LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

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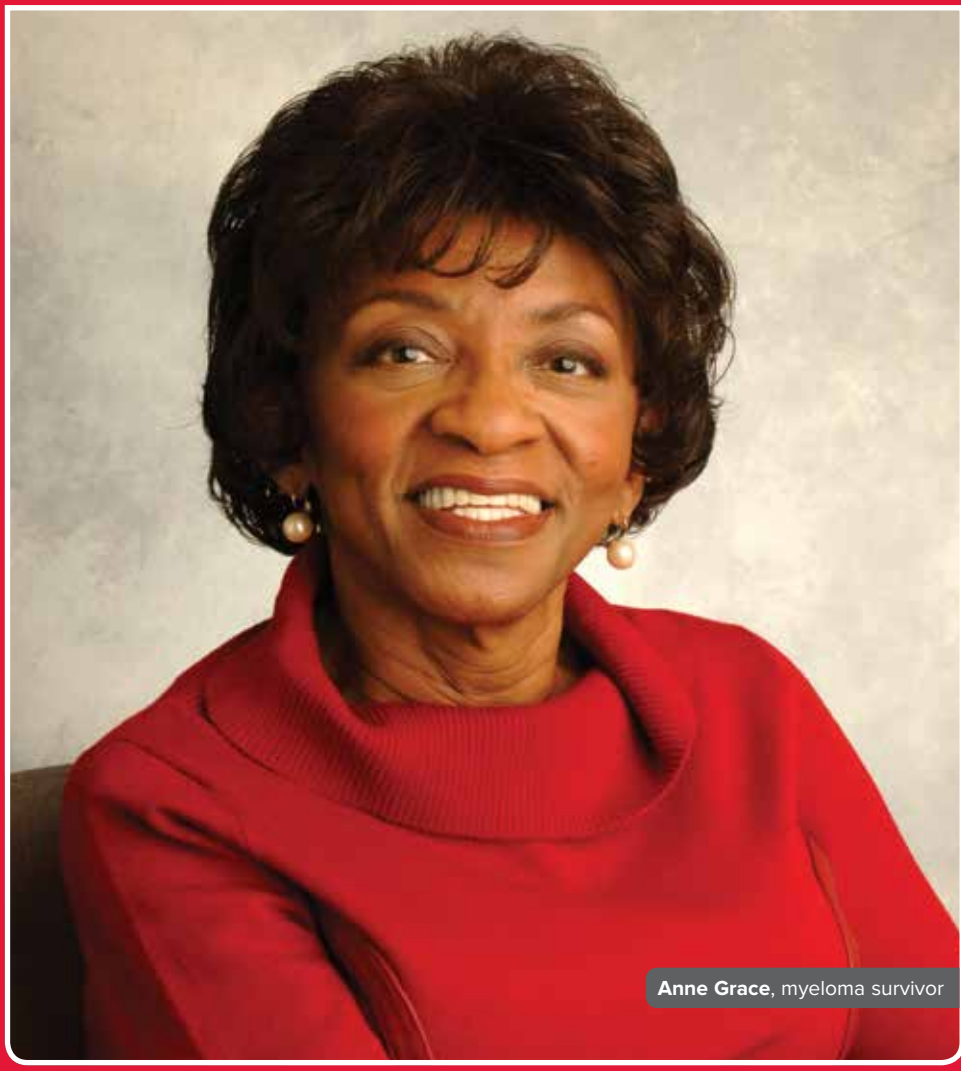
Myeloma



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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 January 2018, the Food and Drug Administration (FDA) approved denosumab (Xgeva®) for the prevention of skeletal-related events in patients with multiple myeloma.

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 Chief Executive Officer
The Leukemia & Lymphoma Society

Inside this Booklet

Acknowledgement

The Leukemia & Lymphoma Society gratefully acknowledges

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Multiple Myeloma and Stem Cell Transplant Clinic
UT Southwestern Medical Center
Dallas, TX

for his critical review and important contributions to the material presented in this publication.

Introduction

This booklet provides information about myeloma for patients and their families. Myeloma is a cancer of plasma cells. A plasma cell is a type of white blood cell found in the bone marrow. Brief descriptions of normal blood and bone marrow and definitions of medical terms are included in this booklet.

An estimated 30,280 people living in the United States are expected to be diagnosed with myeloma in 2017.[1] Although myeloma is incurable in most cases, this is a very hopeful time for patients. Dramatic advancements in new treatments over the past decade are resulting in better overall survival, allowing many patients to maintain a good quality of life for years. There are an estimated 110,345 people either living with, or 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. New approaches to therapy are being studied in clinical trials for patients of all ages and at all stages of the disease.

[1]Source: Facts 2016-2017. The Leukemia & Lymphoma Society. April 2017.

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 that can be helpful 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, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists.

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

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

Continuing Education. LLS offers free continuing education programs for healthcare professionals. For more information, please visit www.LLS.org/professionaled.

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

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. To join, please visit 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, patient care and other needs. For more information, please visit www.LLS.org/resourcedirectory.

Clinical Trials (Research Studies). New treatments for patients 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. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of 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 a member of your healthcare team know if you need a language interpreter or some other resource, 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 2-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. It belongs to a group of disorders known as "plasma cell dyscrasias" or "plasma cell neoplasms." 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.

In myeloma, a plasma cell undergoes a malignant change caused by one or more acquired genetic mutations. These malignant cells multiply and eventually crowd out the healthy plasma cells and the normal stem cells in the bone marrow that form white blood cells, red blood cells and platelets. The malignant plasma cells produce abnormal proteins, which may cause tumors, damage the kidneys, disrupt normal blood production and affect immune system function.

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, the malignant cells may cause a single tumor, called a "solitary plasmacytoma." Plasmacytomas may occur 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. Some patients progress to myeloma.

Myeloma may also be described as "localized myeloma" (cancer that is 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). Some individuals may have myeloma that progresses slowly and does not present any symptoms (also known as "smoldering" or "indolent" 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). The median age at diagnosis is 69 years. Myeloma affects slightly more men than women, and the incidence is twice as high in blacks as it is in whites.

