

# MULTIPLE MYELOMA

## DISEASE OVERVIEW



**MMRF**<sup>®</sup>  
Multiple Myeloma  
Research Foundation

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## **ABOUT THE MULTIPLE MYELOMA RESEARCH FOUNDATION**



The Multiple Myeloma Research Foundation (MMRF) was founded in 1998 by identical twin sisters Kathy Giusti

and Karen Andrews soon after Kathy was diagnosed with multiple myeloma, an incurable blood cancer. The mission of the MMRF is to relentlessly pursue innovative means that accelerate the development of next-generation multiple myeloma treatments to extend the lives of patients and lead to a cure.

Thanks to the support and generosity of people like you, and by working closely with researchers, clinicians and our partners in the biotech and pharmaceutical industry, we helped bring multiple myeloma patients four new treatments that are extending lives around the globe. Today, we are on the cusp of the next breakthrough treatment, and are

supporting a pipeline of more than 50 promising compounds and combination treatments, including more than 30 clinical trials we advanced through our sister organization, the Multiple Myeloma Research Consortium (MMRC).

As the multiple myeloma community's most trusted source for information, the MMRF supports patients from the point of diagnosis throughout the course of the disease. No matter where you are in your journey with multiple myeloma, you can count on the MMRF to get you the information you need about multiple myeloma and its treatment options, including clinical trials. All information on our Web site, [www.themmr.org](http://www.themmr.org), is tailored to patients by disease stage so we can make sure you get information you need at the right time.

To learn more about the MMRF, visit [www.themmr.org](http://www.themmr.org).

Accredited by:



## **CONTENTS**

|  |           |
|--|-----------|
| <b>Introduction</b>  | <b>2</b>  |
| <b>What Is Multiple Myeloma?</b>                               | <b>2</b>  |
| <b>How Common Is Myeloma?</b>                                  | <b>4</b>  |
| <b>What Causes Myeloma?</b>                                    | <b>4</b>  |
| <b>How Does Myeloma Affect the Body?</b>                       | <b>4</b>  |
| <b>What Are the Symptoms of Myeloma?</b>                       | <b>6</b>  |
| <b>What Tests Are Done to Diagnose Myeloma?</b>                | <b>6</b>  |
| <b>Seeing a Myeloma Specialist</b>                             | <b>9</b>  |
| <b>How Is Myeloma Classified and Staged?</b>                   | <b>10</b> |
| <b>Can Outcome Be Predicted?</b>                               | <b>14</b> |
| <b>What are the Possible Goals of Treatment?</b>               | <b>14</b> |
| <b>How Do You Decide Which Treatment Is Appropriate?</b>       | <b>15</b> |
| <b>How Do You Know if a Treatment Is Working?</b>              | <b>17</b> |
| <b>What Therapies Are Used in Myeloma?</b>                     | <b>17</b> |
| <b>Initial Therapy for Newly Diagnosed Symptomatic Disease</b> | <b>17</b> |
| <b>Treatment Options for Relapsed or Refractory Myeloma</b>    | <b>22</b> |
| <b>What Does the Future Look Like for Myeloma Treatments?</b>  | <b>23</b> |
| <b>Questions to Ask Your Doctor</b>                            | <b>24</b> |
| <b>References</b>  | <b>25</b> |
| <b>Glossary</b>  | <b>26</b> |

## INTRODUCTION

This booklet is designed primarily to help individuals with newly diagnosed multiple myeloma and their friends and families better understand this disease. The booklet explains what myeloma is and how it develops within the body. Words that may be unfamiliar are **bolded** throughout the text at first mention and defined in the Glossary (page 26). Learning as much as possible about multiple myeloma will help you be more involved in making decisions about treatment.

The information in this booklet is not intended to replace the services of trained healthcare professionals (or to be a substitute for medical advice). Please consult with your healthcare professional regarding specific questions relating to your health, especially questions about diagnosis or treatment.

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The MMRF booklet, *Multiple Myeloma: Treatment Overview*, and the MMRF Web site ([www.themmr.org](http://www.themmr.org)) provide more information about current therapies for myeloma and emerging treatment options.

