

MULTIPLE  
MYELOMA  
**RESEARCH**  
**FOUNDATION**



**MMRF**

Accelerating the  
Search for a Cure

# Multiple Myeloma: Disease Overview

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# MMRF

**Accelerating the Search for a Cure**

The Multiple Myeloma Research Foundation (MMRF) is an international nonprofit foundation driven by a single purpose: **to accelerate the search for a cure for multiple myeloma.**

**The MMRF focuses on five goals:**

- Raising awareness of multiple myeloma
- Funding the most promising myeloma research
- Fostering collaboration among researchers worldwide
- Educating the myeloma community
- Advocating for optimal patient care

[www.multiplemyeloma.org](http://www.multiplemyeloma.org)

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## Introduction

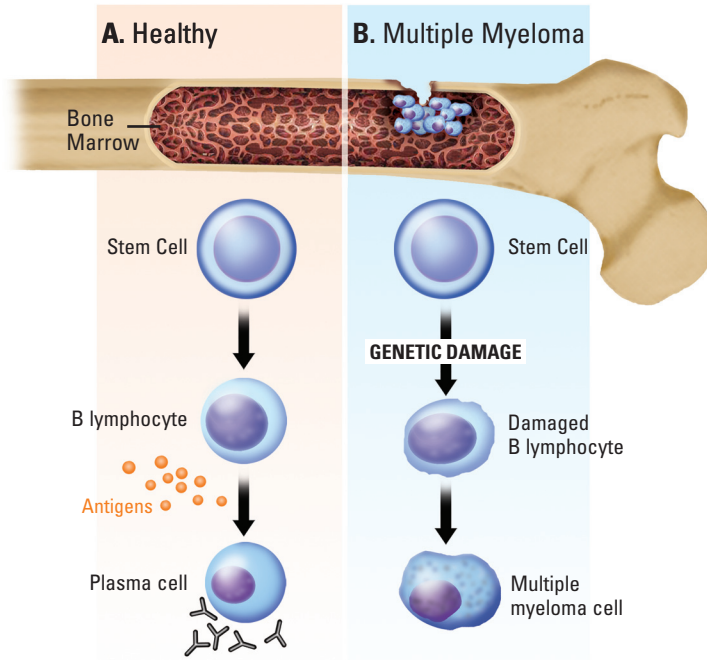
This booklet is designed primarily to help newly diagnosed patients, and their friends and families, better understand multiple myeloma. It offers an overview of the disease as an addition to the information provided by your doctor. Learning as much as you can about multiple myeloma will help you be more involved in making treatment decisions. Words you may not know are **bolded** throughout the text and defined in the Glossary (page 23).

The booklet explains what myeloma is and how it develops within the body. Discussions of symptoms, diagnosis, and staging, as well as an introduction to the standard treatment options for myeloma are included. A separate booklet produced by the Multiple Myeloma Research Foundation (MMRF), *Multiple Myeloma: Treatment Overview*, explains current standard therapy and emerging treatment options being tested in clinical trials. Please read that booklet to learn more about your treatment choices. The booklet, *Multiple Myeloma: Supportive Care*, provides detailed information on the symptoms and complications of myeloma and how they are treated. Another MMRF booklet, *Multiple Myeloma: Stem Cell Transplantation*, explains the process of stem cell transplantation and the various types of transplants used in the treatment of myeloma.

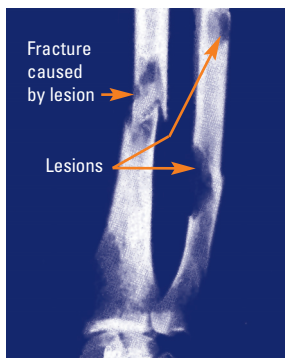
The information in this booklet is not intended to replace the services of trained health-care professionals (or to be a substitute for medical advice). Please consult with your healthcare professional if you have specific questions relating to your health, especially questions about diagnosis or treatment. To get copies of these booklets for yourself, your doctor's office or cancer center, or your support group, contact the MMRF at 203-229-0464 or [info@themmrf.org](mailto:info@themmrf.org).

## What is multiple myeloma?

Multiple myeloma (also known as myeloma or **plasma cell** myeloma) is a hematologic cancer, or a type of cancer that develops in the blood, **bone marrow**, or **lymph nodes**. Specifically, multiple myeloma develops in the bone marrow, the spongy substance that fills the center cavity of bone. One type of cell in bone marrow is the plasma cell, which produces **immunoglobulins (Igs)**, proteins that help fight disease and infection. In myeloma, normal plasma cells transform into malignant cells, which multiply and interfere with the production of all types of blood cells. These cells also produce large quantities of **monoclonal (M) protein**. Myeloma cells and M protein crowd out normal blood cells and Igs in the bone marrow. In addition, groups of the abnormal cells penetrate the solid part of the bone and may cause **osteolytic lesions**, or soft spots in the bone (Figure 1). These lesions are the hallmark of multiple myeloma and occur throughout much of the skeleton (Figure 2).



**Figure 1.** In healthy bone marrow (A), hematopoietic **stem cells** produce all types of blood cells, including **lymphocytes**, a type of **white blood cell**. **B lymphocytes** develop into normal plasma cells when foreign substances (antigens) enter the body. Normal plasma cells make up only a small percentage of the cells in the bone marrow. In multiple myeloma (B), genetic damage to a developing B lymphocyte transforms the normal plasma cell into a malignant cell (multiple myeloma cell). The malignant cell multiplies, leaving less space for normal blood cells in the bone marrow, and produces large quantities of M protein. In addition, myeloma cells release substances that stimulate the activity of cells that dissolve bone (**osteoclasts**) as part of the normal process of bone repair and growth. The development of cells that form bone (**osteoblasts**) cannot keep up with the production of osteoclasts, and the bone becomes weaker, increasing the risk of fractures, especially in the rib cage and spine (Figure 2). Multiple myeloma cells can also penetrate into the solid portion of the bone, creating soft spots in the damaged tissue (osteolytic lesions).