Myeloma: Age-Specific SEER Incidence Rates 2009-2013

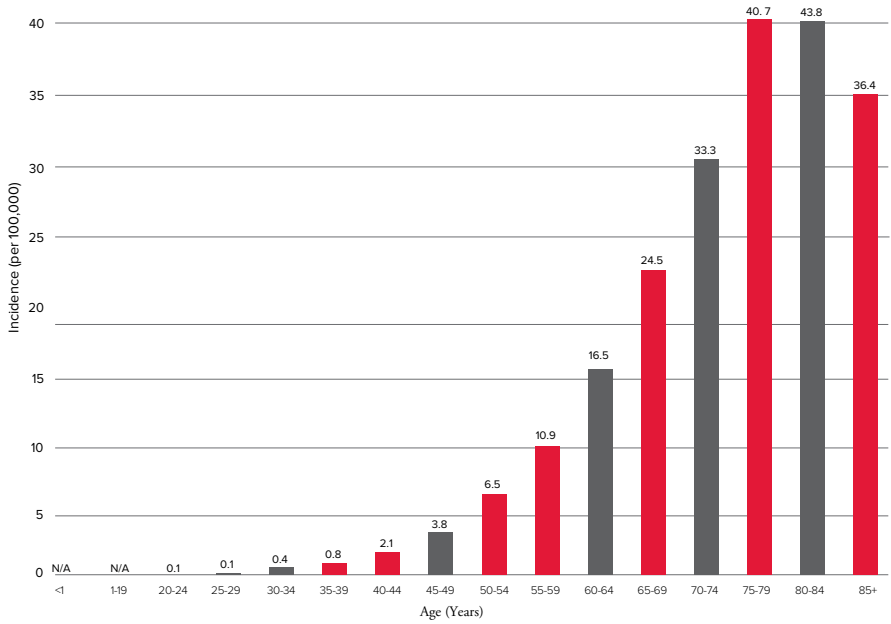

Figure 1. | The horizontal axis shows the age at diagnosis, in 5-year increments, of people in the United States who develop myeloma. The vertical axis represents the number of new cases of myeloma per 100,000 people. Thus, the risk of myeloma is about 10 times greater in those aged 75 to 79 years (about 40.7 cases/100,000 people) compared to those aged 45 to 49 years (about 3.8 cases/100,000 people).
Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed June 7, 2017.

Causes and Risk Factors. The exact cause of myeloma is not known, but doctors do know that myeloma starts when a change occurs in a single-cell B lymphocyte (B cell). Normally, some B lymphocytes develop into plasma cells, which produce the antibodies that help the body fight infection. With myeloma, the B lymphocyte becomes a myeloma cell instead of a healthy plasma cell. Researchers are studying the DNA of plasma cells to determine what changes cause healthy 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 genetic abnormalities that likely contributed to the development of cancer in these cells.

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 have more than twice the age-adjusted incidence rate of myeloma than whites.
- Medical history—People with a history of MGUS (monoclonal gammopathy of unknown significance) (see page 37).
- 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.
- Presence of chronic immunodeficiency
- Presence of known inflammatory diseases or conditions (eg, cardiovascular disease or type II diabetes).

Signs and Symptoms

In the early stages of myeloma, some patients may have no signs or symptoms of disease. The cancer is sometimes 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. When symptoms are present, the most common ones are bone pain and fatigue.

Doctors sometimes refer to the acronym, **CRAB**, to describe signs 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 deposits of myeloma protein in 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 symptoms are said to have "smoldering" or "asymptomatic myeloma," and these patients may be followed with a watch-and-wait approach (see *Smoldering Myeloma* on page 18).

Effects on Bone. Bone pain caused by osteolytic lesions 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. In myeloma, the normal equilibrium between osteoblastic (bone building) and osteoclastic (bone breakdown and resorption) processes is skewed towards bone loss. Myeloma cells secrete a chemical called a "cytokine," which stimulates the cells that dissolve bone and inhibits cells that form bone. 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. Slightly increased activity, such as coughing and minor falls or injuries, can also result in broken bones and cause pain. Bone lesions are present in about 80 percent of patients.

Effects on Blood and Marrow. Myeloma patients may experience fatigue very 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 occurs in approximately 75 percent of 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 increase slightly in the marrow because of the body's response to an infection, especially a virus. 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.

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.

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.

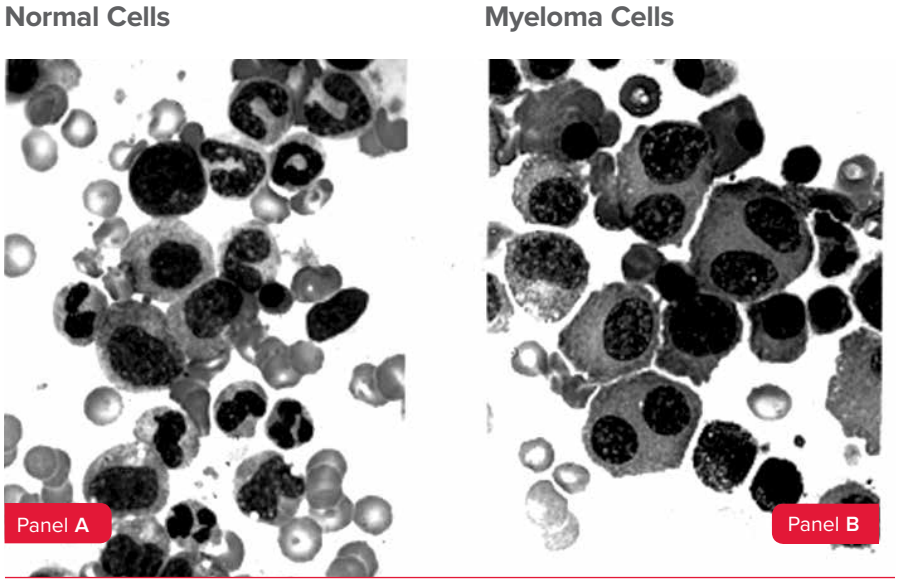

Figure 2. | **Panel A** is a photograph of normal marrow cells. The variations in the shape and appearance of the cells are characteristic of the developmental stages of normal cells. **Panel B** is a photograph of marrow cells from a patient with myeloma. The normal marrow cells are replaced by plasma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

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 may 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 monoclonal (M) protein in the blood. Symptoms of hyperviscosity syndrome are abnormal bleeding, headaches, chest pain, decreased alertness or shortness of breath.

See *Myeloma Complications, Treatment Side Effects and Supportive Care* beginning on page 32, for more information about kidney impairment, hyperviscosity syndrome and peripheral neuropathy.

Diagnosis

An accurate diagnosis is one of the most important aspects of a person's care. Obtaining a precise diagnosis will help the doctor

- Estimate how the disease will progress
- Determine the appropriate treatment.

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.

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

- Increased numbers of malignant plasma cells (myeloma cells) found by bone marrow aspiration and biopsy. Bone marrow aspiration and biopsy findings indicate the percentage of myeloma cells in the marrow, as well as 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) found in the blood and/or urine. See *Monoclonal Immunoglobulins (Monoclonal Protein [M Protein] and Light Chains [Bence Jones Proteins])* on page 11 and Figure 3 on page 12.
- Evidence of end-organ damage as defined by the CRAB criteria (see Table 1 on page 11).

The International Myeloma Working Group (IMWG) recently updated the diagnostic criteria for multiple myeloma to include biomarkers in addition to the existing requirements of CRAB features. Table 1 on page 11 outlines the revised IMWG criteria for the diagnosis of multiple myeloma.

Revised International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma

Both of the following criteria must be met:

1. Malignant plasma cells in the bone marrow ≥10% or presence of bony or extramedullary plasmacytoma, confirmed by biopsy
2. Any one or more of the following myeloma defining events:
   - **Evidence of end-organ damage that can be attributed to the disease: CRAB features**
     - **C**alcium elevation—serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
     - **R**enal insufficiency—creatinine clearance <40 mL per minute or serum creatinine >177 umol/L (>2 mg/dL)
     - **A**nemia—hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value of <10 g/dL
     - **B**ony lesions—one or more osteolytic lesions found on skeletal radiography, CT or PET-CT
   - **Biomarkers**
     - Clonal plasma cells in the bone marrow ≥60%
     - Ratio of involved/uninvolved serum free light chain (FLC) ratio ≥100
     - One or more focal lesions found on MRI studies (at least 5 mm in size)

Table 1. Abbreviations: CT, computed tomography; FLC, free light chain; IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging; PET, positron emission tomography; PET-CT, positron emission tomography-computed tomography.

