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Myeloma

Revised **2019**

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A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/ happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.

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- **Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff**
- **Accurate and cutting-edge disease updates**
- **The opportunity to participate in surveys that will help improve care**

Inside This Booklet

Acknowledgement

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Introduction

Myeloma is a cancer of plasma cells. A plasma cell is a type of white blood cell found in the bone marrow. This booklet includes a section with brief descriptions of blood and bone marrow in normal conditions (pages 44-46) and definitions of health terms (pages 50-60).

An estimated 32,110 people living in the United States are expected to be diagnosed with myeloma in 2019. 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 a better overall survival rate, allowing many patients to maintain a good quality of life for years. There are an estimated 124,483 people either living with or in remission from myeloma.[1]

This progress in disease management is expected to continue as a result of the concerted scientific research effort under way and because of patients' participation in clinical trials, with the ultimate goal of finding a cure. New treatment approaches are being studied in clinical trials for patients of all ages and at all stages of the disease.

1. Source: *Facts 2018-2019*. The Leukemia and Lymphoma Society. March 2019.

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Myeloma Basics

Myeloma is a cancer of plasma cells. It is part of a group of disorders known as "plasma cell dyscrasias" or "plasma cell neoplasms." B lymphocytes (B cells), a type of white blood cell that is found in the bone marrow, develop into plasma cells. 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. The cell multiples into many malignant plasma cells that eventually crowd out the healthy white blood cells, red blood cells and platelets in the bone marrow, interfering with their normal production. The malignant plasma cells (also called "myeloma cells") produce abnormal proteins and form amyloid when they accumulate in the tissues, which can damage the kidneys or affect immune system function.

While the malignant plasma cells are most commonly found in the bone marrow, they may accumulate in any part of the body. These accumulations are known as "plasmacytomas." They most commonly occur in the bones, skin, muscle or lungs. If the malignant cells form a single tumor, the tumor is called a "solitary plasmacytoma." The plasmacytoma can often be cured with radiation therapy alone, although it may recur or later develop into myeloma.

The term "smoldering myeloma" refers to a slow-growing type of myeloma in which malignant plasma cells produce too much of an abnormal antibody. Usually there are no symptoms at diagnosis, so this type of myeloma requires monitoring but no treatment. Patients need to be checked often for signs of progression to fully developed myeloma that requires treatment.

In most patients with myeloma, the disease already involves multiple sites at the time of diagnosis. Because of this, the term "multiple myeloma" is sometimes used to refer to the disease in its most common form.

Signs and Symptoms

In the early stages of myeloma, some patients have no signs or symptoms of the disease. It is sometimes detected before symptoms appear, when results of laboratory tests done as part of a routine medical examination show abnormalities in the 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 the following:

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

R for renal failure (poor function of the kidneys that may be due to deposits of monoclonal protein in the kidneys)

A for anemia (low red blood cell count)

B for bone abnormalities (lesions)

Patients with one or more of the CRAB criteria, or with recurrent infections, are considered to have myeloma that requires treatment. Those who do not exhibit any of these symptoms are classified as having smoldering myeloma and may be monitored with a watch-and-wait approach (see *Smoldering Myeloma* on page 15).

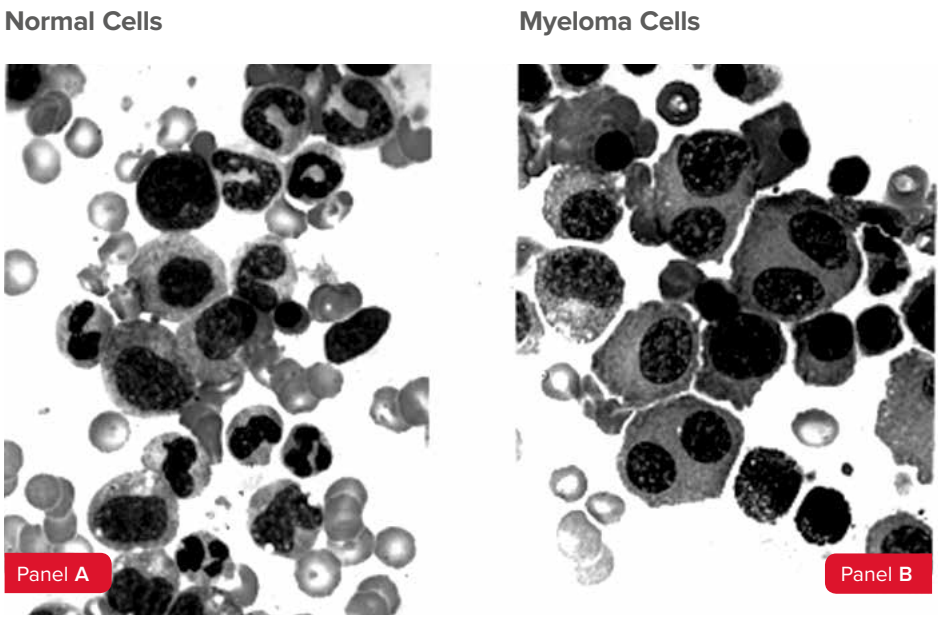
Effects on Bone. Bones are constantly in a process of remodeling, maintaining a balance between bone destruction and formation. Myeloma causes an imbalance, with greater bone destruction and less new bone formation. This

may result in bone thinning (osteoporosis) or holes in the bones (lytic lesions). Bones may break easily from activities as simple as coughing. The damage is most commonly found in the back or ribs, but it can occur in any bone. The pain is usually constant and made worse by movement. Bone lesions are present in about 80 percent of myeloma patients, most commonly in the spine and pelvis, but could affect any bone. Bone lesions are not usually found in joints.

When more bone destruction than bone formation occurs, calcium may be released into the blood. If the level becomes too high, patients may experience symptoms such as confusion, increased blood pressure, nausea/vomiting, constipation and excessive thirst.

Effects on Blood and Marrow. When myeloma cells crowd out the normal bone marrow cells, the decrease in the number of red blood cells or hemoglobin concentration causes anemia, which is characterized by fatigue and/or a pale complexion. Anemia occurs in approximately 75 percent of myeloma patients. The number of white blood cells may also be decreased, resulting in recurrent infections, most commonly of the urinary or respiratory tract. The number of platelets (cell fragments that help the blood to clot) is sometimes also low, resulting in easy bruising or bleeding. Myeloma cells accumulate in an uncontrolled manner and form tumors in the marrow (see **Figure 1**).

Figure 1. Normal Cells versus Myeloma Cells



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 a sign of abnormal plasma cells (myeloma cells).

Other Effects. High levels of antibodies (proteins) may be harmful to the kidneys. If proteins are entering the urine, it may look foamy and the patient may notice swelling of the legs.

An early symptom can be numbness, tingling, burning or pain in the hands and/or feet, a condition called "peripheral neuropathy," caused when antibodies attack the nerves.

Abnormal protein deposition (buildup), a condition called "amyloidosis," may occur in any part of the body, most commonly the heart and kidneys.

If antibody levels in the blood become too high, the blood may become thick (viscous), resulting in "hyperviscosity syndrome." This rarely occurs. Symptoms of hyperviscosity syndrome include abnormal bleeding, headaches, chest pain, decreased alertness and shortness of breath.

See *Complications, Side Effects and Supportive Care,* beginning on page 32, for more information.

Diagnosis

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

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

The results of blood tests that accompany periodic medical examinations may indicate the need for further evaluation for myeloma. These include an elevated protein level, anemia and abnormalities in kidney function or calcium levels.

Diagnostic Criteria. The diagnosis of myeloma is based on the following three principal findings:

- Malignant plasma cells. Test results must confirm the presence of more than 10 percent plasma cells in a bone marrow biopsy sample, or any atypical plasma cells indicating a plasmacytoma. In addition, pathology tests may provide information about genetic abnormalities that helps to predict the risk of relapse.
- Unusually large amounts of monoclonal protein, referred to as "M spike." Monoclonal proteins can be either 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)* and **Figure 2** on page 7.
- Evidence of end-organ damage as defined by the CRAB criteria (see **Table 1** on page 6).

The International Myeloma Working Group (IMWG) recently updated the diagnostic criteria for myeloma to include biomarkers, in addition to the existing CRAB features. **Table 1**, below, outlines the revised IMWG criteria for the diagnosis of myeloma.