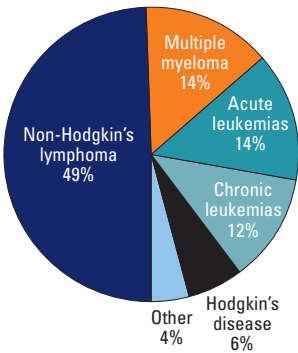


**Figure 2.** Myeloma cells in the bone marrow cause osteolytic lesions, which appear as “holes” on an x-ray. Weakened bones increase the risk of fractures, as shown in this x-ray of a forearm. DeVita Jr VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. 1997:2350. Adapted with permission from Lippincott Williams & Wilkins.

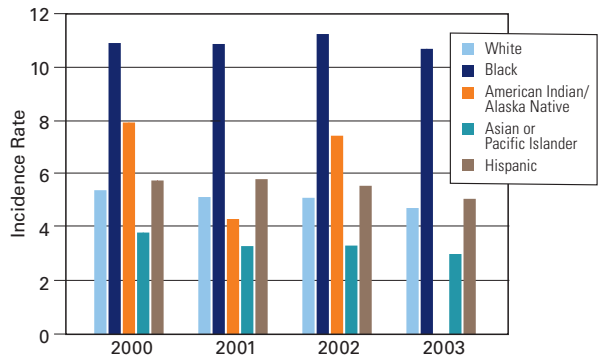
## How common is myeloma?

Multiple myeloma is the second most prevalent blood cancer, after non-Hodgkin's lymphoma, occurring in more individuals than any of the leukemias or Hodgkin's disease (Figure 3). It makes up approximately 1% of all cancers and 2% of all cancer deaths. The American Cancer Society estimates that about 16,570 new cases of multiple myeloma will be diagnosed during 2006. The prevalence of disease varies according to gender, age, and race or ethnicity.

Multiple myeloma is more common among men than women and develops twice as often among black individuals than among white individuals (Figure 4). The disease occurs more frequently with increasing age, with an average age of 68 years at the time of diagnosis.



**Figure 3.** Multiple myeloma is the second most common blood cancer, occurring more often than any type of acute or chronic leukemia or of Hodgkin's disease.



**Figure 4.** The prevalence of multiple myeloma varies according to race/ethnicity, with the highest rate in the black population and the lowest rate in the Asian or Pacific Islander population.

## What causes myeloma?

To date, no cause for myeloma has been identified. Research suggests possible associations with a decline in the immune system, particular occupations, exposure to specific chemicals, and exposure to radiation. However, there are no strong associations, and in most cases, multiple myeloma develops in individuals who have no clear risk factors. Multiple myeloma may be the result of several factors acting together. It is uncommon for myeloma to develop in more than one member of a family.

## How does myeloma affect the body?

The primary effect of multiple myeloma is on the bone. The blood and the kidneys are also affected (Figure 5).

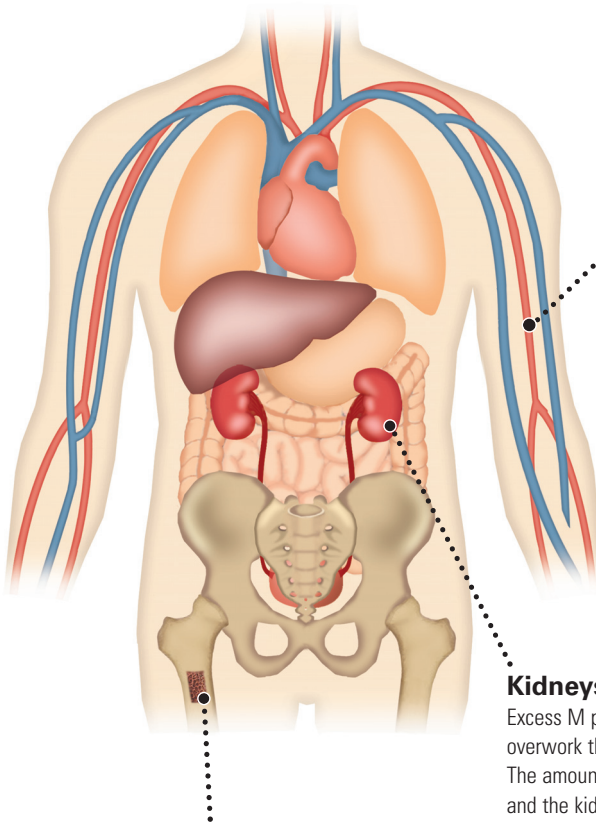


Figure 5.

### Blood

The growing number of myeloma cells has a negative affect on the production of all types of blood cells. A reduction in the number of white blood cells can increase the risk of infection, whereas decreased **red blood cell** production can result in **anemia**. A reduction in **platelets** can prevent normal blood clotting. In addition, high levels of M protein and **light chains** (portions of immunoglobulin molecules, also known as **Bence Jones proteins**), crowd out normal functioning immunoglobulins and “thicken” the blood, causing additional symptoms.

### Kidneys

Excess M protein and calcium in the blood overwork the kidneys as they filter blood. The amount of urine produced can increase, and the kidneys fail to function normally.

### Bone

The rapid growth of myeloma cells damage bone in two ways. First, the cells gather to form masses that disrupt the normal structure of bone. Second, myeloma cells secrete substances that interfere with the normal process of bone repair and growth. The most commonly affected bones are the pelvis, spine, rib cage, skull, shoulders, and hips. Bone destruction can cause the level of **calcium** in the blood-stream to rise, a condition called **hypercalcemia**.

## What are the symptoms of myeloma?

There are often no symptoms in the early stages of myeloma. When present, symptoms may be vague and similar to those of other conditions. Some of the more common symptoms are the following:

- Bone pain
- Weakness
- Fatigue
- Infection

In addition, symptoms related to high levels of calcium in the blood may include the following:

- Loss of appetite
- Restlessness
- Increased urination
- Confusion
- Increased thirst
- Nausea and vomiting

## What tests are done to diagnose myeloma?

Once your physician has diagnosed multiple myeloma, he or she may strongly recommend that you consult a specialist experienced in treating multiple myeloma to further evaluate your disease and help develop a treatment plan. You can usually find such a specialist at a National Cancer Institute(NCI)-designated cancer center. You can locate a cancer center or a myeloma specialist in your area in the “About Myeloma” section of the MMRF website ([www.multiplemyeloma.org](http://www.multiplemyeloma.org)) under “Other Resources.”