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## WHAT IS MULTIPLE MYELOMA?

Multiple myeloma is a blood cancer that develops in the **bone marrow** (Figure 1). In myeloma, normal **antibody**-producing **plasma cells** transform into **malignant myeloma cells**. Myeloma cells produce large quantities of one antibody (or **immunoglobulin**) called **monoclonal (M) protein**. These malignant cells also crowd out and inhibit the production of normal blood cells and antibodies in the bone marrow. In addition, groups of myeloma cells cause other cells in the bone marrow to remove the solid part of the bone and cause **osteolytic lesions**, or soft spots in the bone (Figure 2). Although common, these lesions or other signs of bone loss do not occur in all individuals with myeloma.

Figure 1.

In healthy bone marrow (A), **B-cells** develop into antibody-producing plasma cells when foreign substances (antigens) enter the body. Normally, plasma cells make up less than 1 percent of the cells in the bone marrow. In multiple myeloma (B), genetic damage to a developing B cell transforms the normal plasma cell into a malignant 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.

**A. Healthy**

**B. Multiple Myeloma**

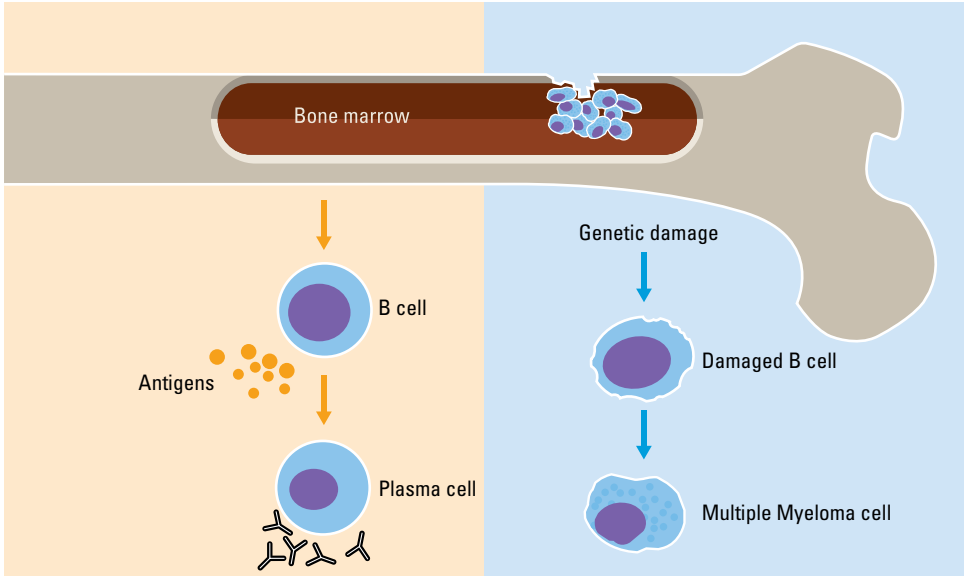
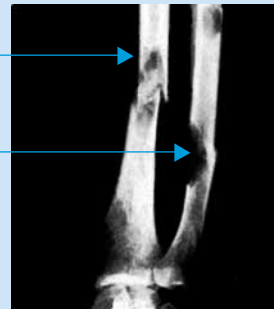


Figure 2.

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 VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. 1997:2350. Adapted with permission from Lippincott Williams & Wilkins.

Fracture caused by lesion  
Lesions



## HOW COMMON IS MYELOMA?

Multiple myeloma is the second most common blood cancer, after non-Hodgkin's lymphoma, and represents approximately 1 percent of all cancers and just under 2 percent of all cancer deaths. The American Cancer Society estimates that multiple myeloma will be diagnosed in 20,520 people during 2011. The number of cases of myeloma reported at a particular time (prevalence) varies according to gender, age, and race or ethnicity. Multiple myeloma is more common among men than women, occurs more frequently with increasing age, and develops twice as often among black individuals than among white individuals.