Table 1. Revised International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma

Both of the following criteria must be met:

- Malignant plasma cells in the bone marrow ≥ 10% or presence of bony or extramedullary plasmacytoma, confirmed by biopsy
- 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 failure—creatinine clearance < 40 mL per minute or serum creatinine > 177 µmol/L (> 2 mg/dL)
    - **A**nemia—hemoglobin concentration of > 2 g/dL below the lower limit of normal, or a hemoglobin concentration of < 10 g/dL
    - **B**ony lesions—one or more osteolytic lesions found on x-ray, CT or PET-CT
  - Biomarkers
    - Clonal plasma cells in the bone marrow ≥ 60%
    - Ratio of involved/uninvolved serum free light chain ratio ≥ 100
    - One or more focal lesions found on MRI studies (at least 5 mm in size)

Key: CT = computed tomography; dL = deciliter; g = gram; IMWG = International Myeloma Working Group; L = liter; mg = milligram; mm = millimeters; mmol = millimole (a mole is an amount of a substance that contains a large number—6 followed by 23 zeros—of molecules or atoms; a millimole is one-thousandth of a mole); MRI = magnetic resonance imaging; osteolytic lesion = the dissolution of bone, especially the loss of calcium from bone; PET = positron emission tomography; PET-CT = positron emission tomography-computed tomography; µmol = micromole (one-millionth of a mole)

Source: Rajkumar, SV. Updated diagnostic criteria and staging system for multiple myeloma. *American Society of Clinical Oncology Educational Book* 2016; e418-e423. doi:10.14694/EDBK_159009

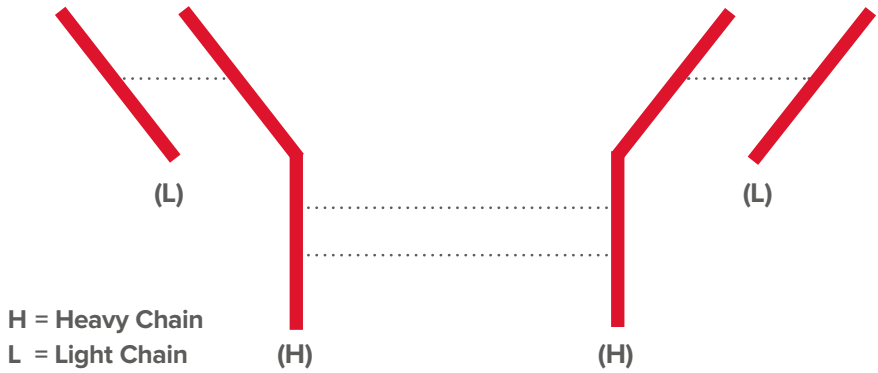
Monoclonal Immunoglobulin: Monoclonal Protein (M Protein) and Light Chains (Bence Jones Proteins). In healthy individuals, plasma cells normally produce proteins called "polyclonal immunoglobulins." These are antibodies that protect the body against all kinds of different invading viruses, bacteria or other infectious agents (antigens).

In myeloma, large amounts of a single antibody are noted as a "monoclonal immunoglobulin spike" or "monoclonal spike" (M spike), indicating that the protein came from cells that originally started as single, malignant cells.

Monoclonal protein (M protein) levels can be measured in blood and/or urine samples (see *Protein Electrophoresis Tests* on page 8), and these levels generally correlate with the extent of the myeloma. Increasing levels usually indicate progression of the disease and decreasing levels usually reflect response to treatment. A small number of patients have "oligosecretory myeloma," in which there is a low level of monoclonal protein detected, or "nonsecretory myeloma," in which no monoclonal protein can be detected. About 2 to 3 percent of patients have nonsecretory myeloma. In some of these patients only monoclonal light chains are produced, which are small pieces of the antibody. These are not always detected as an M spike. These patients can be monitored with a blood test that measures the level of serum free light chains.

An intact 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, referred to as kappa (k) and lambda (λ). See **Figure 2** below.

Figure 2. Immunoglobulin Molecule



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 coordinated process of making and attaching light chains and heavy chains fails in the malignant plasma cells, and light chains leave the cell unattached. They are small enough to pass through the kidneys and enter the urine, where they can be detected. Light chains in the urine are also referred to as "Bence Jones proteins."

This whole (intact) 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 coordinated process of making and attaching light chains and heavy chains fails in the malignant plasma cells. 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, Bence Jones proteins (free light chains) can sometimes make the urine appear foamy and they can cause injury to the kidneys (see *Urine Testing* below).

Each plasma cell produces one of five types of antibodies: IgG, IgA, IgM, IgE or IgD. Myeloma cells produce many copies of its antibody. The most common type of myeloma is IgG (occurring in approximately 50 percent of patients), in which the monoclonal protein is composed of two long chains and two short chains (see **Figure 2** on page 7). The next most common type is light chain myeloma, in which no intact immunoglobulin is produced. Some patients have the IgA type (about 20 percent of patients), and a small number of patients have the IgM type (about 0.5 percent of patients), the IgD type (about 2 percent of patients) or the IgE type of myeloma.

Protein Electrophoresis Tests. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are tests in which proteins in blood and urine samples are separated so that individual antibodies can be identified and quantified. These tests are done in conjunction with immunofixation, for example, serum immunofixation electrophoresis (SIFE), which identifies immunoglobulins in blood samples. All five types of immunoglobulins (IgG, IgA, IgM, IgE, and IgD) are measured by these tests. If present, an excessive production of a monoclonal immunoglobulin may be shown in laboratory test results as a spike on a graph (M spike). Most patients with untreated myeloma have a monoclonal immunoglobulin spike in serum, urine, or both.

Serum Free Light Chain (SFLC) Assay. Serum free light chain testing provides complementary information to the two 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 indicates an excess of abnormal plasma cells.

Additional Diagnostic Tests

Urine Testing. In some patients, the myeloma cells do not make a complete monoclonal immunoglobulin molecule with two heavy and two light chains (see **Figure 2** on page 7). Instead, they only make light chains. In these cases of "light

chain myeloma," serum test results may not show the characteristic increase of M protein (M spike), but there may be large amounts of monoclonal light chains in the urine.

A 24-hour urine sample test allows for an accurate measurement of the level of kidney function and can indicate possible kidney damage from myeloma. When there is damage to the kidneys, other proteins such as albumin may also be present in the urine. 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.

Blood Cell Count. A complete blood cell count (CBC) measures the numbers 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) is ordered, a test that also measures the number of the different types of white blood cells present in the blood.

Blood Calcium Level. 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.

Blood Chemistry Tests. Abnormal levels of certain chemicals may indicate that an organ is not working properly, or they may be caused by cancer or other health conditions. The following tests measure the levels of different substances in the blood.

- Blood urea nitrogen (BUN) is a waste product made by the liver which is filtered out of the blood and into the urine. High BUN levels may be a sign of kidney damage and must be monitored carefully in myeloma patients, since too much urea in the blood causes increased risk for developing kidney disease.
- Creatinine is a waste product from muscles that is also filtered out of the blood and into urine by the kidneys. High creatinine levels may be a sign of kidney damage.
- Albumin is the main protein of blood plasma. Low levels of this protein may be a sign of advanced myeloma, or indicate the presence of amyloidosis.
- β_2-microglobulin is a small protein made by many types of cells. A high level of β_2-microglobulin may be a sign of fast disease progression. Levels of this protein, together with levels of albumin, are significant and will be taken into account when staging myeloma.
- Lactate dehydrogenase (LDH) is a protein made by many different types of cells, including myeloma cells. High LDH levels may be an indication of advanced myeloma. This finding is also used in staging of myeloma.

Cytogenetic Analysis. Fluorescence in situ hybridization (FISH) is a type of laboratory test that uses special dyes to mark specific abnormal chromosomes in cells. Chromosomal abnormalities play a crucial role in identifying malignancies and determining the risk of relapse. 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 11, shows the most common cytogenetic abnormalities in myeloma.

These abnormalities can indicate how rapidly the disease may progress and predict the chances of a long-lasting response to certain therapies. These cytogenetic findings are used to classify myeloma as “high risk” or “standard risk.”

Next-Generation Sequencing (NGS). This is a broad term encompassing a number of modern technologies that increase the speed and reduce the cost of DNA (deoxyribonucleic acid) sequencing. Next-generation sequencing allows researchers to sequence DNA and RNA (ribonucleic acid) much more quickly and cost effectively than they could with older technologies. It identifies mutations present in the genes of the myeloma cells. Since the expression levels of these genes and also how (or if) they are mutated influence the behavior of the myeloma cells, these techniques may be helpful in better predicting outcomes and developing new and improved targeted therapies. This is currently being done on a research basis but may soon be used in routine practice.

Table 2. Most Common Cytogenetic Abnormalities in Myeloma

Cytogenetic Abnormality	Gene(s)/ Chromosomes Affected	Prognostic Risk in Smoldering Myeloma	Prognostic Risk in Myeloma
Trisomic myeloma	Trisomies of one or more odd-numbered chromosomes	Intermediate	Standard
IgH translocated multiple myeloma:			
t(11;14) (q13;q32)	*CCND1* (cyclin D1 gene)	Standard	Standard
t(4;14) (p16;q32)	*FGFR3* and *MMSET*	High	Intermediate
t(14;16) (q32;q23)	*C-MAF*	Standard	High
t(14;20) (q32;q11)	*MAFB*	Standard	High
Other IgH translocations	*CCND3* (cyclin D3 gene) t(6;14) (p21;q32)	Standard	Standard
Combined IgH translocation/trisomy	Trisomies plus any one IgH translocation	Standard	IgH translocation makes this higher risk, however, the trisomy may make prognosis better
Isolated monosomy 13 or 14		Standard	Effect on prognosis not clear
Gain(1q21)	*CKS1B, ANP32E*	High	Intermediate
Del(17p)	*TP53*	High	High
Normal cytogenetics		Low	Standard

Key: del = deletion; Ig = immunoglobulin; p = the short arm of a chromosome (the upper half); q = the long arm of a chromosome (the lower half); t = a translocation between chromosomes; trisomies = three copies of a chromosome instead of two.

Source: Rajkumar, SV. Updated diagnostic criteria and staging system for multiple myeloma. American Society of Clinical Oncology Educational Book 2016; e418-e423. doi:10.14694/EDBK_159009. Rajkumar SV and Kumar S. Multiple myeloma: diagnosis and treatment. Mayo Clinic Proceedings. 2016;91(1):101-119.

Imaging Tests. The following imaging tests are a very important part of the diagnosis, staging and management of myeloma:

- **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)**. This imaging test is done in select cases. It uses a powerful magnet to measure water and fat in the body. It is useful for detecting abnormalities in the bone marrow signal and effects of disease on the spinal cord, known as "cord compression."
- **Positron emission tomography imaging and computed tomography (PET-CT) scan**. A PET/CT scanner combines the techniques of both PET and CT in one machine. A single imaging session is all that is needed to produce a PET-CT scan that reveals information about both the structure and function of cells and tissues in the body. It provides a more detailed picture of where the cancer is located in the body than either test can by itself, and it is the only imaging test used to evaluate treatment response.