Patients most commonly see a hematologist/oncologist, a doctor who specializes in blood diseases and disorders as well as cancer. Some hematologist/oncologists further specialize in hematologic cancers, such as multiple myeloma. Your doctor may also consult with a radiation oncologist (a doctor who specializes in treating cancer with radiation therapy). Your doctor or the myeloma specialist will make the appropriate referrals.

A number of laboratory tests and medical procedures should be carried out as part of an initial evaluation to help confirm a diagnosis of myeloma. Diagnostic evaluation involves tests done on blood, urine, bone, and bone marrow (Table 1).

**Table 1. Laboratory tests and medical procedures to confirm diagnosis of myeloma**

Diagnostic Test	Purpose	Results
<b>Blood Specimen</b>		
<b>Complete blood count</b> (hemoglobin; hematocrit; number of red blood cells, white blood cells, and platelets; and relative proportion of white blood cells)	Determine the degree to which myeloma is interfering with the normal production of blood cells	Low levels may signal anemia, increased risk of infection, and poor clotting ( <i>see Table 2 for normal values</i> )
Chemistry profile ( <b>albumin</b> , calcium, <b>lactate dehydrogenase [LDH]</b> , <b>blood urea nitrogen [BUN]</b> , and creatinine)	Assess general health status and the extent of disease	Abnormal levels may indicate kidney damage and increased size/number of tumors
<b>Beta-2 microglobulin (<math>\beta_2</math>-M) level</b>	Determine the level of a serum protein that reflects both disease activity and renal function	Higher levels indicate more extensive disease; aids in staging of disease
<b>C-reactive protein</b>	Obtain an indirect measure of the number of cancer cells/size of tumors	Higher levels indicate more extensive disease and may predict a poor outcome
Immunoglobulin (Ig) levels	Define the levels of antibodies that are overproduced by myeloma cells	Higher levels suggest the presence of myeloma; result aids in classification and monitoring of disease
Serum protein <b>electrophoresis</b>	Detect the presence and level of various proteins, including M protein	Higher levels indicate more extensive disease; aids in classification of disease
<b>Immunofixation electrophoresis (IFE)</b> or <b>immuno-electrophoresis</b>	Identify the type of abnormal antibody proteins in the blood	
Freelite™	Measure immunoglobulin light chains	Recently developed test can confirm presence of light chains in serum, avoiding need for test on 24-hour sample of urine
<b>Urine Specimen</b>		
Urinalysis	Assess kidney function	Abnormal findings may suggest kidney damage
Bence Jones protein level (performed on 24-hour specimen)	Define the presence and level of Bence Jones protein	Presence indicates disease and higher levels indicate more extensive disease
Urine electrophoresis	Detect the presence and levels of specific proteins in the urine, including M protein and Bence Jones protein	Presence of M protein or Bence Jones protein indicates disease

*Table 1 continued on next page*

Table 1 continued from previous page

Diagnostic Test	Purpose	Results
<b>Bone/Bone Marrow Specimen</b>		
Imaging studies ( <b>bone [skeletal] survey</b> , x-ray, <b>magnetic resonance imaging [MRI]</b> , <b>computerized tomography [CT]</b> , <b>positron emission tomography [PET]*</b> )	Assess changes in the bone structure and determine the number and size of tumors in the bone	
Biopsy (on either fluid aspirated from the bone marrow or on bone tissue)	Determine the number and percentage of normal and malignant plasma cells in the bone marrow	Presence of myeloma cells confirms the diagnosis, and higher percentage of myeloma cells indicate more extensive disease
Plasma cell labeling index (PCLI)	Define the relative percentage of plasma cells actively growing	Higher level indicates more extensive disease
Cytogenetic analysis (eg, <b>fluorescence in situ hybridization [FISH]</b> )	Assess the number and normalcy of <b>chromosomes</b> and identify the presence of translocations	Loss of specific chromosomes (deletions) or mismatching of chromosome parts (translocations) may be associated with poor outcome

\*The clinical value of this test has not yet been determined.

**Table 2. Normal range of blood cell counts**

Count	Normal Range*
Hemoglobin (oxygen-carrying substance in red blood cells), g/dL	
Women	12.0-16.0
Men	13.0-18.0
Hematocrit (percentage of red blood cells), %	
Women	36.0-46.0
Men	37.0-49.0
Erythrocytes (red blood cells), $10^{12}/L$	
Women	4.1-5.1
Men	4.5-5.3
Leukocytes (white blood cells, total), $10^9/L$	3.5-10.5
Neutrophils	1.7-7.0
Monocytes	0.3-0.9
Lymphocytes	0.9-2.9
Basophils	0-0.3
Eosinophils	0.05-0.5
Platelets, $10^9/L$	150-450

\*Normal ranges may vary.

It is very important for a patient to have all the appropriate tests done, as they help physicians to determine treatment options and to better predict prognosis. Many of these tests are also used to assess the extent of disease and to plan and monitor treatment.

Cytogenetic analysis and plasma cell labeling index (PCLI) are not routinely done for patients with newly diagnosed myeloma, but a number of institutions perform these tests. The results of these tests may enable your doctor to suggest specific treatment options and strategies that will work better than others. Several genetic abnormalities have been identified in myeloma, and studies have shown that response to treatment and prognosis may vary according to specific subtypes of myeloma, but the connection is not clear. In addition, correlations between myeloma genetics and response to various therapies are now beginning to be identified.

The results of cytogenetic analysis are not fully understood or interpretable, but as more patients have such testing, researchers will be better able to understand the role of genetic abnormalities in treatment and prognosis. If you are interested in this testing, your doctor can recommend an appropriate testing site near you and your family.

## How is myeloma classified and staged?

Myeloma is classified according to the results of diagnostic testing, and these results indicate whether or not immediate treatment is needed. In addition, a stage is assigned to denote the extent of disease. Both classification and staging are useful in determining treatment options.

### Classification

Myeloma is classified into three categories (Table 3). Some individuals may have a diagnosis of **monoclonal gammopathy of undetermined significance (MGUS)**. MGUS is not a malignant condition but is considered to be a precursor to myeloma, with myeloma subsequently developing in up to 20% of individuals. No immediate treatment is necessary for MGUS.