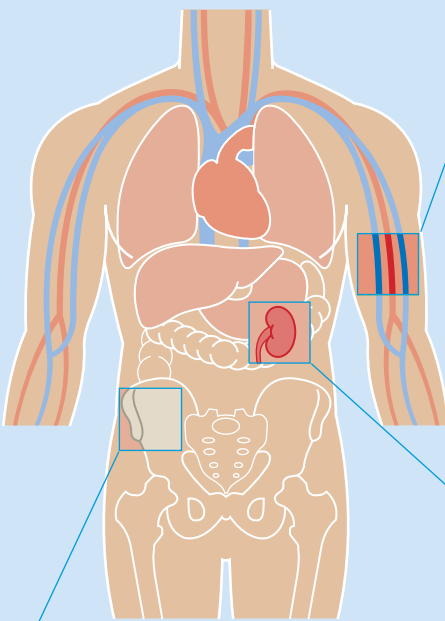
## WHAT CAUSES MYELOMA?

To date, no cause for myeloma has been identified. Research suggests possible associations with a decline in the immune system, some occupations, exposure to certain chemicals, and exposure to radiation. However, there are no strong associations, and in most cases, multiple myeloma develops in individuals who have no known 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 3).

**Figure 3. Effect of myeloma on major organs in the body**



**Blood**

The growing number of myeloma cells can interfere with 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**

Myeloma cell damage leads to bone loss in two ways. First, the cells gather to form masses in the bone marrow that may disrupt the normal structure of the surrounding bone. Second, myeloma cells secrete substances that interfere with the normal process of bone repair and growth. The most commonly affected bones are the spine, pelvis, and rib cage. Bone destruction can cause the level of calcium in the bloodstream to rise, a condition called **hypercalcemia**, which can be a serious problem if appropriate treatment is not given immediately.

## 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:

- Bone pain
- Fatigue
- Weakness
- Infection
- Loss of appetite and weight loss

In addition, symptoms related to high levels of calcium in the blood (hypercalcemia) or kidney problems may include:

- Increased or decreased urination
- Increased thirst
- Restlessness, eventually followed by extreme weakness and fatigue
- Confusion
- Nausea and vomiting

## WHAT TESTS ARE DONE TO DIAGNOSE MYELOMA?

A number of laboratory tests are typically carried out as part of an initial evaluation to help confirm a diagnosis of myeloma. These tests are done on samples of blood, urine, bone, and bone marrow (Table 1).

**TABLE 1. COMMON LABORATORY TESTS AND MEDICAL PROCEDURES TO CONFIRM DIAGNOSIS OF MYELOMA**

| Diagnostic Test   | Purpose  | Results   |
|---|--|---|
| <b>Blood Specimen</b>   |  |   |
| <b>Complete blood count</b> (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      |
| Chemistry profile ( <b>albumin</b> , calcium, <b>lactate dehydrogenase [LDH]</b> , <b>blood urea nitrogen [BUN]</b> , and <b>creatinine</b> ) | Assess general health status and the extent of disease   | Abnormal levels may indicate kidney damage and increased size/number of tumors    |
| <b>Beta<sub>2</sub>-microglobulin (β<sub>2</sub>-M)</b> level   | 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                                       | Higher levels indicate more extensive disease                                     |
| Immunoglobulin levels   | Define the levels of antibodies that are overproduced by myeloma cell                          | Higher levels suggest the presence of myeloma                                     |
| 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> ; also called immunoelectrophoresis )   | Identify the type of abnormal antibody proteins in the blood                                   | Aids in classification of disease   |
| Freelite™ serum free light chain assay  | Measure immunoglobulin light chains  | Abnormal levels and/or ratio suggest the presence of myeloma or a related disease |