Questions to Ask Your Doctor About Testing:

- What tests are necessary before I start treatment?
- When will the tests take place?
- Where will the tests take place?
- How long will the tests take?
- Will my insurance provider pay for all my tests? If not, is there someone who can help me to find out how I can get my tests covered?
- What are my options if my insurance plan does not cover the tests that are needed?
- Will the tests need to be repeated after the end of the induction (initial) treatment?

Staging and Prognostic Factors

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

For decades, a myeloma staging system called the "Durie-Salmon Staging System" has been used. The Durie-Salmon system measures the patient's hemoglobin concentration, the level of blood calcium and the presence of bone lesions visualized on imaging studies to determine the extent of the myeloma, the amount of the monoclonal protein (M protein) in the blood and urine, and the level of kidney function.

The "International Staging System (ISS)" for multiple myeloma uses the degree of increase in β_2-microglobulin and the degree of decrease in serum albumin levels to determine prognosis at the time of diagnosis. The ISS was recently revised to include an elevated lactate dehydrogenase (LDH) level or the presence of high-risk cytogenetic abnormalities to create a more powerful prognostic index. These measurements allow the doctor to classify the patient's myeloma as stage I, stage II or stage III. See **Table 3** on page 14.

Doctors also consider other factors in treatment planning, including:

- 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
- The risk of treatment-induced complications
- Whether treatment is required
- Which treatment approach to take

Table 3. Myeloma Staging Systems

Stage	Durie-Salmon Staging System	Revised International Staging System

I	**All of the following:**
	○ Hemoglobin concentration > 10.5 g/dL
	○ Serum calcium value normal or ≤ 12 mg/dL
	○ X-ray studies of bone showing normal bone structure (scale 0) or solitary bone plasmacytoma only
	○ Low M-component production rate
	  ○ IgG value < 5 g/dL
	  ○ IgA value < 3 g/dL
	○ Urine light chains < 4 g/24 hours
		○ Serum albumin > 3.5 g/dL
		○ Serum β_2-microglobulin < 3.5 mg/L
		○ No high-risk cytogenetic features
		○ 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 concentration < 8.5 g/dL
	○ Serum calcium value > 12 mg/dL
	○ X-ray studies of bone showing > 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
		○ AND one of the following:
		  ○ (a) High-risk cytogenetics
		  t(4;14)
		  t(14;16)
		  del(17p)
		  ○ (b) Elevated serum lactate dehydrogenase level

Key: del = deletion; dL = deciliter g = gram; Ig = immunoglobulin; L = liter; M-component = monoclonal component; M protein = monoclonal (myeloma) protein; mg = milligram; t = a translocation between chromosomes.

Treatment Options

New treatments may have been approved since this book was printed.
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The goals of treatment for myeloma patients are to reduce symptoms, slow disease progression, provide prolonged remissions and lengthen survival while preserving quality of life. The goals of research for myeloma treatment include developing curative therapies and improving quality of life during treatment.

Getting a Second Opinion. If you have been diagnosed with myeloma, you may want to consult one or more myeloma specialists before proceeding with a treatment plan, to make sure that you receive the therapy that is right for you. Many health insurance companies will authorize a second opinion. When you go to the appointment for a second opinion, make sure that all your medical records (including laboratory and imaging test results and the findings from your bone marrow aspiration and biopsy) are available for examination. Upon review of your medical records, the second doctor can either confirm a proposed treatment plan and/or suggest modifications. This review will also reassure you that you have explored all of your options.

Smoldering Myeloma. Some patients have minimal extent of disease and little evidence of disease progression at the time of diagnosis. This is referred to asymptomatic or "smoldering" myeloma. For patients without symptoms who have this indolent form of the disease, "watchful waiting" may be an appropriate approach. In the watch-and-wait approach, treatment is delayed until there are signs of disease progression. Frequent and careful observation by a doctor is required so that effective treatment can be started when the disease starts advancing. Patients with active (symptomatic) myeloma need immediate treatment.

Treatment Planning. In order to initiate treatment, patients must meet the diagnostic criteria for myeloma as outlined in **Table 1** on page 6. The treatment approach for each patient is customized based on a number of factors, including the:

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

Patients are advised to consult a doctor who specializes in myeloma treatment and to discuss the most appropriate treatment option for their situation. Most treatment plans include a combination of different therapies.

Some patients will need supportive (palliative) 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 *Complications, Side Effects and Supportive Care* on page 32).

The following myeloma-specific therapies are used to treat disease progression and induce remission:

- Combination drug therapy (see **Table 5** on page 21)
- High-dose chemotherapy with one of three types of stem cell transplantation
  - Autologous
  - Standard allogeneic
  - Reduced-intensity allogeneic
- Radiation therapy for localized disease (for example, solitary plasmacytoma)
- New and emerging drug therapies (as part of clinical trials)

While there is no cure for 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, combinations of different drug therapies and the use of bisphosphonate drugs with autologous stem cell transplantation.

Drug Therapy. Systemic drug therapy (meaning treatment that travels through the bloodstream to kill malignant cells) is the main treatment for myeloma. The initial therapy for myeloma usually includes a combination of targeted agents and/or standard chemotherapy (see **Table 4** on page 20). This "induction" therapy is often followed by stem cell transplantation in patients who are eligible (see *Autologous Stem Cell Transplantation* on page 21).

For transplant candidates, drug treatment begins with an induction phase consisting of a combination of agents that do not cause marrow damage—for example, bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone (a combination known as VRD); bortezomib, cyclophosphamide (Cytoxan®) and dexamethasone (a combination known as VCD or CyBorD); or other combinations. Note that long-term treatment with lenalidomide may decrease stem cell production, so for transplant candidates, stem cell collection is often performed after three to six cycles, once a good treatment response has been achieved.

Researchers continue to study the most effective drugs and drug combinations for the treatment of myeloma, including newly diagnosed, refractory and relapsed cases. The following is a list of drug options for myeloma patients.

Proteasome Inhibitors (PIs). These drugs block the function of proteasome, leading to the accumulation of proteins in the cancer cells and thereby causing their destruction.

- **Bortezomib (Velcade®)** is given intravenously (IV) or subcutaneously (sub-Q or SC) and is approved by the Food and Drug Administration (FDA) to treat myeloma. It can also be used for retreatment of patients with relapsed myeloma.
- **Carfilzomib (Kyprolis®)** 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 myeloma who have received one to three prior therapies. It is also indicated as a single agent for the treatment of patients with relapsed or refractory myeloma who have received at least one or more prior therapies.
- **Ixazomib (Ninlaro®)** is an oral medication approved for use in combination with lenalidomide and dexamethasone for the treatment of myeloma 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 treatment injections.

Immunomodulatory Drugs (IMiDs). Immunomodulatory drugs act in multiple ways to kill myeloma cells and affect other cells in the bone marrow, including other immune system cells and structural cells. These drugs elicit a cancer suppressor response directed by the immune system. They are well tolerated and are often used in multiple combinations with other agents.

- **Lenalidomide (Revlimid®)** is an oral medication 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 (Pomalyst®)** is an oral medication which has been approved by the FDA for use 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 (Thalomid®)** is an oral medication that is FDA approved for use in combination with dexamethasone for the treatment of patients who have newly diagnosed myeloma.

Histone Deacetylase (HDAC) Inhibitors. These are substances that cause a chemical change that stops cancer cells from dividing.

- **Panobinostat (Farydak®)** is an oral medication that is FDA approved for use 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.

Monoclonal Antibodies. These 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" (harness) other parts of the immune

system to destroy cells that contain the antigen. Some monoclonal antibodies work by themselves and are therefore known as “naked antibodies”. Others are coupled with a chemotherapy drug or attached to a radioactive particle, so they 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.

- **Elotuzumab (Empliciti™)** is given intravenously and targets SLAMF7, a protein expressed on myeloma and natural killer (NK) cells but not on normal tissues. This drug is FDA approved for use in combination with lenalidomide and dexamethasone for the treatment of patients with myeloma who have received one to three prior therapies. It has also been approved in combination with pomalidomide and dexamethasone to treat adult myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- **Daratumumab (Darzalex®)** is a monoclonal antibody given intravenously that targets the CD38 surface protein on myeloma cells (CD stands for “cluster of differentiation”). It has been approved for use:
  - In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory myeloma who have received at least one prior therapy
  - In combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed myeloma who are ineligible for autologous stem cell transplant
  - In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
  - In combination with 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 and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent.

Daratumumab may interfere with blood typing. So it is important to notify the blood bank at treatment centers if a patient has received this medication, in case a blood transfusion is needed.

- **Melphalan hydrochloride (Evomela®)** is an alkylating agent given intravenously that is FDA approved for use as a:

- High-dose conditioning treatment prior to stem cell transplantation in patients with myeloma
- Palliative treatment in myeloma patients for whom no oral therapy options are appropriate

- **Denosumab (Xgeva®)** is a RANKL inhibitor that corrects the imbalance between bone formation and destruction found in myeloma. It is given subcutaneously and is FDA approved for the prevention of skeletal-related problems in patients with myeloma.

Bisphosphonates. Bisphosphonates are drugs that fight myeloma-related bone disease.

- **Pamidronate (Aredia®)** and **zoledronic acid (Zometa®)** are potent inhibitors of bone resorption and are both given intravenously. These drugs block osteoclasts (cells involved in bone breakdown) and alleviate the effects of bone disease by decreasing the pain, likelihood of fractures and high blood calcium levels 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 *Bisphosphonate use* on page 33). Bisphosphonate use is not recommended in patients with monoclonal gammopathy of undetermined significance (MGUS), unless osteoporosis is present.

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

Taking a drug by mouth has many benefits, including improved quality of life, convenience and time. Unfortunately, poor adherence to a prescribed oral drug regimen can result in the following: drug resistance; poor response to therapy; disease progression; increased doctor visits, laboratory tests and hospitalizations; and even death.