**Table 3. Classification of multiple myeloma**

Classification	Characteristics	Management
Monoclonal gammopathy of undetermined significance (MGUS)	<ul style="list-style-type: none"> <li>• Serum M protein &lt; 3 g/dL <i>and</i></li> <li>• Bone marrow clonal plasma cells &lt;10% <i>and</i></li> <li>• No evidence of other B-cell disorders</li> <li>• No related organ or tissue impairment*</li> <li>• Risk of progression to malignancy: 1% per year</li> </ul>	<ul style="list-style-type: none"> <li>• Observation</li> </ul>
Asymptomatic, or smoldering, myeloma	<ul style="list-style-type: none"> <li>• Serum M protein ≥ 3 g/dL <i>and/or</i></li> <li>• Bone marrow plasma cells ≥ 10%</li> <li>• No related organ or tissue impairment or symptoms</li> <li>• Risk of progression to malignancy: 10% to 20% per year</li> </ul>	<ul style="list-style-type: none"> <li>• Observation, with treatment beginning at disease progression</li> <li>• Participation in a clinical trial</li> </ul>
Symptomatic myeloma	<ul style="list-style-type: none"> <li>• M protein in serum and/or urine</li> <li>• Bone marrow clonal plasma cells or <b>plasmacytoma</b></li> <li>• Related organ or tissue impairment</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate treatment</li> <li>• Treatment with <b>bisphosphonates</b> for <b>osteoporosis</b> or <b>osteopenia</b></li> <li>• Participation in a clinical trial</li> </ul>

\*Myeloma-related organ or tissue impairment (end-organ damage) includes hypercalcemia (increased serum calcium levels), impaired kidney function noted by increased serum creatinine, anemia, or bone lesions. These classifications are based on those recently proposed by the International Myeloma Working Group.

For patients with asymptomatic myeloma, treatment can usually wait until the first sign of disease progression. Waiting to start treatment helps avoid the side effects and risk of complications associated with therapy, especially **chemotherapy**, and delays the development of resistance to chemotherapy. Immediate treatment is needed, however, for symptomatic myeloma, in which patients already have such symptoms as anemia, increased levels of calcium in the blood, bone lesions, or kidney failure at the time of diagnosis. Thus, knowing the classification of disease is very important in deciding when it is appropriate to begin treatment. Participation in a clinical trial is also an option for many patients.

## Staging

The process of staging myeloma is crucial to developing an effective treatment plan. The system most widely used since 1975 has been the Durie-Salmon Staging System, in which the clinical stage of disease (stage I, II, or III) is based on four measurements: the hemoglobin value (a measure of the number of red blood cells in the blood), the serum calcium level, the number of osteolytic lesions, and the production rate of M protein (as measured by serum levels of IgG and IgA and the amount of Bence Jones protein in a 24-hour urine sample). Stages are further divided according to renal (kidney) function (classified as A or B) (Table 4).

**Table 4. The Durie-Salmon Staging System**

Criteria	Measured Myeloma Cell Mass (cells x 10 <sup>12</sup> /m <sup>2</sup> )
<b>Stage I (low cell mass)</b>	
<i>All of the following:</i> <ul style="list-style-type: none"> <li>• Hemoglobin value &gt;10 g/dL</li> <li>• Serum calcium value normal or ≤ 12 mg/dL</li> <li>• Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only</li> <li>• Low M-component production rate (IgG value &lt; 5 g/dL; IgA value &lt; 3 g/dL; Bence Jones protein &lt; 4 g/24 hr.)</li> </ul>	< 0.6
<b>Stage II (intermediate cell mass)</b>	
<i>Fitting neither stage I nor stage III</i>	0.6 -1.2
<b>Stage III (high cell mass)</b>	
<i>One or more of the following:</i> <ul style="list-style-type: none"> <li>• Hemoglobin value &lt; 8.5 g/dL</li> <li>• Serum calcium value &gt; 12 mg/dL</li> <li>• Advanced lytic bone lesions (scale 3)</li> <li>• High M-component production rate (IgG value &gt; 7 g/dL; IgA value &gt; 5 g/dL; Bence Jones protein &gt; 12 g/24 hr.)</li> </ul>	> 1.2
<b>Subclassification (either A or B)</b>	
<b>A:</b> Relatively normal renal function (serum creatinine value < 2.0 mg/dL)	
<b>B:</b> Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL)	

A more recently developed classification, the International Staging System (ISS), is being used more frequently, as it provides a simpler alternative to the Durie-Salmon system, as well as better discrimination of prognosis. The ISS is validated and based on the assessment of two blood test results:  $\beta_2$ -M and albumin (Table 5). Taken together,

the results of these two tests, among other tests, have been shown to provide the most accurate prediction of how the disease will respond to treatment. The three stages in this system indicate different levels of projected survival and may help patients and physicians in their decision-making about a treatment approach.

**Table 5. International Staging System**

Stage	Criteria
I	$\beta_2$ -M < 3.5 mg/dL and albumin $\geq$ 3.5 g/dL
II	$\beta_2$ -M < 3.5 and albumin < 3.5 g/dL <i>or</i> $\beta_2$ -M 3.5 – 5.5 mg/dL
III	$\beta_2$ -M > 5.5 mg/dL

## Can outcome be predicted?

Several clinical and laboratory findings provide important information about prognosis, or the predicted course of disease and outcome (Table 6). Most of the laboratory studies that can predict outcome are done as part of the initial work-up, and the values can be monitored throughout the course of disease to help your doctor determine how fast the tumor is growing, the extent of disease, the response to therapy, and your overall health status. These prognostic indicators may also help your doctor decide when treatment should begin. Many tests can be performed routinely in any laboratory, whereas others are performed only in specialized laboratories or a research setting.

**Table 6. Prognostic indicators**

Test	Indication	Values Indicating a More Favorable Prognosis (at Diagnosis)*
$\beta_2$ -M level	Higher levels reflect more extensive disease and poor renal function	< 3.5 $\mu$ g/mL
Albumin level	Higher levels may indicate a better prognosis	3.5 g/dL
Plasma cell labeling index (PCLI)	Higher index may indicate poorer prognosis	< 1%
C-reactive protein	Higher levels may indicate poorer prognosis	< 6 $\mu$ g/mL
LDH level	Higher levels indicate more extensive disease	Age $\leq$ 60 y: 100-190 U/L Age > 60 y: 110-210 U/L
Plasmablastic morphology	Increased number of immature plasma cells ( <b>plasmablasts</b> ) indicates poor prognosis	
Chromosome analysis (cytogenetic testing)	Presence of specific abnormalities may indicate poor prognosis	Absence of abnormalities

\*Note that these values are often different at other stages of the disease process (ie, prior to or following transplant). Individual centers may also define these values differently.