Monoclonal Immunoglobulin (Monoclonal Protein [M Protein] and Light Chains [Bence Jones Proteins]). In healthy individuals, plasma cells normally 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).

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

M protein can be measured in the blood and/or urine (See *Protein Electrophoresis Tests* on page 13). M protein levels in the blood generally correlate with the extent of the myeloma. Increasing levels 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. About 2 to 3 percent of patients have nonsecretory myeloma. 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 (polyclonal) immunoglobulin (Ig) molecule is composed of two larger pieces (heavy chains) and two smaller pieces (light chains) that are attached to each other. There are five types of heavy chains and each type is assigned a specific letter: IgG, IgA, IgD, IgE and IgM. There are two types of light chains and they are referred to as "kappa (k)" and "lambda (λ)."

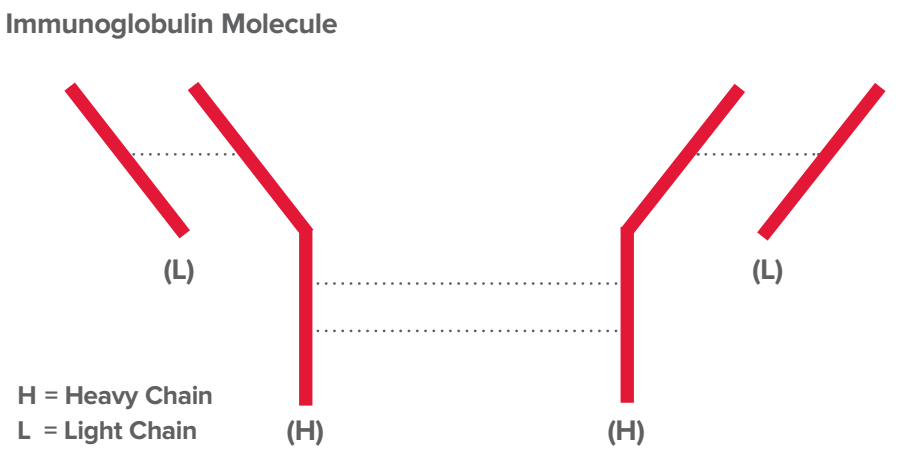

Figure 3. | The M protein in myeloma, like normal immunoglobulin, is made up of two heavy chains and two light chains attached to each other. In many cases, the coordination of making and attaching light chains and heavy chains in the malignant plasma cells is lost, and light chains leave the cell unattached. 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 "free" light chains enter the blood and are excreted rapidly in the urine. The light chain is also called the "Bence Jones protein," named for the English doctor Henry Bence Jones, who studied its characteristics. When excreted in large amounts, the Bence Jones proteins (free 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 13).

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," (occurring in approximately 50 percent of patients) in which the monoclonal protein (just like the intact polyclonal immunoglobulin) is composed of two long chains and two short chains as shown in Figure 3 on page 12. The next most common type is light chain myeloma, where an intact immunoglobulin is not made. Some patients have "IgA myeloma," (about 20 percent of patients) and a small number of patients have "IgM," (about 0.5 percent of patients) "IgD," (about 2 percent of patients) or "IgE" myeloma.

Protein Electrophoresis Tests. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), both of which need to be performed with a technique called "immunofixation" (IFX), are tests used to identify the presence of abnormal proteins, to identify the absence of normal proteins, and to determine increased and decreased amounts of the different groups of proteins in serum or urine. These tests are typically ordered to detect and identify excessive production of specific 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.

Serum Free Light Chains (SFLC) Assay. Serum free light chain testing provides complementary information to the protein electrophoresis tests SPEP and UPEP. The SFLC assay can detect abnormal levels of free light chains, which may be an indication of a plasma cell disorder. It can also detect changes in the ratio of kappa and lambda light chain production, which indicate an excess of malignant plasma cells. Initially, serum free light chain testing is ordered along with a serum protein electrophoresis test to detect abnormal monoclonal protein (M protein) production and to calculate a kappa/lambda free light chain ratio. If the protein electrophoresis test findings are abnormal, then an immunofixation electrophoresis test is performed to determine which immunoglobulin is present in excess. If a plasma disorder is detected, then the free light chain test may be ordered periodically to monitor the condition and to evaluate the effectiveness of treatment.

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 12); their myeloma cells make only light chains. In these cases of myeloma, referred to as "light chain myeloma," the examination of serum may not show the characteristic increase of M protein, but there will be large amounts of monoclonal light chains in the urine.

Blood Cell Counts. Doctors will also order a complete blood cell 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 Tests. Kidney function tests (measuring 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. Blood urea nitrogen (BUN) is a measurement of the level of urea in the blood. Urea nitrogen is the byproduct of protein breakdown. BUN levels must be monitored carefully in myeloma patients since too much urea in the blood puts them at increased risk for developing kidney disease. Creatinine is a chemical waste product of a substance called "creatine." Creatine is a chemical made by the body used to supply energy to the muscles. If kidney function is abnormal, the creatinine level increases in the blood.

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; all these measurements provide information about the extent of the disease.

Cytogenetic Analysis. Dividing cells are studied to see if any chromosomal abnormalities are present. Fluorescence in situ hybridization (FISH) is a type of lab test that uses special dyes to look for abnormal chromosomes in cells. Chromosomal abnormalities play a crucial role in identifying malignancies and helping determine the most effective course of treatment.

Genetic or chromosomal abnormalities in the myeloma cells are identified by FISH testing. Approximately 40 percent of myeloma cases are characterized by the presence of trisomies (three copies of a chromosome) in the malignant plasma cells, while most of the rest have a translocation involving chromosome 14 (the site of a gene for the immunoglobulin heavy chain). A small number of patients have both trisomies and IgH translocations. Table 2, on page 15, shows the most common cytogenetic abnormalities in myeloma and their associated prognostic risk.

These abnormalities can suggest how rapidly the disease may progress in the future, and predict the chances of a good, long-lasting response to therapy. Importantly, based on findings from cytogenetic analysis, myeloma can be classified as "high risk" or "standard risk."

Gene-expression profiling (GEP) is a newer technique that looks at which genes are expressed, and at what levels, in myeloma cells. Another approach that is, for now, being done largely on a research basis, but that may soon be used in routine practice, is called "next-generation sequencing (NGS)." Next-generation sequencing is a broad term encompassing a number of modern technologies that increase the speed and reduce the cost of DNA sequencing. NGS allows researchers to sequence DNA and RNA much more quickly and cost effectively than they could using older technologies. NGS identifies mutations 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 and developing new and improved targeted therapies.

