma.

Stem Cells. Primitive cells in marrow that are essential to the formation of red cells, white cells and platelets. Stem cells are largely found in the marrow, but some of these cells leave the marrow and circulate in the bloodstream. Using special techniques, the stem cells in the blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation; Reduced-Intensity Stem Cell Transplantation.

Thrombocytes. See Platelets.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is often altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

Urine Immunofixation Electrophoresis (UIFE). A laboratory test that can identify the subtype of M protein (myeloma protein) being produced by the myeloma cells.

Urine Protein Electrophoresis (UPEP). A 24-hour urine collection used to determine the presence of urinary M protein (myeloma protein) and to detect light chain type disease.

White Cells. Any of the five major types of infection-fighting, basically colorless cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White cells are also called “leukocytes.”

More Information

Free LLS publications include

Cancer-Related Fatigue Facts
Choosing a Blood Cancer Specialist or Treatment Center
Long-Term and Late Effects of Treatment in Adults Facts
Pain Management Facts
The Myeloma Guide: Information for Patients and Caregivers
Understanding Clinical Trials for Blood Cancers
Understanding Lab and Imaging Tests
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Visit www.LLS.org/publications to reach these booklets and other information about blood cancer. Visit "Suggested Reading" at www.LLS.org/resourcecenter to see a list of helpful books on a wide range of topics.

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