*Table 1 continued on next page*

**TABLE 1. (CONTINUED) COMMON LABORATORY TESTS AND MEDICAL PROCEDURES TO CONFIRM DIAGNOSIS OF MYELOMA**

| Diagnostic Test   | Purpose  | Results  |
|---|--|--|
| <b>Urine Specimen</b>   |  |  |
| Urinalysis  | Assess kidney function   | Abnormal findings may suggest kidney damage  |
| Bence Jones protein level (performed on 24-hour specimen of urine)  | Define the presence and level of Bence Jones protein   | Presence indicates disease, and higher levels indicate more extensive disease  |
| Urine protein electrophoresis   | Determine 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   |
| <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 |
| Cytogenetic analysis (e.g., <b>fluorescence in situ hybridization [FISH]</b> )  | Assess the number and normalcy of <b>chromosomes</b> and identify the presence of translocations (mismatching of chromosome parts) | Loss of certain chromosomes (deletions) or translocations may be associated with poor outcome                            |

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

It is very important for you to have all the appropriate tests done, as the results will help your doctor to better determine treatment options and **prognosis**, or the predicted course of disease and outcome. Many of these tests are also used to assess the extent of disease and to plan and monitor treatment.

Cytogenetic analysis is not routinely done for individuals with newly diagnosed myeloma, but is being performed more frequently at some medical institutions that specialize in the treatment of multiple myeloma. How the results of cytogenetic analysis affect the selection of newer treatment agents is still evolving.

## SEEING A MYELOMA SPECIALIST

Once your doctor has diagnosed multiple myeloma, it is important that you consult a specialist experienced in treating 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.

Doctors usually refer individuals with multiple myeloma to a hematologist/oncologist, a doctor who specializes in blood diseases and disorders, as well as cancer. Some hematologists/oncologists further specialize in hematologic cancers, such as multiple myeloma.

To find a cancer center or myeloma specialist, look in the “Newly Diagnosed Patients Section” under “Living With Multiple Myeloma” on the MMRF Web site ([www.themmrp.org](http://www.themmrp.org)) and go to “Choosing Your Doctor.”

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 the disease, but the connection has not been defined adequately enough to aid in decision-making about the best treatment options.

### **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 staging and classification are useful in determining treatment options.

#### **Classification**

Myeloma is classified into three categories (Table 2). Individuals in the first two categories are considered asymptomatic and do not have to receive anti-myeloma treatment immediately. However, clinical trials are being conducted to determine if newer agents can delay disease progression and improve survival for this group of individuals.

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Individuals with myeloma are encouraged to talk to their doctors about participating in a clinical trial.

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**TABLE 2. CLASSIFICATION OF MULTIPLE MYELOMA**

| Classification   | Characteristics  | Management   |
|--|--|--|
| <b>Monoclonal gammopathy of undetermined significance (MGUS)</b> | <ul style="list-style-type: none"> <li>• Considered a precursor to myeloma</li> <li>• Blood M protein &lt;3 g/dL <i>and</i></li> <li>• Bone marrow plasma cells &lt;10% <i>and</i></li> <li>• No evidence of other B-cell disorders</li> <li>• No related organ or tissue impairment<sup>a</sup></li> <li>• Risk of progression to malignancy: 1% per year (about 20%-25% of individuals during their lifetime)</li> </ul> | <ul style="list-style-type: none"> <li>• Close follow-up (also known as “observation”)</li> </ul>  |
| Asymptomatic, or smoldering, myeloma                             | <ul style="list-style-type: none"> <li>• Blood 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% 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> <li>• Treatment with <b>bisphosphonates</b> for individuals with bone loss (<b>osteoporosis</b> or <b>osteopenia</b>) similar to that used for the treatment of osteoporosis in general</li> </ul> |
| Symptomatic myeloma  | <ul style="list-style-type: none"> <li>• M protein in blood and/or urine</li> <li>• Bone marrow 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 bisphosphonates for individuals with osteolytic lesions, osteoporosis, or osteopenia</li> <li>• Participation in a clinical trial</li> </ul>  |

<sup>a</sup>*Myeloma-related organ or tissue impairment (end-organ damage) includes **hypercalcemia** (increased blood calcium levels), impaired kidney function, **anemia**, or bone lesions. These classifications are based on those proposed by the International Myeloma Working Group.*

## Staging

The process of staging myeloma is crucial to developing an effective treatment plan. Historically, the system most widely used 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, the level of calcium in the blood,

the number of osteolytic lesions, and the production rate of M protein (Table 3). Stages are further divided according to renal (kidney) function.