Most Common Cytogenetic Abnormalities in Multiple Myeloma

Subtype	Gene(s)/ chromosomes affected	Percentage of myeloma patients	Prognostic risk
Trisomic multiple myeloma	Trisomies of one or more odd-numbered chromosomes	42	Standard
IgH translocated multiple myeloma		30	
t(11;14)(q13;q32)	*CCND1* (cyclin D1)	15	Standard
t(4;14) (p16;q32)	*FGFR3* and *MMSET*	6	Intermediate
t(14;16) (q32;q23)	*C-MAF*	4	High
t(14;20) (q32;q11)	*MAFB*	<1	High
Other IgH translocations	*CCND3* (cyclin D3) in t(6;14) multiple myeloma	5	
Combined IgH translocation/trisomy		15	May ameliorate adverse prognosis conferred by high-risk IgH translocation
Isolated monosomy 14		4.5	Effect on prognosis not clear
Gain (1q)	*CKS1B, ANP32E*	40	High
del(17p)	*TP53*	7	High
Normal cytogenetics		3	Standard

Table 2. Shows the most common chromosomal and molecular abnormalities in multiple myeloma and their associated prognostic risk.

Imaging Tests. Imaging is a very important part of the diagnosis, staging and management of myeloma. Imaging tests may include

- Bone/skeletal survey—X rays of all the bones in the body are taken and examined to identify areas of decreased bone density and bone lesions.
- Magnetic resonance imaging (MRI)—Magnetic resonance imaging is used in select cases. MRI uses a powerful magnet and radio waves linked to a computer to create clear and detailed cross-sectional images (slices) of the body. The "slices" can then be displayed on a video monitor and saved on a disk for future analysis. MRI findings help doctors to diagnose multiple myeloma by identifying the areas where there is bone damage and detecting myeloma lesions in the bone marrow.
- PET-CT scan—This test combines the techniques of both positron emission tomography (PET) imaging and computed tomography (CT) into one machine. A PET-CT scan reveals information about both the structure and function of cells and tissues in the body during a single imaging session. It provides a more detailed picture of where the cancer is located in the body than either test does by itself.

Staging and Prognostic Factors

Doctors use imaging tests, laboratory tests and bone marrow examination findings to determine the extent of disease. This determination is called "staging." Staging provides important information for treatment planning. In multiple myeloma there is great variation in patient outcomes, depending on a group of factors that include the extent of disease (stage), the presence of cytogenetic abnormalities and the patient's response to therapy.

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 level of blood calcium, the presence of bone lesions on imaging studies to determine the extent of the myeloma, the amount of the M protein in the blood and urine, and the level of kidney function.

The "International Staging System (ISS) for Multiple Myeloma," includes other measurements such as the degree of decrease in serum albumin levels and the degree of increase in beta$_2$-microglobulin concentration—two serum measurements done on virtually all patients—to determine prognosis (outlook) at the time of diagnosis. The ISS was recently revised to include additional factors, such as elevated lactate dehydrogenase (LDH) level or the presence of high-risk cytogenetic abnormalities, to create a unified prognostic index that can be useful in clinical care as well as in comparing research data. These measurements allow the doctor to classify the patient's myeloma as stage I, stage II or stage III disease. See Figure 4 on page 17.

In treatment planning, doctors also consider other factors. The general health of the patient, the presence of other significant diseases such as heart disease or diabetes, the presence of kidney disease, other findings that influence the patient's tolerance to treatment, and the risk of treatment-induced difficulties are all considered when doctors are making treatment decisions, including whether to treat and what approach to take.

Myeloma Staging Systems

Stage	Durie-Salmon Staging System	Revised International Staging System
I	All of the following: ○ Hemoglobin >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 <4g/24 hours	○ Serum albumin >3.5 g/dL ○ Serum β_2-microglobulin <3.5 mg/L ○ No high-risk cytogenetics ○ Normal serum lactate dehydrogenase level
II	Neither stage I nor stage III ○ A—No renal failure (creatinine ≤2 mg/dL) ○ B—Renal failure (creatinine >2 mg/dL)	Neither stage I nor stage III
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 β_2-microglobulin >5.5 mg/L ○ High-risk cytogenetics t(4;14) t(14;16) del(17p) ○ Elevated serum lactate dehydrogenase level

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

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.

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 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.

Smoldering Myeloma. Some patients have minimal disease and little evidence of progression (asymptomatic or smoldering myeloma) at the time of diagnosis. For patients without symptoms and with indolent disease, appropriate management may be "watchful waiting." The watch-and-wait approach means that the treatment is deferred or delayed until signs of disease progression occur. Frequent and careful observation by a doctor is required so that effective treatment can be started if the disease starts advancing. Patients with active (symptomatic) myeloma need immediate treatment.

Treatment Planning. In order to initiate therapy, patients must meet the criteria for multiple myeloma as outlined within Table 1 on page 11. The approach for treating each patient is customized, based on a number of factors that include the

- 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
- The patient's age (note that the patient's overall health is considered in determining his or her ability to tolerate intensive therapy, rather than age alone).

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 the symptoms and complications of the disease, such as anemia, high blood calcium levels, infections and/or bone damage or osteoporosis (see *Myeloma Complications, Treatment Side Effects and Supportive Care* on page 32).

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 (eg, solitary plasmacytoma)
- New and emerging drug therapies (as part of clinical trials).

While there is no cure for multiple myeloma, new therapies have improved patient quality of life and survival rates. Treatment has significantly progressed in the last decade with the development of novel agents and the use of bisphosphonate drugs with autologous stem cell transplantation (ASCT). New approaches have focused on combining specific proteasome inhibitors (PIs) with immunomodulatory drugs (IMiDs), the use of monoclonal antibodies and histone deacetylase (HDAC) inhibitors.

Drug Therapy. Drug therapy to kill myeloma cells is the mainstay of treatment for myeloma. Chemotherapeutic agents commonly used for multiple myeloma include melphalan, cyclophosphamide, doxorubicin and liposomal doxorubicin. These agents are often used in conjunction with autologous stem cell transplantation, which is able to replenish stem cells. This treatment combination has shown to increase overall survival in myeloma patients. 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 23).

For transplant candidates, drug treatment begins with a combination of induction agents that do not cause marrow damage—for example, bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone; cyclophosphamide (Cytoxan®), bortezomib and dexamethasone; or other combinations. However, prolonged therapy with lenalidomide may decrease stem cell yields, so stem cell collection is often performed after three to six cycles.

Researchers continue to study the most effective drugs and drug combinations for the treatment of myeloma including newly diagnosed, refractory or relapsed cases.

The following drugs (see Table 3 on page 22) are used to treat myeloma:

Melphalan hydrochloride (Evomela®) is an alkylating agent, administered via injection that is FDA approved for use in two indications: 1) use as a high-dose conditioning treatment prior to stem cell transplantation in patients with multiple myeloma and 2) for the palliative treatment of myeloma patients for whom oral therapy is not appropriate.

Bortezomib (Velcade®), carfilzomib (Kyprolis®) and **Ixazomib (Ninlaro®)** are therapies called "proteasome inhibitors" (PIs). PIs block the function of proteasome, leading to the accumulation of proteins in the cancer cells and causing their destruction. In studies, bortezomib has been shown to promote cell death in myeloma cells as well as reduce bone loss.

- Bortezomib which can be given intravenously (IV) or subcutaneously (sub-Q, or SC) and is FDA approved to treat people with myeloma and can be used for retreatment of patients with myeloma.
- Carfilzomib is given intravenously and is FDA approved for use in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. It is also indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one or more prior therapies.
- Ixazomib is an oral proteasome inhibitor approved by the FDA for patients with myeloma. It is approved for use in combination with lenalidomide and dexamethasone for the treatment of patients who have received at least one prior therapy. It is a good option for patients who have difficulty going to their doctor's office for injections and is also well tolerated, even by older patients.