For additional information about oral drug adherence, including treatment barriers as well as solutions and strategies, please visit www.LLS.org/booklets to see the free LLS booklets *Myeloma Oral Treatment Adherence Facts* and *A Medication Resource for Myeloma Patients*.

Table 4. Some Drugs Used in the Treatment of Myeloma

Immunomodulatory Drugs (IMiDs)

- ○ Lenalidomide (Revlimid®)
- ○ Thalidomide (Thalomid®)
- ○ Pomalidomide (Pomalyst®)

Proteasome Inhibitors (PIs)

- ○ Bortezomib (Velcade®)
- ○ Carfilzomib (Kyprolis®)
- ○ Ixazomib (Ninlaro®)

Monoclonal Antibodies

- ○ Daratumumab (Darzalex®)
- ○ Elotuzumab (Empliciti™)
- ○ Denosumab (Xgeva®)

Histone Deacetylase Inhibitor (HDAC)

- ○ Panobinostat (Farydak®)

Selective Inhibitor of Nuclear Export (SINE)

- ○ Selinexor (Xpovio™)

Alkylating Agents (DNA-damaging Drugs)

- ○ Carmustine (BicNU®)
- ○ Cyclophosphamide (Cytoxan®)
- ○ Melphalan (Alkeran®)
- ○ Melphalan hydrochloride (Evomela™)

Antitumor Antibiotics

- ○ Doxorubicin (Adriamycin®)
- ○ Liposomal doxorubicin (Doxil®)

Antimetabolite

- ○ Cytarabine (Cytosine arabinoside, Ara-C, Cytosar-U®)

Bisphosphonates

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

Corticosteroids

- ○ Dexamethasone
- ○ Prednisone

New treatments may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Table 5. Some Drug Combinations Used to Treat 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
- Bortezomib (Velcade®) and liposomal doxorubicin (Doxil®)
- Daratumumab (Darzalex®), bortezomib, melphalan, prednisone
- Daratumumab (Darzalex®), lenalidomide (Revlimid®), dexamethasone
- Elotuzumab (Empliciti™), lenalidomide (Revlimid®), dexamethasone
- Panobinostat (Farydak®), bortezomib (Velcade®), dexamethasone
- Ixazomib (Ninlaro®), lenalidomide (Revlimid), dexamethasone

Stem Cell Transplantation. High-dose chemotherapy and stem cell transplantation are important parts of treatment plans for eligible, recently diagnosed myeloma patients. One of the following types of transplants may be used:

- Single or tandem autologous stem cell transplant
- Standard or reduced-intensity allogeneic stem cell transplant

Autologous Stem Cell Transplantation. The patient's own stem cells are collected for this type of stem cell transplant. If needed, a doctor may use **plerixafor (Mozobil®)**—which is FDA approved for use in combination with a granulocyte colony-stimulating factor (G-CSF)—to help mobilize stem cells and move them into the peripheral blood for collection. "Mobilizing" stem cells means stimulating them to move from the marrow into the bloodstream so that 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's bloodstream by IV infusion (similar to a blood transfusion). The goal is to "rescue" the bone marrow from the effects of the high doses of chemotherapy, infusing healthy stem cells in order to restore normal blood cell production. This procedure is associated with good response rates and remains the standard of care, after completion of primary therapy, for eligible patients. 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, bone marrow tests and imaging studies. Myeloma patients who have undergone an autologous transplant may require maintenance therapy.

Maintenance Therapy. The use of continued therapy to maintain a response obtained with induction therapy or stem cell transplantation is showing a benefit in overall survival rate. **Lenalidomide (Revlimid®)** is the preferred agent for post-transplant maintenance, based on the results of several clinical trials. Lenalidomide is FDA approved for patients with myeloma as maintenance therapy following an autologous stem cell transplant. It does not produce the neurotoxicity of other immunomodulatory drugs, such as thalidomide. However, there appears to be an increased risk for the development of a secondary cancer, especially after transplantation or after therapy with a regimen that contains melphalan. More information is needed about the effects of maintenance therapy on overall survival, as well as second cancer risk.

Tandem Autologous Stem Cell Transplantation. This term refers to a planned second course of high-dose chemotherapy and stem cell transplant within 6 months of the first course. According to recent studies, this should only be considered as a treatment option in patients who fail to achieve a good response with the first transplant, or in select patients with high-risk cytogenetic features, such as del(17p).

Standard and Reduced-Intensity Allogeneic Stem Cell Transplantation. These are other types of stem cell transplants that are used to treat certain types of blood cancer. The main difference between an autologous and an 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 an autologous transplant. Therefore, allogeneic transplantation has a limited role in myeloma treatment and it should only be done in the context of a clinical trial. Allogeneic transplantation is mainly considered to be a therapeutic option for young patients with high-risk disease who have experienced a relapse and are willing to accept the risk associated with this type of transplant, in exchange for a better chance at long- term survival. In a reduced-intensity allogeneic transplant, patients receive

lower doses of chemotherapy drugs and/or radiation before the transplant. This protocol may be safer than a standard allogeneic stem cell transplant, especially for older patients.

Talk to your doctor to find out if a stem cell transplant is a treatment option for you. **Please visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Radiation Therapy. This treatment uses high-energy rays (x-rays) to kill cancer cells; it may be used in select circumstances in myeloma treatment to kill malignant plasma (myeloma) cells. Radiation therapy is the main treatment for solitary plasmacytoma, and 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 areas of painful bone involvement the body.

Treatment Outcomes. It is not unusual for myeloma patients to live 10 years or longer after diagnosis. Outcomes are influenced by a series of patient factors, including disease stage, chromosome abnormalities, age and presence of other medical problems. Patients should discuss their own potential outcomes with their doctors.

Measuring Treatment Response

During myeloma treatment, patients should be monitored for treatment response and for symptoms related to the disease or its treatment (see **Table 6** on page 25). Treatment response should be evaluated after one or two cycles of therapy. Most of the same tests that were used to diagnose the disease may be used to monitor the response to treatment. These may include:

- Bone imaging studies, such as x-rays, positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. The combined PET-MRI scans can detect residual bone lesions that are still active in the body. Depending on the number and location of the lesions, a targeted therapy such as focal radiotherapy may be used as treatment.
- Blood tests to measure blood cell numbers (blood counts); monoclonal (M) protein, calcium and creatinine levels; and levels of free light chains
- Urine tests, such as a 24-hour urine collection that is tested for the presence of 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). This term refers to the low level of myeloma cells that are still present in the body, either

during or after treatment. A number of techniques can be used to detect MRD, including:

- Immunophenotyping of a bone marrow aspirate by flow cytometry. 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. For example, it can help in determining whether plasma cells in the marrow are normal or malignant. This technique uses methods that are widely available and does not require comparison to a previous sample, so it is particularly useful.
- Polymerase chain reaction using allele-specific oligonucleotide probes (referred to as ASO-PCR), usually performed on a bone marrow sample. This technique is used to expand trace amounts of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) 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 with a microscope. The technique can detect the presence of one malignant cell among 500,000 to 1 million healthy cells. This test is not commonly available in most clinical laboratories, so its use is limited.
- Next-generation sequencing (NGS) of either a bone marrow or blood sample. This 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. This test can detect one malignant plasma cell among 1 million bone marrow cells. The Food and Drug Administration (FDA) has approved the use of the NGS assay called clonoSEQ as a test for MRD in patients with myeloma or acute lymphoblastic leukemia (ALL).

In general, clinical trials have shown that patients with MRD-negative status (no detectable residual disease) have better outcomes than those with MRD-positive status (detectable residual disease), based on an MRD measurement. Other terms that are sometimes used in this context include "MRD-zero" (MRD-negative status based on several consecutive tests), "immunophenotypic complete response" (all of the criteria for complete response are met and plasma cells are normal, per flow cytometry tests), and "molecular complete response" (all of the criteria for complete response are met and there are no detectable signs of the disease by ASO-PCR and/or NGS). These techniques, not yet in general use, will likely be used more in coming years.

Please visit www.LLS.org/booklets to see the free LLS booklet *Minimal Residual Disease*.

Table 6. Some Terms Used to Describe Myeloma Treatment Responses

- **Remission**
  - No detectable disease
  - The terms “complete remission” (or “complete response”) and “partial remission” (or “partial response”) are sometimes used (see *Remission* on page 59).
- **Complete response**
  - No sign of monoclonal (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 disease based on bone marrow flow cytometry
- **Very good partial response**
  - A 90% or greater decrease in M protein level in the blood
  - Urine M protein level < 100 mg in 24-hour urine collection
- **Partial response**
  - A 50% or greater decrease of M protein level in the blood
  - A 90% reduction in M protein level in 24-hour urine collection
  - A 50% or greater reduction in the size of soft tissue plasmacytoma (if present at diagnosis)
- **Minimal response**
  - A reduction between 25% and 50% in M protein level in the blood
  - A reduction between 50% and 89% in M protein level in 24-hour urine collection
  - A 50% or greater reduction in the size of soft tissue plasmacytoma (if present at diagnosis)
- **Stable disease**
  - Not meeting criteria for a complete response, very good partial response, partial response, minimal response or progressive disease
- **Progressive disease**
  - At least a 25% increase in M protein level 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

Treatment Options for Relapsed and Refractory Myeloma

Almost all myeloma patients will experience relapse (when the disease returns after a remission), and/or the disease will become refractory (meaning it does not respond to treatment). The choice of a treatment regimen after relapse is dependent on a series of patient, disease and treatment-related factors, including:

- Previous therapy—if a previous therapy worked and was well tolerated, it can be considered for use again, along with stem cell transplantation.
- Rate of relapse—patients with rapidly progressing myeloma should be treated with more aggressive combinations. In contrast, patients with slowly progressing myeloma may be treated with a milder combination therapy.
- Patient health and comorbidities—these are key factors for choosing a treatment regimen, since most patients with relapsed myeloma are older than 70. The general health of the patient and the presence of other health conditions help to determine the type of therapy and dosage used.
- Genetic abnormalities—there is increasing evidence that, in high-risk patients in particular, the disease may progress if additional cytogenetic abnormalities develop over time. Disease progression will be taken into consideration because the treatment team will have to decide whether to re-use prior therapies (to which the patient may have become sensitized), or whether to use different and/or more aggressive treatment options.