## What are the treatment options for myeloma?

Deciding on a particular treatment for myeloma is a complex process. Treatment is tailored to each patient according to several factors, including:

- Results of the physical exam and laboratory tests
- The specific stage or classification of disease
- Age and general health status
- Presence of symptoms and complications
- Whether the patient has previously received therapy for myeloma
- Lifestyle and quality-of-life issues

Treatment approaches may be designed to meet one or more different therapeutic goals, which can include the following:

- Destroying all evidence of disease, which may require accepting higher levels of toxicity
- Controlling disease activity to prevent damage to other organs of the body, using a regimen with an acceptable toxicity level
- Preserving normal performance and quality of life for as long as possible with minimal intervention
- Providing lasting relief of pain and other disease symptoms, as well as managing side effects of treatment
- When applicable, managing myeloma that is in remission over the long-term

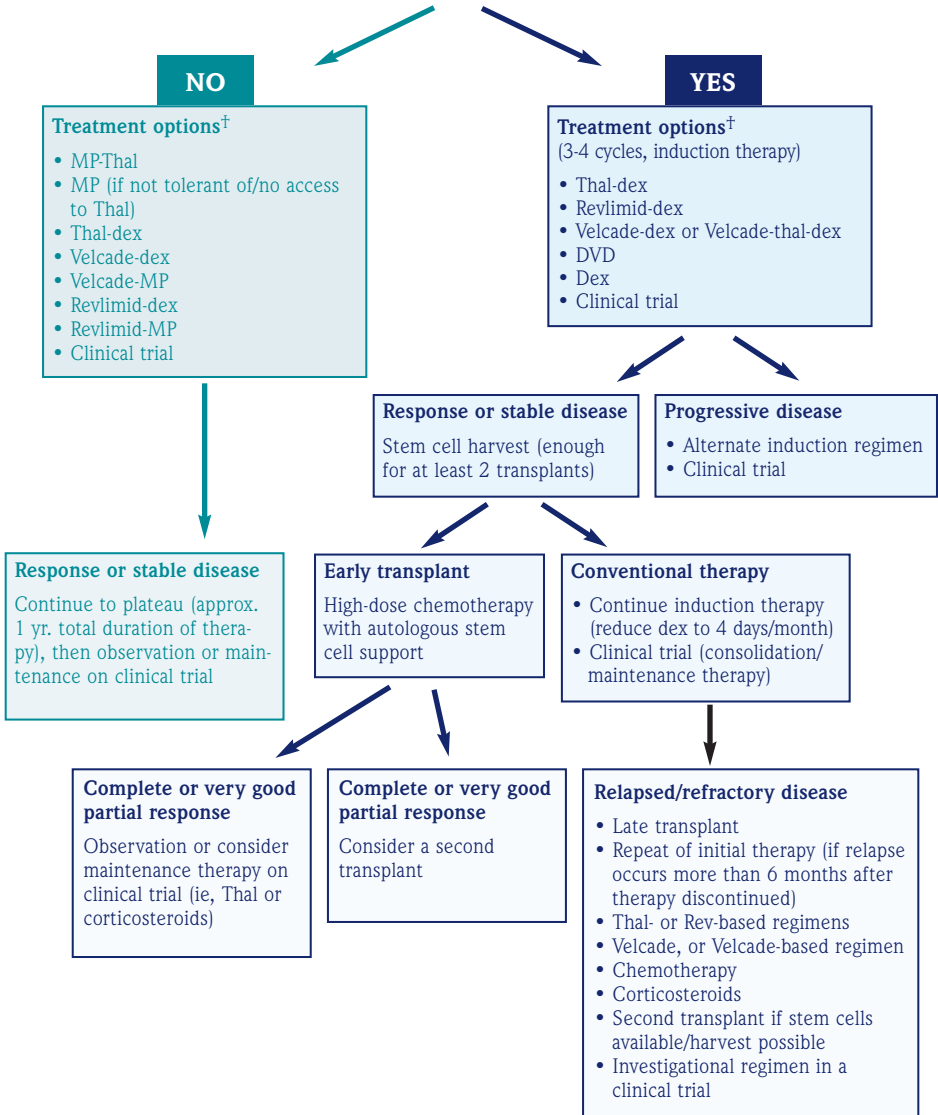
Many therapies are available for myeloma (Table 7), and it is important to note that there is no one “standard therapy” for myeloma. The treatment approaches that are often referred to as standard are those used because of strong scientific evidence of their effectiveness. Some treatments are associated with greater toxicity; these treatments may be more potent against disease but cause more side effects.

**Table 7. Therapies for myeloma**

Therapy	Description
Thalomid <sup>®</sup> (thalidomide, Celgene <sup>®</sup> )	Oral agent shown to be effective across the spectrum of myeloma disease; approved in combination with dexamethasone for the treatment of newly diagnosed disease
Velcade <sup>®</sup> (bortezomib, Millennium <sup>®</sup> )	<b>Proteasome</b> inhibitor approved for use for patients who have received at least one prior therapy; data show activity in front-line setting
Revlimid <sup>®</sup> (lenalidomide, Celgene)	Oral agent approved for use in combination with dexamethasone for patients who have received at least one prior therapy; data show activity in front-line setting
Steroids ( <b>corticosteroids</b> )	Drugs similar to steroid hormones; may be used alone or in combination with other therapies. Examples include dexamethasone and prednisone
Conventional (standard-dose) chemotherapy	The use of drugs, administered intravenously or orally, to kill cancer cells. Chemotherapy is given in cycles (treatment followed by rest periods) and may be used alone or in combination with other agents. Low-dose melphalan is an oral chemotherapy agent used frequently in treating myeloma
High-dose chemotherapy and <b>stem cell transplantation</b>	The use of higher doses of chemotherapy drugs followed by transplantation of stem cells to replace those damaged by the chemotherapy. <b>Autologous transplants</b> are the most commonly performed
<b>Radiation therapy</b>	The use of high-energy rays to damage cancer cells and prevent them from growing
Supportive therapy	Therapies that treat symptoms and complications of the disease and its treatment, such as bisphosphonates for bone disease, growth factors, antibiotics, intravenous immunoglobulin, orthopedic interventions, and low-dose radiation therapy or analgesics for pain relief

The pathway shown in Figure 6 outlines the typical options available to a patient with symptomatic myeloma requiring treatment. Subsequent treatment options are often selected based on previous treatments received and the outcome. In addition to specific treatment aimed at stopping the progression of disease, patients receive supportive care, such as bisphosphonates to relieve bone pain and reduce the risk of fracture, blood transfusions or agents (such as erythropoietin) to relieve fatigue and weakness due to anemia, drugs to strengthen immunity, and antibiotics to treat infection. Participation in a clinical trial is an option at virtually every step in the pathway.