Pamidronate (Aredia®) and zoledronic acid (Zometa®), both given intravenously, are types of drugs called "bisphosphonates," which are potent inhibitors of bone resorption. These drugs block osteoclasts (cells involved in bone breakdown) and 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 more information on osteonecrosis of the jaw [ONJ] on page 33).

Lenalidomide (Revlimid®), pomalidomide (Pomalyst®) and thalidomide (Thalomid®), given by mouth, are immunomodulatory drugs (IMiDs). They enhance the sensitivity of myeloma cells to other drugs, such as bortezomib and dexamethasone. They also promote tumor-suppressor actions directed by the immune system. For these reasons, they are often used in multiple combination therapies to improve treatment response.

- Lenalidomide, given by mouth, is approved for use in combination with dexamethasone for the treatment of myeloma. Lenalidomide is also approved for patients with myeloma to use as maintenance therapy following autologous stem cell transplant.
- Pomalidomide, given by mouth, is FDA approved in combination with dexamethasone to treat people with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression either on or within 60 days of completion of the last therapy.
- Thalidomide, given by mouth, is approved in combination with dexamethasone for the treatment of patients who have newly diagnosed myeloma. Its use, in combination with several other drugs, is under study in clinical trials.

Panobinostat (Farydak®), given by mouth, is a histone deacetylase (HDAC) inhibitor. These agents belong to a class of drugs that address "epigenetic" changes in the DNA. HDACi agents have been shown to inhibit cell growth and induce myeloma cell death both as a single agent and in combination with bortezomib treatment. Panobinostat is FDA approved in combination with bortezomib and dexamethasone for the treatment of patients with myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

Elotuzumab (Empliciti™) and daratumumab (Darzalex®) are monoclonal antibodies which are immunotherapy drugs designed to target specific proteins (antigens) on the surface of cancer cells. Once the antibody finds and attaches to its target, it can recruit other parts of the immune system to destroy the cell that contains the antigen. Some monoclonal antibodies (known as "naked antibodies") work by themselves. Others are coupled with a chemotherapy drug or attached to a radioactive particle and are called "conjugated monoclonal antibodies." They circulate throughout the body until they attach to the target antigen and then deliver the toxic substance to the cancer cell. In multiple myeloma, several surface molecules are being explored as potential targets of monoclonal antibodies including SLAMF7 (CS1), CD38, CD40, CD138, CD56 and IL-6 among others.

- **Elotuzumab,** given intravenously, targets the signaling lymphocytic activation molecule F7 (SLAMF7), a protein expressed on myeloma and natural killer cells but not on normal tissues. This drug is FDA approved for use in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
- **Daratumumab,** given intravenously, is a monoclonal antibody that targets the CD38 surface protein on myeloma cells. It has been approved in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with myeloma who have received at least one

prior therapy; in combination with pomalidomide and dexamethasone for the treatment of patients with myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor; as monotherapy, for the treatment of patients with myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

For more information on relapsed myeloma, please see *Treatment for Relapsed or Refractory Myeloma* on page 28.

Some Drugs Used in the Treatment of Myeloma

Alkylating Agents
(DNA-Damaging Drugs)
- Carmustine (BicNU®)
- Cyclophosphamide (Cytoxan®)
- Melphalan (Alkeran®)
- Melphalan hydrochloride (Evomela®)

Antitumor Antibiotics
- Doxorubicin (Adriamycin®)
- Liposomal doxorubicin (Doxil®)

Antimetabolites
- Cytarabine (cytosine arabinoside, Ara-C, Cytosar-U®)

Bisphosphonates
- Pamidronate (Aredia®)
- Zoledronic acid (Zometa®)

Corticosteroids
- Dexamethasone
- Prednisone

Drugs that Prevent Cell Division by Blocking Mitosis
- Vincristine (Oncovin®)

Histone Deacetylase Inhibitors
- Panobinostat (Farydak®)

Immunomodulatory Drugs
- Lenalidomide (Revlimid®)
- Thalidomide (Thalomid®)
- Pomalidomide (Pomalyst®)

Monoclonal Antibodies
- Daratumumab (Darzalex®)
- Elotuzumab (Empliciti™)

Proteasome Inhibitors
- Bortezomib (Velcade®)
- Carfilzomib (Kyprolis®)
- Ixazomib (Ninlaro®)

Table 3. This table includes drugs that are used in the treatment of myeloma.

Some Drug Combinations Used to Treatment Myeloma

- MP: melphalan (Alkeran®), prednisone
- TD: thalidomide (Thalomid®), dexamethasone
- RD: lenalidomide (Revlimid®), dexamethasone
- Pom/Dex: pomalidomide (Pomalyst®), dexamethasone
- VD: bortezomib (Velcade®), dexamethasone
- MPT: melphalan (Alkeran®), prednisone, thalidomide (Thalomid®)
- VMP: bortezomib (Velcade®), melphalan (Alkeran®), prednisone
- VTD: bortezomib (Velcade®), thalidomide (Thalomid®), dexamethasone
- VCD or CyBorD: bortezomib (Velcade®), cyclophosphamide (Cytoxan®), dexamethasone
- VRD: bortezomib (Velcade®), lenalidomide (Revlimid®), dexamethasone
- CCyD: Carfilzomib (Kyprolis®), cyclophosphamide (Cytoxan®), dexamethasone
- KRD: Carfilzomib (Kyprolis®), lenalidomide (Revlimid®), dexamethasone
- Elotuzumab (Empliciti™), lenalidomide (Revlimid®), dexamethasone
- Panobinostat (Farydak®), bortezomib (Velcade®)
- Ixazomib (Ninlaro®), lenalidomide (Revlimid®), dexamethasone

Table 4. This table includes some of the drug combinations that are used to treat myeloma.

Stem Cell Transplantation. High-dose chemotherapy and stem cell transplantation are an important part of the treatment plan for eligible, recently diagnosed myeloma patients. The types of transplants used may be

- Single autologous stem cell transplant
- Tandem stem cell transplant
- Allogeneic stem cell transplant.

Autologous Stem Cell Transplantation. During this procedure stem cells are collected from the patient. If needed, a doctor may use plerixafor (Mozobil®) in combination with G-CSF to help mobilize stem cells to the peripheral blood for collection. Mobilizing stem cells means helping to move them from the marrow to the blood so enough cells can be collected for an autologous transplant. The patient is then treated with high doses of chemotherapy, often using melphalan. After chemotherapy, the stem cells are 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 and remains the standard of care, after primary therapy, for eligible patients. 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 level tests, marrow tests and imaging studies. Myeloma patients who have had an autologous transplant may require maintenance therapy (see *Maintenance Therapy* below).

Tandem Stem Cell Transplantation (SCT). Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first course. According to recent studies, tandem autologous SCT should be considered only if patients fail to achieve a good response with the first transplant, or in select patients with high-risk cytogenetic features, such as the 17p deletion (del[17p]).