In some instances, if the patient had a good response to a drug or combination of drugs initially, that treatment option may be repeated. Trying one or more of the other therapies that are typically used in initial treatment is another option. These include the following drug combinations:

- **Bortezomib (Velcade®), lenalidomide (Revlimid®), dexamethasone**
- **Carfilzomib (Kyprolis®), dexamethasone**
- **Carfilzomib (Kyprolis®), lenalidomide (Revlimid®), dexamethasone**
- **Daratumumab (Darzalex®), bortezomib (Velcade®), dexamethasone**
- **Daratumumab (Darzalex®), lenalidomide (Revlimid®), dexamethasone**
- **Elotuzumab (Empliciti™), lenalidomide (Revlimid®), dexamethasone**
- **Ixazomib (Ninlaro®), lenalidomide (Revlimid®), dexamethasone**

Bortezomib (Velcade®) is given intravenously (IV) or subcutaneously and is usually combined with other treatments. Bortezomib is approved by the Food and Drug Administration (FDA) for the treatment of myeloma patients who have previously responded to bortezomib (either alone or in combination with other drugs) and who relapsed at least 6 months after their prior bortezomib therapy.

Carfilzomib (Kyprolis®) is given intravenously and is approved by the FDA for use in combination with dexamethasone, or with lenalidomide plus dexamethasone, in patients with relapsed or refractory myeloma who have received one to three prior lines of therapy. It is also used as a single agent for patients with relapsed or refractory myeloma who have received at least one or more prior therapies.

Daratumumab (Darzalex®) is given intravenously and is approved by the FDA for use:

- In combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone, for myeloma patients 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 therapies including a proteasome inhibitor and an immunomodulatory agent or who have failed to respond to both a proteasome inhibitor and an immunomodulatory agent

Dexamethasone (Decadron®) is an oral medication. It is a corticosteroid hormone (glucocorticoid) used to treat myeloma.

Elotuzumab (Empliciti™) is an intravenous medication that is FDA approved for use in combination with lenalidomide and dexamethasone for myeloma patients who have received one to three prior therapies. Elotuzumab has also been approved in combination with pomalidomide and dexamethasone for adult myeloma patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

Ixazomib (Ninlaro®) is an oral medication approved in combination with lenalidomide and dexamethasone for the treatment of patients with myeloma who have received at least one prior therapy.

Lenalidomide (Revlimid®) is an oral medication approved for myeloma treatment in combination with dexamethasone and as maintenance therapy following autologous hematopoietic stem cell transplantation.

Liposomal doxorubicin (Doxil®), given intravenously, is a specially formulated version of the chemotherapy agent doxorubicin. A liposomal medication contains the active drug inside small, fat-like particles. This type of preparation is easier for the body to absorb and allows more medication to get to its target. 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 increases the time to disease progression, compared to bortezomib given alone. Doxorubicin is also approved by the FDA for use in treating other forms of cancer.

Panobinostat (Farydak®) is an oral medication that is approved by the FDA for use in combination with bortezomib and dexamethasone in myeloma patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent.

Pomalidomide (Pomalyst®) is an oral medication approved by the FDA for use in combination with dexamethasone in myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Selinexor (Xpovio™) is an oral medication approved by the FDA for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents and an anti-CD38 monoclonal antibody.

Thalidomide (Thalomid®) is an oral medication once used routinely for newly diagnosed myeloma patients, until the adoption of treatment with lenalidomide and bortezomib. Now, thalidomide is one of the drugs often used for treating relapsed/refractory myeloma. It is usually given in combination with either dexamethasone or other drugs.

The use of high-dose chemotherapy followed by autologous stem cell transplantation may also be an option for some patients with relapsed/refractory myeloma—those who have either not been treated with a transplant 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* on page 29).

Research and Clinical Trials

New approaches to myeloma treatment are being studied in clinical trials that hold the promise of increasing the rate of remission and finding a cure for myeloma. Many of these clinical trials are being supported by LLS research programs.

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 reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment options are discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find a clinical trial based on their needs and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

Research Approaches. A number of approaches are under study in clinical trials for the treatment of patients with myeloma.

The Promise Study: Screening Individuals at High Risk of Myeloma. This research study identifies, screens and tracks individuals who are at high risk of developing myeloma. The goal of the PROMISE study is to increase early detection of myeloma precursor conditions in order to develop new therapies that prevent disease progression and improve survival. The study is looking for individuals from 45 to 75 years of age who are African American, and/or individuals with a first-degree relative with a plasma cell disorder such as myeloma. All participation is online or by mail. Call, send an email or visit the study's website to learn more.

- Call: 617-582-7002
- Email: promisestudy@partners.org
- Website: promisestudy.org

Drugs and Drug Combinations. Recent advances in the treatment of myeloma have resulted in improved treatment response and overall survival rates in newly diagnosed patients and in patients with relapsed myeloma. Eventually, however, nearly all patients will experience a relapse of the disease 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.

Proteasome Inhibitors (PIs). These drugs block proteasome activity, leading to cancer cell death. Several studies are examining the efficacy and safety of PIs, in combination with other agents, for the treatment of newly diagnosed and also relapsed and refractory myeloma.

- **Marizomib** is a second-generation proteasome inhibitor that targets multiple activities in proteasome. It is under study for treatment of relapsed and refractory myeloma.
- **Oprozomib** is a new oral proteasome inhibitor that is being studied in various clinical trials for treating either newly diagnosed patients or patients with relapsed or refractory myeloma.

Patients With High-Risk Cytogenetic Abnormalities. A number of cytogenetic abnormalities are associated with poor prognosis, including (del)17p, t(4;14), t(14;16) and gain(1q21). See **Table 2** on page 11 for more information. Data from recent studies has shown that three-drug combinations may improve outcomes for patients with high-risk cytogenetic abnormalities, compared to two-drug combinations. An aggressive treatment approach should be used for patients in this category. This approach may require patients to have breaks from treatment to recover, or to have shorter treatment cycles than they would if they were being treated with less aggressive regimens.

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

For more information about all types of stem cell transplantation, please visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Immunotherapy. Various forms of immunotherapy are being studied in clinical studies, including:

- **B-Cell Maturation Antigen (BCMA).** This antigen, also called TNFRSF17 (part of the tumor necrosis factor superfamily of proteins), is an important cell surface protein that is involved in supporting the survival of myeloma cells. It is expressed at significantly higher levels in all myeloma cells, but not on other normal tissues (except normal plasma cells).
- **Dendritic Cell/Tumor Fusion Vaccines.** Proteins on the surface of myeloma cells may be especially well-suited targets for 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.

- **Monoclonal Antibodies.** These immunotherapy agents are increasingly being used to treat myeloma, both to target the cancer cells directly and to modulate the patient's immune system. While some monoclonal antibodies (called "naked" antibodies) work by themselves, others are coupled with a chemotherapy drug or attached to a radioactive particle (and are therefore known as "conjugated monoclonal antibodies").
  - **AMGEN-420** is a type of bispecific antibody that targets BCMA. Bispecific antibodies target the tumor and T cells, bringing them into contact, leading to cancer cell death.
  - **Isatuximab**, an investigational anti-CD38 monoclonal antibody, is being studied for the treatment of patients with relapsed and refractory myeloma. (CD is the abbreviation for cluster of differentiation.)
  - **Milatuzumab** is an anti-CD74 monoclonal antibody that is being evaluated for the treatment of patients with relapsed and refractory myeloma.
  - **Belantamab mafodotin** is an antibody drug conjugate (ADC) that combines an antibody that targets BCMA with the toxic substance monomethyl auristatin F. The antibody binds to the antigen on the surface of tumor cells and then is absorbed together with the toxic substance. After the ADC is internalized, the toxic chemical is released, causing the malignant cell's death.
  - **Ulocuplumab (BMS-936564)**, which targets CD184 (also known as CXCR4), is under investigation for use in patients with relapsed and refractory 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 cells. 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.
  - The B-cell maturation antigen (BCMA) is being targeted by CAR T cells in clinical studies for patients with relapsed or refractory myeloma.
  - Various ongoing studies are focusing on CAR T-cell therapies that target other cell antigens, such as CD19, CD38 and the signaling lymphocytic activation molecule F7 (SLAMF7), for the treatment of myeloma patients.

Maintenance Therapy. Recent studies have shown that other drugs may be good maintenance therapy options for newly diagnosed patients who are not candidates for stem cell transplantation. There are several ongoing maintenance therapy trials evaluating the effectiveness of single and combination therapies.

Contact our Information Specialists at (800) 955-4572 for more information about specific treatments under study in clinical trials.

Complications, Side Effects and Supportive Care

Supportive (palliative) care for myeloma helps manage the complications of the disease and the adverse side 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 side effects, physical immobility, sleep disturbances, nutritional deficits, depression, stress and anxiety. Each patient 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 issues causing or related to fatigue.