## Autologous stem cell transplant candidate?



**Figure 6.** Treatment pathway for myeloma (adapted)\*

\* Rajkumar SV, Kyle RA. *Mayo Clin Proc.* 2005;80:1371-1382.

† Full names of treatment regimens are on page 17.

## Initial therapy for newly diagnosed disease

The initial treatment options available to an individual with newly diagnosed symptomatic myeloma are based on whether he or she is a candidate for high-dose chemotherapy and autologous stem cell transplantation. Further treatment options are often dependent on the response to therapy. With this treatment, higher than conventional doses of chemotherapy are given and the stem cells provided by the transplant replace normal cells damaged by the chemotherapy. This approach offers a chance for a good response and survival, but patients must be able to tolerate the side effects of the higher doses. Therefore, potential candidates must be in good physical condition. More information on stem cell transplants can be found in the MMRF booklet *Multiple Myeloma: Stem Cell Transplantation*.

### **Patients who are not candidates for a transplant**

Advances in myeloma research have expanded the treatment options for patients who are not candidates for stem cell transplantation. For these patients, drugs are given at standard doses to avoid damage to normal cells. At one time, the most common initial treatment was the combination of melphalan and prednisone (MP), an alkylating agent and a corticosteroid, both of which worked to kill myeloma cells and reduce the size of the tumors. Older patients may not be able to tolerate the side effects of some therapies. New agents have been combined with more traditional drugs and have been found to provide good outcomes for older patients, with fewer side effects. These combinations include:

- Melphalan, prednisone, and thalidomide (MP-Thal)
- Thalidomide and dexamethasone (Thal-dex)
- Velcade and dexamethasone (Velcade-dex)
- Velcade, melphalan, and prednisone (Velcade-MP)
- Revlimid and dexamethasone (Revlimid-dex)
- Revlimid, melphalan, and prednisone (Revlimid-MP)

Initial therapy is continued for about a year or until the response of the disease to the treatment reaches a plateau. At that time, the patient may be observed or consider receiving maintenance therapy as part of a clinical trial. **Relapse** (progression of disease) will occur at some point in patients who have an initial response. Patients who relapse within 6 months after the completion of initial therapy, or do not respond to initial therapy, are said to have **refractory disease**. Refractory disease may not respond to the initial medications used, and a new treatment approach is necessary. Treatments for relapsed or refractory disease are noted on page 18.

## **Patients who are candidates for a transplant**

For patients who are candidates for a stem cell transplant, initial chemotherapy, referred to as induction therapy, is given before the transplant. Three or four cycles of chemotherapy are given to reduce the amount of myeloma cells, and then the patient's own stem cells are collected (also called "harvested") to be reintroduced during the transplant. The chemotherapy agents used in induction therapy may differ from those used for patients who do not have a transplant, as the prolonged use of some chemotherapy agents, such as melphalan, impairs the ability to collect stem cells for use in an autologous transplant.

Until recently, the most commonly used induction therapy was the combination of vincristine, Adriamycin<sup>®</sup> (doxorubicin; Pharmacia), and dexamethasone, often referred to as VAD. The combination of thalidomide and dexamethasone (Thal-dex) is now used most frequently, especially in the United States. In addition, newer agents approved for use as second-line therapy, such as Velcade and Revlimid, are now being integrated into induction therapy in combination with dexamethasone and other agents. Other options for induction therapy include a modification of the VAD regimen known as DVD (Doxil<sup>®</sup> [doxorubicin HCl liposome injection, Ortho Biotech], vincristine, and short-schedule dexamethasone), and an investigational regimen in the context of a clinical trial.

There are two types of transplant—early and late. An early transplant is done most often, with transplant being carried out directly after the collection of stem cells. Early transplantation minimizes the amount of time a patient receives chemotherapy and overall quality of life may be improved. With late transplant, induction therapy is continued until the response plateaus and transplantation is done when relapse occurs.

## **Treatment options for relapsed or refractory disease**

As with the primary treatment of myeloma, recent advances in research have created more options for treating relapsed or refractory disease. These options include the following:

- Repeat of initial therapy if relapse occurs more than 6 months after discontinuing therapy
- Thalidomide- or Revlimid-based regimens
- Velcade or a Velcade-based regimen
- Chemotherapy
- Corticosteroids
- Second transplant if stem cells available/harvest possible
- Investigational regimen in a clinical trial

Participating in a clinical trial offers patients access to the very latest advances in treatment. Therefore, patients and their physicians should always discuss what clinical trials may be appropriate. The MMRF website includes comprehensive information on clinical trials across the country.

## What does the future look like for myeloma treatments?

Current myeloma research focuses on the development of newer agents and the evaluation of current drugs in combinations, to determine the optimal combination and the best sequencing of treatment. As research in myeloma evolves, newer treatment options have the potential to substantially enhance survival and quality of life for individuals with multiple myeloma.

If you want to learn more about current and emerging treatment options in myeloma, please read *Multiple Myeloma: Treatment Overview*, produced by the Multiple Myeloma Research Foundation (MMRF). Your doctor and the MMRF can also help you get more information on myeloma and ongoing clinical trials.

### Questions to ask your doctor

1. Should I be treated now or should therapy be delayed until I have symptoms?
2. What is the expected outcome of the treatment? What are the goals of this therapy (is it given primarily to extend survival or to relieve symptoms)?
3. What is the recommended treatment? Is it a single drug or a combination of drugs? How is the drug administered: orally or intravenously (by IV)? How often must I visit the clinic? Will I need to stay in the hospital? How long is treatment given?
4. Am I a candidate for stem cell transplantation? If so, what kind—autologous, allogeneic, or mini-allogeneic?
5. How likely is a complete or partial remission? What factors contribute to better or worse odds?
6. How will I feel during and after treatment? What should I do if I experience side effects? What kind of impact will treatment have on my daily life?
7. How long is the typical recovery time? Are there any follow-up or maintenance programs?
8. What is the cost of therapy? What costs will my insurance cover and what costs will I have to pay?
9. What are the alternatives to this treatment? How do the different therapies (standard and alternative) compare with respect to effectiveness and safety?
10. Are there any clinical trials that are appropriate for me? If so, what is involved? What are the potential risks and benefits? What are the costs?
11. If one or more types of treatment fail, what are my options?