Allogeneic Stem Cell Transplantation and Reduced-Intensity Allogeneic Stem Cell Transplantation. Allogeneic and reduced-intensity allogeneic transplantation are other types of stem cell transplants that are used to treat certain blood cancers. The main difference between autologous and allogeneic transplant is that in an allogeneic transplant, the stem cells are obtained from a donor whose cells are compatible with those of the patient, usually a brother or sister, or an unrelated donor. Associated side effects and mortality are more likely to occur with an allogeneic transplant than with autologous transplants. Thus, allogenic transplant has a limited role in multiple myeloma therapy and it should be done in the context of a clinical trial. Allogeneic transplant is mainly considered to be a therapeutic option for young patients with high-risk disease who have experienced a relapse and who are willing to accept the risk associated with this transplant in exchange for a better chance at long-term survival.

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 booklet *Blood and Marrow Stem Cell Transplantation.*

Maintenance Therapy. The use of lenalidomide as post-transplant maintenance is emerging as a preferred regimen. Lenalidomide is FDA approved for patients with multiple myeloma as maintenance therapy following autologous hematopoietic stem cell transplant. Lenalidomide lacks the neurotoxicity of other immunomodulatory drugs, such as thalidomide. However, there seems to be an increased risk for the development of secondary cancers, especially after transplantation or after therapy with a regimen that contains melphalan. More information is needed about the effects of maintenance on overall survival as well as the risk of second cancers.

Recent studies have shown that bortezomib may be a good maintenance option for newly diagnosed patients who are not eligible for transplantation. There are several

ongoing maintenance therapy trials evaluating the effectiveness of treatment with lenalidomide, bortezomib, ixazomib and combinations that are based on these and other approved drugs.

Oral Adherence. Many new myeloma drugs are now taken orally (by mouth). It is important to make sure patients continue to take their medications, as prescribed, at home if they are not going to the outpatient clinic to receive treatment. "Adherence" means staying on a set plan or regimen; taking the medication as prescribed—on the right day and at the right time.

There are many benefits of taking a drug by mouth. These include improved quality of life, convenience and time. Unfortunately, poor adherence can result in drug resistance; poor response to therapy; progression of disease; increased doctor visits, lab tests, and hospitalizations; and death.

For additional information about adherence, including barriers to treatment, solutions and strategies, please see the free LLS booklets *Myeloma Oral Treatment Adherence Facts* and *A Medication Resource for Myeloma Patients.*

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 solitary 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. See *Research and Clinical Trials* on page 29.

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.

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 51).
- **Complete response**
  - No sign of M protein using standard tests
  - Disappearance of any soft-tissue plasmacytomas
  - Less than 5% plasma cells in bone marrow aspirates
- **Stringent complete response**
  - No detectable disease by serum or urine immunofixation
  - Normal kappa (k)/lambda (λ) light chain ratio
  - No detectable myeloma on bone marrow flow cytometry
- **Very good partial response**
  - A 90% or greater decrease in blood M protein
  - Urine M protein level <100 mg in 24-hour urine collection
- **Partial response**
  - 50% or greater decrease of M protein in the blood
  - 90% reduction in M protein in 24-hour urine collection
  - 50% or greater reduction in the size of soft-tissue plasmacytoma (if present at diagnosis)
- **Minimal response**
  - Reduction between 25% and 50% in M protein in the blood
  - Reduction between 50% and 89% in M protein in 24-hour urine collection
  - 50% or greater reduction in the size of soft-tissue plasmacytoma (if present at diagnosis)
- **Stable disease**
  - Not meeting criteria for complete response, very good partial response, partial response, minimal response or progressive disease
- **Progressive disease**
  - At least a 25% increase in M protein in the blood and urine
  - Appearance of new lesions or 50% or greater increase in the size of previous lesions
  - If associated with symptoms, usually indicates the need to start therapy or to change therapies if the patient is already receiving treatment

Table 5. Lists terms used to describe myeloma treatment response.

Measuring Treatment Response. Patients receiving treatment should be monitored for response to therapy and for symptoms related to the myeloma or its treatment. Treatment response should be evaluated after one or two cycles of therapy. Most of the same tests that were used in diagnosing the disease may be used to monitor response to treatment. These may 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 leftover myeloma, or if they are normal plasma cells.
- Polymerase chain reaction (PCR) using allele-specific oligonucleotide probes (ASO-PCR), usually on bone marrow. PCR is a technique used to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be determined. This method is useful because it allows the hematopathologist to detect a very low concentration of residual myeloma cells—too few to be seen by using a microscope. The technique can detect the presence of one malignant cell among 500,000 to 1 million healthy cells.
- Next-generation sequencing (NGS) of either the bone marrow or blood. NGS is a highly sensitive technique that employs sequences of immunoglobulin heavy chains for B lymphocytes and plasma cells to detect the presence of malignant cells.

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 either 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). The choice of a treatment regimen at relapse is affected by many factors including the type of prior therapy, the number of previous lines of therapy and the aggressiveness of the relapse.

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. Please see pages 19-22 for complete prescribing information.

- **Bortezomib- and Lenalidomide-based Regimens.** Approximately one third of patients with relapsed or refractory multiple myeloma respond well to bortezomib when used as a single agent. As in newly diagnosed myeloma, bortezomib may be combined with other active agents to produce highly effective triple drug combinations, such as
  - VCD: bortezomib (Velcade®), cyclophosphamide (Cytoxan®), dexamethasone
  - VTD: bortezomib (Velcade®), thalidomide (Thalomid®), dexamethasone
  - VRD: bortezomib (Velcade®), lenalidomide (Revlimid®), dexamethasone
- **Bortezomib 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 bortezomib and liposomal doxorubicin combination is approved by the FDA to treat myeloma patients who have not previously received bortezomib and have received at least one prior treatment. Study findings indicate that this drug combination improves the time-to-disease progression as compared to that of bortezomib given alone.
- **Carfilzomib (Kyprolis®)**
- **Ixazomib (Ninlaro®).** A triple drug combination of ixazomib, lenalidomide and dexamethasone is an all-oral regimen which is convenient, has a low-toxicity profile and has shown to be very effective. It may become one of the new standards of care for relapsed multiple myeloma patients.
- **Thalidomide (Thalomid®).** This drug, given by mouth, was once used routinely for newly diagnosed myeloma patients until the adoption of treatment with lenalidomide and bortezomib. Now, thalidomide is one of the drugs that is often used for treating relapsed/refractory myeloma. This therapy is usually given in combination with either the corticosteroid dexamethasone or other drugs.

- **Pomalidomide (Pomalyst®)**
- **Panobinostat (Farydak®)**
- **Elotuzumab (Empliciti™)**
- **Daratumumab (Darzalex®)**

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 either 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. (See *Research and Clinical Trials*).

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. 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. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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, with time, myeloma cells become resistant 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.

- A new proteasome inhibitor named oprozomib is being studied in various clinical trials. It is used in combination with dexamethasone, for treating either newly diagnosed patients or patients with relapsed or refractory myeloma.
- High-dose carfilzomib (Kyprolis®), a proteasome inhibitor, is being evaluated to be given in combination with lenalidomide and dexamethasone for the treatment of newly diagnosed myeloma.
- The drug venetoclax (Venclexta™) is a BCL-2 inhibitor that is FDA approved to treat CLL patients who have a chromosomal abnormality called "17p deletion." It is being studied in clinical trials, as part of combination therapy with carfilzomib and dexamethasone, for the treatment of multiple myeloma patients who have received one to three prior lines of therapy.
- An ongoing trial is evaluating the efficacy of the combination ixazomib-lenalidomide-dexamethasone compared with placebo-lenalidomide-dexamethasone for the treatment of relapsed and refractory myeloma patients.
- The triple-drug combination pomalidomide-bortezomib-dexamethasone is being evaluated in patients with relapsed and refractory multiple myeloma.