Erythropoietin (EPO) therapy. In some patients with severe anemia due to the effects of chemotherapy, the administration of an engineered form of the red blood cell growth factor called erythropoietin may alleviate the anemia and decrease the need for blood transfusions. However, some studies suggest that treating anemia too aggressively 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 just a troublesome medical problem for patients with myeloma; they can also contribute to the risk of dying from the disease. Patients with myeloma may have decreased ability 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 decrease in the number of white blood cells, which further contributes to the risk of infection. To prevent infections:

- Intravenous immunoglobulin therapy should be considered for patients who experience frequent and life-threatening infections.
- Pneumococcal and influenza vaccination should also be considered.

- Prophylactic treatment against *pneumocystis carinii* pneumonia, herpes and fungal infections is recommended if a high-dose drug regimen has been given.
- Herpes prophylactic treatment should be considered in patients who are receiving proteasome inhibitors or **daratumumab (Darzalex®)**, since they are associated with incidence of herpes zoster.

Bone Pain. Bone pain may occur due to bone thinning and lesions caused by the growth of myeloma cells in the bones. 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, including narcotics. Of note: nonsteroidal drugs should be avoided in patients with myeloma, given the increased risk of kidney failure. **Please visit www.LLS.org/booklets to see the free LLS booklet *Pain Management Facts*.**

Treatment options for bone pain include:

- **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 result from bone destruction. Because of the increased risk of developing osteonecrosis of the jaw (ONJ) that is associated with bisphosphonates, this treatment should be managed by an experienced oncologist, with close coordination between the oncologist and oral surgeon and/or dental specialist.

  Osteonecrosis of the jaw is an uncommon but serious condition that has occurred in some patients receiving bisphosphonates. Although no cause-and-effect relationship has been established between bisphosphonate therapy and osteonecrosis, it is suspected. Osteonecrosis of the jaw may develop when the jaw fails to heal after a minor procedure, 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 (a low red blood cell count), infection, poor dental health, alcohol abuse or cigarette smoking, poor nutrition, poor blood circulation or clotting problems.

  Before beginning therapy with intravenous bisphosphonates, it is important to have a dental examination performed by an experienced dentist who has seen and understands ONJ. 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 (non-invasive) 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 it is needed and can be helpful in some cases.

- **Denosumab (Xgeva®)** is a monoclonal antibody that has been approved by the Food and Drug Administration (FDA) to prevent bone fractures in myeloma patients. Denosumab is administered through subcutaneous injection. This medication is recommended when bisphosphonates cannot be prescribed due to potential damage to the kidneys.
- **Vertebroplasty and kyphoplasty** are surgical techniques that may be used to help myeloma patients who have back pain. In vertebroplasty, chemical cement is inserted into the damaged or broken vertebrae through a catheter. Kyphoplasty involves inserting and inflating a balloon in the vertebrae to get it into its normal position 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 between 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 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, in most cases, potentially even return it to normal. When this is not the case, some patients may need dialysis.

In rare cases, when patients have very recent or acute kidney failure due to high levels of antibody proteins in the blood, a procedure known as “plasmapheresis and exchange” may be helpful in limiting kidney damage, though this approach is controversial. It provides temporary removal of proteins from the blood,

which will accumulate again if the source of the problem (the myeloma) is not eliminated. 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.

Myelosuppression. Bone marrow is constantly producing red blood cells, white blood cells and platelets. Interruption or inhibition of this crucial function is called "myelosuppression." Chemotherapy agents, immunomodulatory drugs such as **lenalidomide (Revlimid®)** and proteasome inhibitors such as **bortezomib (Velcade®)** can cause myelosuppression. If not managed effectively, myelosuppression can be life threatening and interfere with treatment planning and quality of life. A reduction in the number of red blood cells can result in anemia, which can make patients feel extremely tired and experience shortness of breath. When there is a decrease in the number of neutrophils, the primary type of white blood cell, a condition called "neutropenia" occurs. Neutropenia can lead to serious infections that require antibiotic therapy and possibly hospitalization. Drugs, such as **filgrastim (Neupogen®)**, **pegfilgrastim (Neulasta®)** or **sargramostim (Leukine®)**, may be prescribed to treat neutropenia. When myelosuppression causes the depletion of the number of platelets in the blood, a condition called "thrombocytopenia" occurs. 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 possible 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 (Velcade®), carfilzomib (Kyprolis®), thalidomide (Thalomid®), pomalidomide (Pomalyst®)** and, less commonly, **lenalidomide (Revlimid®).** Other problems that can either cause or contribute to neuropathy include diabetes, nerve compression caused by vertebral fractures and vitamin deficiencies, particularly of 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 while receiving chemotherapy should tell their healthcare providers as soon as the symptoms appear. Often, 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. The term "deep vein thrombosis (DVT)" refers to the condition caused by a blood clot that forms in the deep veins of the body, usually in the legs. Patients who receive myeloma treatments that are associated with DVT risk are usually prescribed medication to reduce the risk of developing 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. A DVT can cause blood flow obstruction, pain and swelling.

Pulmonary embolism is a sudden blockage in a lung artery. It usually happens when a blood clot breaks loose, travels through the bloodstream and lodges in the arteries of the lungs. Depending on the size and number of clots that reach the pulmonary arteries, a patient may experience chest pain, shortness of breath and other potentially severe or even life-threatening effects. **Thalidomide (Thalomid®)** and **lenalidomide (Revlimid®)** 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 blood cell growth factors, for example **epoetin alpha (Procrit®)** or **darbepoetin alfa (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.

Please visit www.LLS.org/booklets to see the free LLS booklets *Blood Transfusion, Cancer-Related Fatigue Facts* and the *Side Effect Management* series for more information about managing side effects.

Hyperviscosity Syndrome. Occasionally, the concentration of monoclonal proteins in the blood of some myeloma patients is so high that it makes the blood "viscous" (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 blood cells slows down, and the work of the heart is increased by the difficulty of pumping blood through the body. This complication can lead to headaches, dizziness, weakness, fatigue, sleepiness, oozing from cuts and other symptoms.

Hyperviscosity syndrome is considered a medical emergency and requires urgent treatment with plasmapheresis and exchange. This procedure rapidly reduces the concentration of monoclonal proteins in the blood. Chemotherapy is needed as well, since plasmapheresis does not reduce the number of cells that are producing these abnormal proteins. If the patient does not receive chemotherapy to kill the myeloma cells, they will continue to produce the abnormal proteins that, with time, will accumulate at high levels again.

Cryoglobulinemia. In rare instances, monoclonal IgM may congeal in the blood and lead to poor circulation, especially if the body is exposed to cold temperatures, most commonly in the fingers, ears and nose. 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. Myeloma patients have an increased risk 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. **Please visit www.LLS.org/booklets to see the free LLS booklet *Acute Myeloid Leukemia* for more information.**

Financial Concerns

Myeloma patients are living longer primarily because of the development of new and effective drugs. It is estimated that the average myeloma patient will live more than 10 years from the time of diagnosis, and perhaps longer. The "triplet" and "quadruplet" drug combinations used in myeloma treatment include costly medications that require continuous use. The economic impact of these medications could result in financial burden for patients, limited access to medications and lower adherence to treatments.

Speak to your doctor if you have any concerns about being able to afford your medications. A member of your treatment team may be able to provide information and resources that can help. Health insurance plans may not cover all the costs of cancer care, but there are a number of resources (from organizations, foundations and prescription assistance programs) available to find assistance in paying for prescription drugs.

In addition, several major pharmaceutical manufacturers provide patient assistance or prescription assistance programs. These companies may be able to help by providing both insured and uninsured patients with either free or reduced-cost medications.

You can contact an LLS Information Specialist at (800) 955-4572 for information about the LLS Co-Pay Assistance Program and other financial assistance programs. For more information and resources to cope with the financial aspects of cancer care, please visit www.LLS.org/booklets to see the free LLS booklet *Cancer and Your Finances*.

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, along with good quality of life. Although myeloma remains incurable, the advent of less toxic, targeted therapies is making it possible to manage myeloma as a chronic disease in most patients. Myeloma survivors are advised to:

- Maintain regular follow-up appointments with their hematologists-oncologists. Their doctors will monitor them for signs of relapse and also be able to detect any side effects from treatment or the onset of other medical problems.
- Keep a record of the treatments they received. This will be helpful for the healthcare professionals who will be monitoring them for potential health problems after treatment ends. It should include the following information: the diagnosis; the names and dates of chemotherapy or other drugs taken; radiation treatment, surgery and transplantation information; information about any other treatments; the names and dates of any significant complications and the treatment received for those complications. This information can help their doctors to develop a personalized follow-up schedule for them.
- Have regular screenings 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 the risks of specific chemotherapy drugs used to treat myeloma, please visit www.LLS.org/booklets to see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Related Diseases

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. Monoclonal gammopathy of undetermined significance 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 finding of routine laboratory tests. Only 10 percent of patients with newly-diagnosed myeloma have a history of MGUS, and its associated risk of progression to myeloma is approximately 1 percent per year. Patients are usually monitored 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 (M) immunoglobulin produced by the malignant B lymphocyte is a very large type of immunoglobulin M (IgM), referred to as a "macroglobulin" (large globulin). **For more information, please visit www.LLS.org/booklets to see the free LLS booklet *Waldenström Macroglobulinemia Facts*.**

Primary Amyloidosis. This is an uncommon disease process associated with the accumulation of "amyloid" in tissues, 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 "amyloid light-chain (AL) amyloidosis," which is caused by the deposit of damaged immunoglobulin light chains (see **Figure 2** on page 7). In some patients with myeloma, the light chains made by plasma cells can result in the formation and deposition (buildup) of amyloid. This type of amyloidosis can occur either with or without overt myeloma and is called "primary amyloidosis." In myeloma patients who have primary amyloidosis, involvement of the heart, intestines or nerves can produce dysfunction in those organs, significantly complicating management of the disease.