## What are the best resources for patients?

### ➤ Sources of information about ongoing trials in multiple myeloma

MMRF's MyelomaTrials.org  
<http://www.myelomatrials.org>

Acurian  
[https://www.acurian.com/nws\\_home\\_page.jsp](https://www.acurian.com/nws_home_page.jsp)

CenterWatch Clinical Trials Listing Service  
[www.centerwatch.com](http://www.centerwatch.com)

Coalition of National Cancer Corporate Groups, Inc.  
<http://www.cancertrialshelp.org/patientsCaregivers/patientsCaregivers.jsp>

EmergingMed.com  
[www.emergingmed.com](http://www.emergingmed.com)

National Cancer Institute  
[www.cancer.gov](http://www.cancer.gov)

National Institutes of Health  
[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

### ➤ Sources of information about multiple myeloma and cancer support

**American Association for Cancer Research (AACR)**  
615 Chestnut Street, 17th Floor  
Philadelphia, PA 19106  
(215) 440-9300  
[www.aacr.org](http://www.aacr.org)

**American Cancer Society (ACS)**  
1599 Clifton Road NE  
Atlanta, GA 30329-4251  
(800) ACS-2345 [(800) 227-2345]  
[www.cancer.org](http://www.cancer.org)

**American Institute for Cancer Research (AICR)**  
1759 R Street NW  
Washington, DC 20009  
(800) 843-8114  
[www.aicr.org](http://www.aicr.org)

**Association of Online Cancer Resources**  
173 Duane Street, Suite 3A  
New York, NY 10013  
(212) 226-5525  
[www.acor.org](http://www.acor.org)

**R. A. Bloch Cancer Foundation, Inc.**  
4400 Main Street  
Kansas City, MO 64111  
(800) 433-0464  
[www.blochcancer.org](http://www.blochcancer.org)

**Blood & Marrow Transplant Information Network**  
2310 Skokie Valley Road, Suite 104  
Highland Park, IL 60035  
(888) 597-7674  
[www.bmtnews.org](http://www.bmtnews.org)

**Cancer Care, Inc.**  
275 Seventh Avenue  
New York, NY 10001  
(800) 813-HOPE [(800) 813-4673]  
[www.cancercare.org](http://www.cancercare.org)

**Cancer Hope Network**  
Two North Road  
Chester, NJ 07930  
(877) HOPENET [(877) 467-3638]  
[www.cancerhopenetwork.org](http://www.cancerhopenetwork.org)

**Cancer Research Foundation of America**  
1600 Duke Street, Suite 500  
Alexandria, VA 22314  
(800) 227-CRFA [(800) 227-2732]  
[www.preventcancer.org](http://www.preventcancer.org)

**Gilda's Club Worldwide**  
322 Eight Avenue, Suite 1402  
New York, NY 10001  
(917) 305-1200  
[www.gildasclub.org](http://www.gildasclub.org)

**HOSPICELINK**  
**Hospice Education Institute**  
3 Unity Square  
PO Box 98  
Machiasport, ME 04655-0098  
(800) 331-1620  
[www.hospiceworld.org](http://www.hospiceworld.org)

**International Myeloma Foundation**  
12650 Riverside Drive, Suite 206  
North Hollywood, CA 91607  
(800) 452-2873  
(818) 487-7455; outside US/Canada  
[www.myeloma.org](http://www.myeloma.org)

**The Leukemia & Lymphoma Society**  
1311 Mamaroneck Avenue  
White Plains, NY 10605  
(800) 955-4572  
[www.leukemia.org](http://www.leukemia.org)

**McCarty Cancer Foundation**  
27387 Woodward Avenue  
Berkley, MI 48072  
(800) 746-0355  
[www.cancerfoundation.org](http://www.cancerfoundation.org)

**National Cancer Institute, NIH**  
6116 Executive Boulevard, MSC 8322  
Suite 3036A  
Bethesda, MD 20892-8322  
(800) 4-CANCER [(800) 422-6237]  
TTY: (800) 332-8615  
[www.nci.nih.gov](http://www.nci.nih.gov)

**National Coalition for Cancer Survivorship (NCCS)**  
1010 Wayne Avenue, Suite 770  
Silver Spring, MD 20910-5600  
(877) NCCS-YES [(877) 622-7937]  
[www.canceradvocacy.org](http://www.canceradvocacy.org)

**National Hospice and Palliative Care Organization (NHPCO)**  
1700 Diagonal Road, Suite 625  
Alexandria, VA 22314  
(703) 837-1500  
[www.nhpco.org](http://www.nhpco.org)

**National Marrow Donor Program**  
3001 Broadway Street, NE, Suite 500  
Minneapolis, MN 55413-1753  
(800) MARROW-2 [(800) 627-7692]  
[www.marrow.org](http://www.marrow.org)

**Patient Advocate Foundation (PAF)**  
753 Thimble Shoals Boulevard, Suite 200  
Newport News, VA 23606  
(800) 532-5274  
[www.patientadvocate.org](http://www.patientadvocate.org)

**People Living with Cancer**  
**American Society of Clinical Oncology**  
1900 Duke Street, Suite 200  
Alexandria, VA 22314  
(703) 797-1914  
[www.plwc.org](http://www.plwc.org)

**Vital Options and "The Group Room"**  
**Cancer Radio Talk Show**  
16501 Ventura Boulevard, Suite 301  
Encino, CA 91436  
(800) GRP-ROOM [(800) 477-7666]  
[www.vitaloptions.org](http://www.vitaloptions.org)

## ➤ Clinical references

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National Cancer Institute. SEER Cancer Statistic Review 1975-2002. Accessed June 19, 2005. Available at: <http://seer.cancer.gov>.

Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc*. 2005;80(10):1371-1382.