Stem Cell Transplantation. A number of approaches are under study, including the use of autologous and nonmyeloablative (reduced intensity) allogeneic stem cell transplantation.

- A current trial is evaluating nonmyeloablative transplant followed by bortezomib for high-risk multiple myeloma patients.
- The role of lenalidomide as maintenance therapy in patients who have received a tandem autologous transplantation is being studied in clinical trials.

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

Immunotherapy. Various forms of immunotherapy are being studied, including

- **Dendritic Cell/Tumor Fusion Vaccines.** Proteins on the surface of myeloma cells may be especially well-suited targets for attack by vaccines. Dendritic cells are generally found in small amounts in the body and are responsible for immune responses against "foreign" substances. To create these fusion vaccines, cells are removed from the patient's tumor and fused (mixed) with dendritic cells obtained from the blood, in order to stimulate a powerful antitumor response. This type of immunotherapy is being evaluated in clinical trials for both newly diagnosed and previously treated patients.
- **Monoclonal Antibodies.** These immunotherapy agents are increasingly being used to treat myeloma patients both to target the cancer cells directly and to modulate the patient's immune system. While some monoclonal antibodies ("naked" antibodies) work by themselves, others are joined with a chemotherapy

drug or attached to a radioactive particle and are known as "conjugated monoclonal antibodies."

- A promising example of this therapy, currently being studied in clinical trials, is the monoclonal antibody indatuximab ravtansine (BT062). This antibody, when coupled with a radioactive isotope, targets the CD138 antigen expressed in greater than 95 percent of myeloma cells.
- Isatuximab, an investigational anti-CD38 monoclonal antibody, is being studied for the treatment of patients with relapsed and refractory multiple myeloma. The trial will compare isatuximab in combination with pomalidomide and dexamethasone against pomalidomide and dexamethasone.
- Milatuzumab is an anti-CD74 monoclonal antibody that is being evaluated, in combination with doxorubicin, for patients with relapsed and refractory myeloma.
- Ulocuplumab (BMS-936564) which targets CD184 is under investigation in patients with relapsed and refractory myeloma, in combination with either lenalidomide and dexamethasone or bortezomib and dexamethasone.
- Denosumab (Xgeva®) is a monoclonal antibody that has been approved to treat osteoporosis in postmenopausal women and also to treat bone-related disease in patients with prostate or breast cancer. It is being evaluated in clinical trials for the prevention of bone fractures in multiple myeloma.

- **Programmed Death (PD-1) Checkpoint Inhibitors.** A vital part of the immune system is its ability to distinguish healthy cells in the body from those that it recognizes as foreign or harmful. The immune system depends on multiple checkpoints—molecules on certain immune cells that need to be activated (or turned off) in order to start an immune response. Cancer cells sometimes take advantage of these checkpoints to escape the detection of active immune cells. PD-1 is a checkpoint protein that is found on the surface of T cells. It normally acts as a type of "off switch" that helps keep immune cells from attacking healthy cells in the body. It accomplishes this when it attaches to a PD-L1, a protein found on some normal cells and also in some cancer cells. When PD1 binds to PD-L1, a message is sent to the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1 receptors, which help them avoid an immune attack.

  Checkpoint inhibitors are drugs created to target the PD1 or PD-L1, blocking their actions, and allowing the immune system to recognize and eliminate cancer cells. The checkpoint inhibitor pembrolizumab (Keytruda®) is being studied, in combination with pomalidomide and low-dose dexamethasone, for the treatment of refractory and relapsed multiple myeloma. Another clinical trial is examining the performance of pembrolizumab, in conjunction with lenalidomide and

dexamethasone, and given post autologous stem cell transplantation, for the treatment of high-risk multiple myeloma.

- **Chimeric Antigen Receptor (CAR) T-Cell Therapy.** This is a type of immunotherapy that consists of engineering a patient's own immune cells to recognize and then attack cancerous tumors. This approach has shown very promising results in patients with blood cancers. The patient's T cells are genetically engineered to produce receptors on their surface called "chimeric antigen receptors (CARs)." The receptors recognize and bind to a specific target found on the cancer cells. In an ongoing clinical trial, which has shown impressive preliminary results, researchers are studying the role of a new B-cell maturation antigen (BCMA) CAR T-cell therapy for patients with relapsed or refractory multiple myeloma.

We encourage you to contact our Information Specialists at (800) 955-4572 for more information about specific treatments under study in clinical trials.

Myeloma Complications, Treatment Side Effects and Supportive Care

Supportive therapy for myeloma helps manage the complications of the disease and the adverse effects of the drugs used for treatment.

Fatigue. Fatigue is one of the most common complaints reported by myeloma patients. It 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 should be evaluated in order to identify other possible causes for the fatigue that are unrelated to myeloma. Management strategies can then be implemented to alleviate the fatigue-causing or fatigue-related issues.

- **Erythropoietin (EPO) Therapy.** 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 and 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.

Infection. Infections are not only troublesome medical problems for patients with myeloma, they can also 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. To prevent infection

- IV immunoglobulin therapy should be considered for frequent and life-threatening infections.
- Pneumococcal and influenza vaccine should also be considered.
- *Pneumocystis carinii* pneumonia, herpes and antifungal prophylaxis is recommended if a high-dose regimen has been given.
- Bortezomib treatment is associated with an incidence of herpes zoster. Herpes prophylactic treatment should be considered in patients who are receiving bortezomib therapy.

Bone Pain. Bone pain may occur because the growth of myeloma cells in the bone causes bone thinning and lesions. 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. Successful treatment of the disease and its complications may relieve bone pain but many patients may require pain medications, such as nonsteroidal anti-inflammatory drugs and, in some cases, narcotics. For more information see the free LLS booklet *Pain Management* Facts.

Treatment of bone pain includes

- **Bisphosphonate use.** Pamidronate (Aredia®) and zoledronic acid (Zometa®) can help reduce bone pain and the risk of bone fractures. These drugs also prevent the elevated levels of calcium in the blood that are the result of bone destruction. Because of the associated increased risk of developing osteonecrosis of the jaw (ONJ), treatment with bisphosphonates should be managed by an experienced oncologist, with close coordination between the oncologist and oral surgeon and/or dental specialist.

  ONJ is an uncommon but serious condition that has occurred in some patients receiving bisphosphonates. 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.

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 started. 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 recommended. 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, in some cases, it is needed and can be helpful.

- **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 relieve pain caused by recent fractures more effectively than they do in cases involving older fractures.

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 monoclonal 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. 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.

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

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 37).

When hyperviscosity syndrome is present, the condition is considered a medical emergency, and it needs urgent treatment with plasmapheresis and exchange. This procedure rapidly reduces the concentration of monoclonal proteins in the blood. Chemotherapy is needed as well, since the plasmapheresis does not reduce the number of cells making these abnormal proteins. If the cells are not treated with chemotherapy, they will produce the proteins that, with time, will 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. See the booklet *Acute Myeloid Leukemia*.