In patients who have primary amyloidosis without myeloma, the number of plasma cells in the marrow may not be increased and the bones may not be affected. In these cases, the malignant B lymphocytes producing the light chains that build up in the tissues and form the amyloid are too few to be detected by a bone marrow biopsy. Diagnosis of amyloidosis relies on some of the same tests used to diagnose myeloma; however, occasionally it is necessary to perform biopsies of other sites, such as the abdominal fat pad, gums, colon,

heart or kidneys. Staging is determined based on the results of blood tests that indicate heart function, including tests to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) and either the troponin T or troponin I level. Many of the drugs that work against myeloma are also effective against amyloidosis, including corticosteroids, **melphalan, bortezomib (Velcade®)** and **daratumumab (Darzalex®)**, while **lenalidomide (Revlimid®)** should be used with caution. 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 called heavy chain diseases because the protein made by the malignant lymphocytes is an incomplete immunoglobulin (the heavy chain of the immunoglobulin). See **Figure 2** on page 7. A 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, corticosteroids and, in some cases, radiation therapy.

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 2** on page 7). 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 eliminate too much protein in the urine). Approximately 50 to 60 percent of patients with LCDD have 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. This is an uncommon marrow disorder related to myeloma. POEMS is an acronym representing the five most common features of the syndrome:

- **P** for peripheral neuropathy
- **O** for organ enlargement
- **E** for endocrine gland dysfunction
- **M** for monoclonal plasma cells and monoclonal immunoglobulin
- **S** for skin changes

Peripheral neuropathy is often the most disabling feature of the syndrome and can include progressive weakness of the arms or legs. Liver or spleen enlargement is less common. The bone alterations related to the accumulation of plasma cells in the marrow are different from bone alterations in classic myeloma (the marrow looks denser than normal, rather than less dense). Thyroid or sex hormone deficiencies caused by endocrine gland dysfunction may require hormone replacement therapy. Other features not included in the POEMS acronym are high red blood cell or platelet counts, extravascular volume overload (swelling) and lung disease. Patients can benefit from radiation or chemotherapy treatment and, in some cases, from autologous stem cell transplantation.

Incidence, Causes and Risk Factors

Myeloma is a relatively rare blood disease. It generally occurs in adults older than 50 years (see **Figure 3** below). The median age at diagnosis is 69 years. Myeloma affects slightly more men than women, and the incidence is more than twice as high in blacks as it is in whites.

Figure 3. Myeloma: Age-Specific SEER Incidence Rates 2011-2015

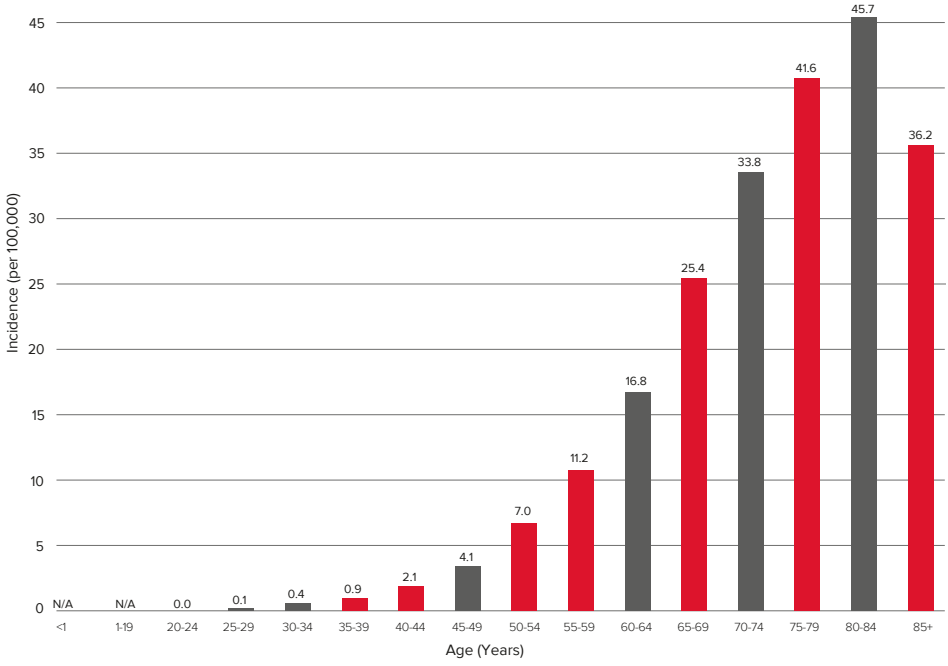


Figure 3. The horizontal axis shows the age at diagnosis, in 5-year increments, of people in the United States who develop myeloma. The vertical axis represents the number of new cases of myeloma per 100,000 people. Thus, the risk of myeloma is about 10 times greater in those 75 to 79 years old (about 41.6 cases/100,000 people) compared to those 45 to 49 years old (about 4.1 cases/100,000 people).
Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, Trends in SEER (Surveillance, Epidemiology, and End Results Program) SEER Cancer Statistics Review 1974-2015.

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 B lymphocyte (B cell). Normally, some B lymphocytes develop into plasma cells which produce the antibodies that help the body fight infection. In myeloma, the B lymphocyte becomes a malignant (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 are described below.

- 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—The incidence is higher in people with a history of monoclonal gammopathy of unknown significance. See *Monoclonal Gammopathy of Undetermined Significance (MGUS)* on page 39.
- Environmental factors—Some studies are investigating a link between the development of myeloma and exposure to radiation or certain kinds of chemicals, such as pesticides, fertilizers and Agent Orange.
- Obesity—Research suggests that obese people have a higher incidence of myeloma.
- Presence of chronic immunodeficiency
- Presence of known inflammatory diseases or conditions (for example, cardiovascular disease or type II diabetes)

Firefighting. Some studies indicate that firefighters have a statistically significant higher risk for multiple types of cancer than the general population. It is estimated that firefighters are at a 1.53 times higher risk of developing myeloma, compared to the risk for members of the general American public.

Two recent studies examined whether exposure to chemicals from the wreckage of the World Trade Center (WTC) disaster, during rescue and recovery efforts after the September 11, 2001 attacks, increased firefighters' risk of developing cancer. One study indicated that there may be a link between WTC firefighters and monoclonal gammopathy of undetermined significance (MGUS), a disease that is considered a precursor to myeloma. The other study estimated that more WTC firefighters will continue to develop certain types of cancer than would be expected if they had not been exposed to the area of the disaster.

Please visit www.LLS.org/booklets to order the free *Firefighters and Cancer Risk* awareness postcards. For information on the World Trade Center Health Program, see pages 48-49.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- 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

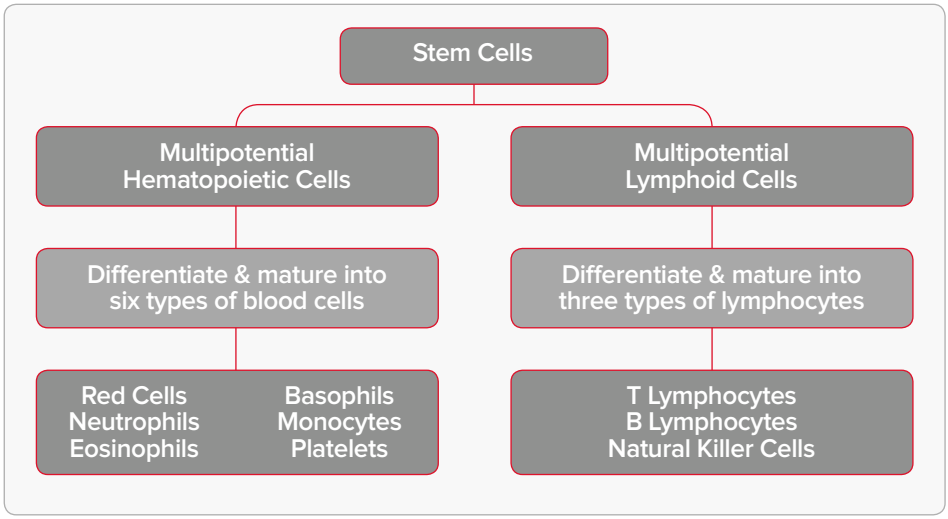
Blood cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 4** on page 45.

Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
   - These make up a little less than half of the body's total blood volume.
   - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
2. Platelets (cells that help blood clot)
   - These are small cells (one-tenth the size of red blood cells).
   - They help stop bleeding from an injury or cut.
   - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (or WBCs, the cells that fight infections), including:
    - Neutrophils and monocytes. These are cells called “phagocytes” that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
    - Eosinophils and basophils. These are the WBCs that respond to allergens or parasites.
    - Lymphocytes. These are the WBCs found mostly in the lymph nodes, spleen and lymphatic channels that are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
        - T lymphocytes (T cells)
        - B lymphocytes (B cells)
        - Natural killer cells (NK cells)

Figure 4. Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

Bone Marrow. In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, 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 blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called "apheresis" is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions and to make the most of the knowledge and skills of the members of your healthcare team.

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, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email: InfoCenter@LLS.org
- Live online chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists

Clinical Trial Support Center. Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find a clinical trial according to their needs and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

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

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

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. Please call or visit our website for more information.

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

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

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. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. Please visit www.LLS.org/chat to join.

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 the nearest chapter, please call or visit our website.

- 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 to obtain our directory.

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. Please call or visit our website for more information.

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

Additional Help for Specific Populations

Información en español (LLS Information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans 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 or visit the web page below.

- Call: (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 who were 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 either in the NYC disaster area, or who lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please call the WTC Health Program or visit their webpage.

- Call: (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 the National Institute of Mental Health (NIMH) or visit their website.