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**Philip R. Greipp, MD**  
**Jesus F. San Miguel, MD, PhD**



## Glossary

**Albumin:** Major protein found in the blood. A patient's albumin level can provide some indication of overall health and nutritional status.

**Anemia:** A decrease in the number of red blood cells in the blood.

**Antibody:** Protein produced by plasma cells that helps protect the body from infection and disease. Also called immunoglobulin (Ig).

**Autologous transplant:** Treatment approach in which bone marrow or peripheral blood stem cells are collected from the patient, stored, and then infused into the patient following high-dose chemotherapy to restore the production of blood cells.

**B lymphocyte:** White blood cell that gives rise to a plasma cell. Also called a B cell.

**Bence Jones protein:** A short (light chain) protein that is produced by myeloma cells.

**Beta 2-microglobulin ( $\beta_2$ -microglobulin or  $\beta_2$ -M):** A protein normally found on the surface of various cells in the body. Increased serum levels are seen in inflammatory conditions and certain lymphocyte disorders, such as myeloma.

**Bisphosphonate:** Type of drug that inhibits the activity of bone-destroying cells (osteoclasts), used to strengthen bone.

**Blood urea nitrogen (BUN):** A byproduct of protein metabolism that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

**Bone (skeletal) survey:** A series of x-rays of the skull, spine, arms, ribs, and legs.

**Bone marrow:** Soft, spongy tissue found in the center of many bones where blood cells are produced.

**C-reactive protein (CRP):** A protein produced by the liver when there is an inflammatory process occurring in the body. Serum levels of CRP are increased in myeloma, as well as in various inflammatory and degenerative diseases and other types of cancer.

**Calcium:** Mineral important in bone formation. Elevated serum levels occur when there is bone destruction.

**Chemotherapy:** The use of drugs to treat cancer.

**Chromosome:** A thread-like structure in a living cell that contains genetic information.

**Complete blood count (CBC):** Blood test that measures the number of red blood cells, white blood cells, and platelets in the blood and the relative proportions of the various types of white blood cells.

**Computerized tomography (CT):** Imaging technique that uses a computer to generate three-dimensional x-ray pictures. Also referred to as computerized axial tomography (CAT).

**Corticosteroid:** A potent class of drugs that has anti-inflammatory, immunosuppressive, and antitumor effects. Dexamethasone and prednisone are examples of corticosteroids.

**Creatinine:** A product of energy metabolism of muscle that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

**Electrophoresis:** Laboratory test used to measure the levels of various proteins in the blood or urine. Uses an electrical current to sort proteins by their charge.

**Erythropoietin:** Growth factor that stimulates the bone marrow to produce red blood cells.

**Fluorescent in situ hybridization (FISH):** A laboratory technique used to determine how many copies of a specific segment of DNA are present or absent in a cell.

**Hypercalcemia:** Condition noted by elevated levels of calcium in the blood due to increased bone destruction.

**Immunoelectrophoresis:** See immunofixation electrophoresis.

**Immunofixation electrophoresis (IFE):** Type of electrophoresis that uses a special antibody staining technique to identify specific types of immunoglobulins; also called immunoelectrophoresis.

**Immunoglobulin (Ig):** See antibody.

**Lactate dehydrogenase (LDH):** An enzyme found in body tissues. Elevated blood levels occur when there is tissue damage and may occur in myeloma, where they reflect tumor-cell burden.

**Light chains:** Short protein chains on immunoglobulins.

**Lymph nodes:** Bean-shaped structures that are found throughout the body that act as filters, collecting bacteria or cancer cells that may travel through the lymphatic system (which is made up of tissues and organs that produce and store cells that fight infection and disease).

**Lymphocyte:** Small white blood cell essential for normal function of the immune system; may be one of two types: a T lymphocyte or B lymphocyte.

**Magnetic resonance imaging (MRI):** Imaging technique that uses magnetic energy to provide detailed images of bone and soft tissue.

**Malignant:** Cancerous.

**Monoclonal gammopathy of undetermined significance (MGUS):** A precancerous and asymptomatic condition noted by the presence of M protein in the serum or urine. MGUS may progress to myeloma.

**Monoclonal (M) protein:** Abnormal antibody (immunoglobulin) found in large quantities in the blood and urine of individuals with myeloma.

**Osteoblast:** Bone-forming cell that works in conjunction with bone-destroying cells (osteoclasts) to repair bone through a process called bone remodeling.

- Osteoclast:** Bone-destroying cell that works in conjunction with bone-forming cells (osteoblasts) to repair bone through a process called bone remodeling.
- Osteolytic lesion:** Soft spot in the bone where bone tissue has been destroyed. The lesion appears as a hole on a standard bone x-ray.
- Osteopenia:** Condition of decreased bone density.
- Osteoporosis:** Generalized bone loss typically associated with old age, but which can also occur in myeloma.
- Plasma cell:** A cell that develops from a B cell and produced proteins that help fight disease and infection.
- Plasmablast:** Immature plasma cell.
- Plasmacytoma:** Single tumor comprised of malignant plasma cells that occurs in bone or soft tissue. Myeloma may develop in patients with a plasmacytoma.
- Platelets:** Small cell fragments in the blood that help it to clot.
- Positron emission tomography (PET):** Imaging technique in which radioactive glucose (sugar) is used to highlight cancer cells.
- Proteasome:** Complex of enzymes that plays a role in the regulation of cell function and growth by breaking down proteins in a cell after they have performed their functions, allowing various cellular processes to continue in an orderly fashion.
- Radiation therapy:** Use of high-energy rays to damage cancer cells and prevent them from growing; sometimes used as palliative treatment to relieve uncontrolled pain and in cases of imminent risk of bone fracture or spinal-cord compression.
- Red blood cell:** Oxygen-transporting blood cell.
- Refractory disease:** Disease that is not responsive to initial therapies or relapsed disease.
- Relapse:** Return of disease or disease progression.
- Stem cell:** Parent cell that grows and divides to produce red blood cells, white blood cells, and platelets. Found primarily in the bone marrow but also in the peripheral blood.
- Stem cell transplantation:** Therapeutic procedure in which bone marrow or peripheral blood stem cells are collected, stored, and infused into a patient following high-dose chemotherapy to restore blood cell production.
- White blood cell:** One of the major cell types in the blood; attack infection and cancer cells as part of the immune system. Lymphocytes are a type of white blood cell. Also called a leukocyte.



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