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 lenalidomide, and proteasome inhibitors, such as bortezomib, 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 vincristine, bortezomib, carfilzomib, thalidomide, pomalidomide and, less commonly, lenalidomide. Other problems that can either 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 the symptoms of neuropathy appear, because often either reducing the dosage of the drugs being used, or stopping them altogether, can alleviate 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 DVT risk with their doctors 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. Thalidomide and lenalidomide are associated with an increased incidence of DVT and pulmonary embolism when they are used in combination with corticosteroids, such as dexamethasone, and in particular, when they are used in combination with liposomal doxorubicin. Some doctors have observed that taking either thalidomide or lenalidomide 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 booklets *Blood Transfusion, Cancer-Related Fatigue Facts* and *Understanding Side Effects of Drug Therapy* for more information about managing side effects.

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.

Multiple myeloma survivors are advised to

- Maintain regular follow-up appointments with their hematologists-oncologists. Their doctor will monitor them for a return of the cancer and also be able to detect any side effects from treatment or the development of other medical problems.
- Keep a record of the treatments they received. The records will be helpful for the healthcare professionals who will be monitoring them for potential health problems after treatment ends. This record should include 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.
- Have regular screening for cancer. Myeloma is associated with an increased risk of developing acute myeloid leukemia, especially after receiving treatment with certain chemotherapy drugs.
- Seek medical and psychosocial support for fatigue, depression and other long-term effects, if needed.
- Follow established guidelines for good health. Some general steps to consider include
  - Maintaining a healthy weight
  - Quitting smoking
  - Eating a healthy diet
  - Staying physically active.

For additional information, including risks of specific chemotherapy agents, see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Myeloma-Related Diagnoses

Monoclonal Gammopathy of Undetermined Significance (MGUS). This condition, also called "benign monoclonal gammopathy," is present in 3 to 4 percent of the general population older than 50 years. MGUS is associated with monoclonal protein in the blood but the condition does not present any symptoms or affect the well-being of the patient, and it is usually found as an incidental laboratory finding. Only 10 percent of patients with newly diagnosed multiple myeloma have a history of MGUS and it is associated with a risk of progression to multiple myeloma of approximately 1 percent per year. 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 booklet *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 12). 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 determined based on the results of blood tests that reflect heart function, including the N-terminal pro-brain natriuretic peptide (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, bortezomib and lenalidomide. In patients who are good candidates, autologous stem cell transplantation is the treatment of choice.

Heavy Chain Diseases. These are a family of rare, systemic syndromes involving B lymphocytes. They are named because the protein made by the malignant lymphocytes is an incomplete immunoglobulin (the heavy chain of the immunoglobulin; see Figure 3 on page 12). 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. Treatment generally involves chemotherapy and corticosteroids and, in some cases, radiation.

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 12). 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 LCDD 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). Approximately 50 to 60 percent of patients with LCDD have multiple myeloma and about 17 percent have monoclonal gammopathy of undetermined significance (MGUS).

Plasma Cell Leukemia (PCL). A rare plasma cell disease that may be primary (without known cause) 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 (greater than 20 percent) circulating in the blood, often creating plasmacytomas throughout the body. 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. They are

- 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 Bone 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.

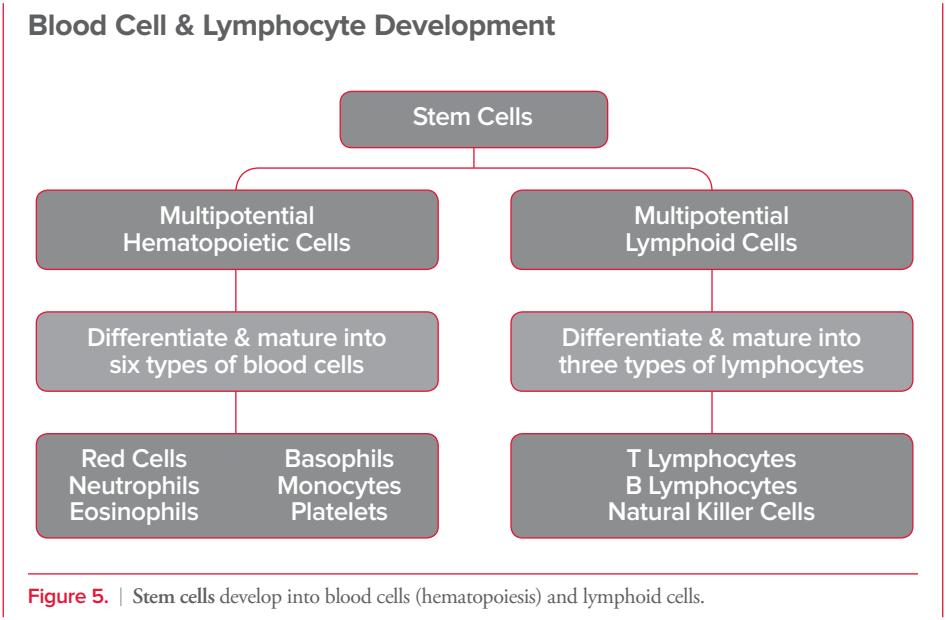

Figure 5. | **Stem cells** develop into blood cells (hematopoiesis) and lymphoid cells.

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 apheresis (see page 43). 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 booklet *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 booklet *Blood and Marrow Stem Cell Transplantation.*

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

Bence Jones Protein. An abnormal protein (light chains) 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 help slow bone loss by turning off osteoclasts (cells that break down bone) from dissolving bone. Bone thinning (osteoporosis) and fracture are major problems for patients who have myeloma.

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 results from the aspirate 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.

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. The contrast does help doctors to get a more detailed picture of what is going on, but intravenous contrast can, in rare cases, 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." Interleukins interact between two types of leukocytes.

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 doctors to detect specific mutations in the chromosomes, but only those for which probes are used.

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 stimulates production of 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 4 months, platelets in 10 days and most neutrophils in 1 to 3 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.

Light Chain. Either of the two small protein chains that, when they are linked to heavy chains, make up the antibody molecule of an immunoglobulin. There are two types of light chains. They are designated kappa (k) and lambda (λ), and they 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, such as 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). A low level of myeloma cells that are still present either during or after treatment. It is detected by 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 it is actually progressing, and the patient usually feels worse. This situation can often be detected by doing a bone marrow aspiration and biopsy; the findings 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 (k) or lambda (λ) 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 Immunofixation Electrophoresis (UIFE); Urine Protein Electrophoresis (UPEP).

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 booklet *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 the disease 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. See Table 5 on page 26.

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 booklets include

Acute Myeloid Leukemia

A Medication Resource for Myeloma Patients

Cancer-Related Fatigue Facts

Choosing a Blood Cancer Specialist or Treatment Center Facts

Long-Term and Late Effects of Treatment in Adults Facts

Myeloma Oral Treatment Adherence Facts

Pain Management Facts

The Myeloma Guide: Information for Patients and Caregivers

Understanding Clinical Trials for Blood Cancers

Understanding Lab and Imaging Tests

Understanding Side Effects of Drug Therapy

Waldenström Macroglobulinemia Facts

Visit www.LLS.org/booklets to reach these booklets and other information about blood cancer. Visit "Suggested Reading" at www.LLS.org/suggestedreading to see a list of helpful books on a wide range of topics.

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