- Call: (866) 615-6464
- Visit: www.nimh.nih.gov and enter “depression” in the search box

Health Terms

Albumin. A major protein in the blood that plays a role in fighting infections and building or repairing muscle tissue. The normal reference 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 laboratory uses to process the blood sample.

Allele-Specific Oligonucleotide Polymerase Chain Reaction (ASO-PCR). An approach to measure patient-specific (or "allele- specific") minimal residual disease (MRD) levels by PCR, using short stretches of DNA called oligonucleotides.

Allogeneic Stem Cell Transplantation. A treatment that uses stem cells from a healthy donor to restore a patient's marrow and blood cells. First, the patient is given a conditioning therapy (high-dose chemotherapy, either with or without total body radiation) to treat the blood cancer. This is done to "turn off" (deactivate) the patient's immune system so that the donor stem cells will not be rejected. A type of allogeneic transplant called "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. See Reduced-Intensity Stem Cell Transplantation. **For more information, please visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Amyloid. In myeloma, an abnormal protein made by malignant plasma cells. An amyloid deposit (buildup) 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 blood 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 specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles, such as bacteria, viruses and harmful toxins.

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 donated blood and returning the unneeded parts to the donor's bloodstream. The process, also called "hemapheresis," circulates blood from a donor through a specialized machine and then back to the donor through an IV line. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white blood 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 the 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 a 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 (palliative) 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, please visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

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

Bence Jones Protein. An abnormal protein (light chain), 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, a normal immunoglobulin molecule is too large to pass through the kidneys in large amounts, so it is present in the blood but usually not in the urine.

β_2-microglobulin. A cell protein found in the blood. A high level of β_2-microglobulin molecule may be a sign of faster-growing myeloma. 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 are helpful in preventing or minimizing bone loss. Bisphosphonates help slow bone loss by turning off osteoclasts (cells that break down bone) so that they cannot dissolve bone. Bone thinning (osteoporosis) and fractures are major problems for patients who have myeloma.

Bone Marrow. A spongy tissue in the hollow, central cavity of the bones, where blood cell formation occurs. 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 bones, the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the bloodstream as it passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A procedure done to obtain a bone marrow sample so the cells can be examined for abnormalities at a lab. 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 with a special needle inserted through the bone into the marrow. The sample is examined under a microscope and assessed not only for the presence of blood cancer but also the extent of the disease. The cells obtained can also be used for cytogenetic analysis, flow cytometry and other tests.

Bone Marrow Biopsy. A procedure done to obtain a bone marrow sample so the cells can be examined for abnormalities at a lab. 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 and bone, a special hollow needle is used to remove a sample 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 have been killed by therapy. Myeloma cells can stick tightly to bone marrow particles called "spicules," so it is often important to perform both an aspiration and biopsy, since the results from the aspirate sometimes underestimate the extent of the disease.

Chemotherapy. The use of chemicals (drugs/medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and some act by injuring 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. Bone marrow cells are also sensitive to these chemicals, which cause injury to the gastrointestinal tract, skin and hair follicles, leading to mouth sores and hair loss. These are the most common side effects of chemotherapy.

Computed Tomography (CT) Scan. A technique for obtaining images of body tissues and organs. X-ray transmissions are converted into detailed images, using a computer to synthesize the 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 body structures, as well as of plasmacytomas, before, during and after treatment. This type of scan is sometimes done with an intravenous and/or oral contrast. The contrast helps doctors get a more detailed picture of what is going on inside the body, 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 cancer, determining treatment approaches and monitoring treatment response. 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 blood cells are called “interleukins.”

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

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

Extramedullary Plasmacytoma. See Plasmacytoma.

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

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

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

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

Hematopathologist. See Pathologist.

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 calcium in the blood and urine. Hypercalcemia can contribute to weakness, loss of appetite, nausea, confusion, constipation, lethargy and other symptoms, as well as to kidney damage.

Immunoglobulin (Ig). A protein that helps the body fight infection. 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. Also called "gamma globulin."

Immunophenotyping. Use of flow cytometry to identify each individual type of cell in a sample (for example, cells in a marrow aspirate). This is done using antibodies that recognize different cell surface proteins that are characteristic for each cell type and are therefore 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 linked to heavy chains, make up the antibody molecule of an immunoglobulin. There are two types of light chains, referred to as kappa (k) and lambda (λ), and they are unrelated to the immunoglobulin classes (IgA, IgD, IgE, IgG and IgM). An example of a light chain is a Bence Jones protein. See Bence Jones Protein; Heavy Chains; Immunoglobulin (Ig).

Lymphocyte. A type of white blood cell that is essential to the body's immune system. There are three major types of lymphocytes: 1) B lymphocytes, which produce antibodies to help combat infectious agents, such as bacteria, viruses and fungi; 2) T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and 3) 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.

Magnetic Resonance Imaging (MRI) Scan. A test that provides detailed images of body structures. It differs from the computed tomography (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. An MRI scan is often done with an intravenous contrast agent that, while different than the one used with CT scans, can also cause kidney damage in rare cases. All patients scheduled for a CT or MRI scan should let the radiology technicians know that they have myeloma and drink lots of fluids before the scan (if allowed by the test procedure) and after it is completed.

Minimal Residual Disease (MRD). A low level of myeloma cells that are still present in the body either during or after treatment. It is detected by techniques that are more sensitive than electrophoresis and immunofixation studies of the blood and/or urine and bone marrow testing by routine pathology alone. 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

they are targeted against. The antibodies are used therapeutically in three ways: 1) as "naked" antibodies (monoclonal antibodies); 2) as antibodies to which radioactive isotopes are attached (radioimmunotherapies); and 3) as antibodies to which toxins are attached (immunotoxins).

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

M Protein. The simplified term 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 blood samples, 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, while decreasing M protein concentration in the blood usually reflects regression of the myeloma. In rare cases, myeloma cells stop making M protein, and based on laboratory test results, the condition can appear to be improving while it is actually progressing, and the patient usually feels worse. This situation can often be detected through a bone marrow aspiration and biopsy; the findings will usually show increasing numbers of plasma cells. M protein is also referred to as "M component" and "M spike," in reference to lab test results.

Mutation. A change in the DNA sequence of a cell. "Germ cell mutations" are mutations present in egg or sperm cells that can be transmitted from parents to their biological children. "Somatic mutations" are mutations that arise in a specific tissue cell after birth and can result in the growth of that cell into a tumor. Most types of cancer arise from a somatic mutation. In leukemia, lymphoma and myeloma, an immature marrow (blood-forming) or lymph node cell undergoes a somatic mutation (or mutations) that lead(s) 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 analysis. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the original mutated cell (called an oncogene).

Myeloma Cells. Malignant plasma cells that are the defining characteristic 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 types of blood cancer or 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 infections. A neutrophil may be referred to as "poly" (polymorphonuclear neutrophil) or "seg" (segmented neutrophil) because its nucleus has several lobes.

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

Nonsecretory Myeloma. A form of myeloma that occurs in a small percentage of patients, in which abnormal proteins cannot be detected through urine protein electrophoresis (UPEP), serum protein electrophoresis (SPEP) or serum immunofixation electrophoresis (SIFE). However, most of these patients have kappa (κ) or lambda (λ) free 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 Myeloma. A form of myeloma that occurs in a small percentage of patients, in which a low a level of abnormal protein is detected.

Pathologist. A doctor who identifies diseases by studying tissues under a microscope. A hematopathologist is a pathologist who studies diseases of blood cells by examining blood, bone marrow, lymph node and other tissue samples. In addition to examining samples with a microscope, a hematopathologist also analyzes laboratory, 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 determines the best treatment based upon the diagnosis.

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

Plasma Cell. A cell derived from the antigen-induced activation and maturation of B lymphocytes; it is the main type of B cell that produces antibodies. Myeloma is a cancer of plasma cells; "myeloma cells" are malignant plasma cells.

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 an "extramedullary plasmacytoma."

Platelets. Small cell fragments that stick to the site of a 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 platelets) or thrombocythemia and thrombocytosis (too many platelets).

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 done as part of testing to evaluate minimum residual disease (MRD).

Positron Emission Tomography (PET) Scan. A test used to detect cancer sites in the body, in which glucose (a type of sugar) is marked with a positron particle that emits a radioisotope, such as fluorine 18. Cancer cells utilize more sugar than in normal tissues, so the isotope becomes concentrated in areas where cancerous cells are present. PET is combined with computed tomography (CT) to establish the precise location of cancer cells, a procedure called "PET-CT." A PET scan can provide complementary information to that obtained by a magnetic resonance imaging (MRI) scan or other radiology tests, but each has its limitations. For example, a very small accumulation of myeloma cells may be undetectable by any or all of these tests.

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

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation now being studied 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, compared to the doses used for standard allogeneic 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 research 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, please visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Refractory. Term used to describe a disease that is either progressing despite ongoing treatment, does not respond at all to treatment, or starts to progress significantly within 60 days of stopping treatment.

Relapse. Term used to describe a disease that initially responds to therapy but then begins to progress. Usually the disease must begin to progress 60 days or more after treatment ends for it to be considered relapsed.

Remission. The disappearance of evidence of a disease, usually as a result of treatment. The terms “complete remission” (or “complete response”) and “partial remission” (or “partial response”) are also used to further classify the remission. See **Table 6** on page 25.

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

Serum Free Light Chain Test. A diagnostic test that measures free light chains (protein components) in blood samples. It is better to perform this test on serum rather than urine samples 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 myeloma cells.

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

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

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

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

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 (monoclonal protein) being produced by myeloma cells.

Urine Protein Electrophoresis (UPEP). A test that uses a 24-hour urine sample to check for the presence of M protein (monoclonal protein) and to detect light chain myeloma.

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

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NOTES

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The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. Find out more at **www.LLS.org**.

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