A newer, simpler, more cost-effective staging system that is being used more often is the International Staging System (ISS).

**TABLE 3. THE DURIE-SALMON STAGING SYSTEM**

| Stage                       | Criteria  | Myeloma Cell Mass <sup>a</sup> |
|-----------------------------|---|--------------------------------|
| I (low cell mass)           | <i>All of the following:</i> <ul style="list-style-type: none"><li>• Hemoglobin value &gt;10 g/dL</li><li>• Blood calcium value normal or &lt;12 mg/dL</li><li>• Bone x-ray, normal bone structure, or solitary bone plasmacytoma only</li><li>• Low M-protein production rate (IgG value &lt; 5 g/dL; IgA value &lt;3 g/dL; <b>Bence Jones protein</b> &lt;4 g/24 hr.)</li></ul> | <0.6                           |
| II (intermediate cell mass) | <i>Fitting neither stage I nor stage III</i>  | 0.6-1.2                        |
| III (high cell mass)        | <i>One or more of the following:</i> <ul style="list-style-type: none"><li>• Hemoglobin value &lt;8.5 g/dL</li><li>• Blood calcium value &gt;12 mg/dL</li><li>• Advanced lytic bone lesions</li><li>• High M-protein production rate (IgG value &gt;7 g/dL; IgA value &gt;5 g/dL; <b>Bence Jones protein</b> &gt;12 g/24 hr.)</li></ul>   | >1.2                           |

<sup>a</sup>The myeloma cell mass is expressed as the number of myeloma cells per body surface area.

### Subclassification (either A or B)

A: Relatively normal renal function (blood creatinine value <2.0 mg/dL)

B: Abnormal renal function (blood creatinine value ≥2.0 mg/dL)

The ISS was developed based on responses to **front-line therapy** with conventional **chemotherapy** and/or high-dose chemotherapy and **stem cell transplantation**. The ISS is based on the assessment of two blood tests, beta<sub>2</sub>-microglobulin (β<sub>2</sub>-M) and albumin (Table 4). The three stages in this system indicate different levels of projected survival and

may help in the treatment decision-making process. The ISS is useful only for individuals with symptomatic myeloma, and its prognostic value when newer, novel agents are used as front-line therapy, as well as following disease **relapse** (progression), is under investigation.

**TABLE 4. INTERNATIONAL STAGING SYSTEM FOR MYELOMA**

| Stage | Criteria  |
|-------|---|
| I     | β <sub>2</sub> -M <3.5 mg/L and albumin ≥3.5 g/dL                                     |
| II    | β <sub>2</sub> -M <3.5 mg/L and albumin <3.5 g/dL or β <sub>2</sub> -M 3.5 – 5.5 mg/L |
| III   | β <sub>2</sub> -M ≥5.5 mg/L   |

*β<sub>2</sub>-M = beta<sub>2</sub>-microglobulin.*

## CAN OUTCOME BE PREDICTED?

Several clinical and laboratory findings provide important information about prognosis (Table 5). These prognostic indicators may also help decide when treatment should begin and aid in monitoring the disease. Many tests can be performed routinely in any laboratory, whereas others are performed only in specialized laboratories or a research setting.

## WHAT ARE THE POSSIBLE GOALS OF TREATMENT?

Depending on an individual's disease and his or her wishes, treatment plans may be designed to meet one or more different goals (Table 6).

**TABLE 5. PROGNOSTIC INDICATORS**

| Test   | Indication   | Values Indicating Lower Risk at Diagnosis <sup>a</sup>                          |
|--|--|---|
| $\beta_2$ -M level   | Higher levels reflect more extensive disease and poor renal function   | <3.5 mg/mL  |
| Albumin level  | Higher levels may indicate a better prognosis  | ≥3.5 g/dL   |
| Lactate dehydrogenase (LDH) level  | Higher levels indicate more extensive disease  | Age ≤60 y: 100-190 U/L<br>Age >60 y: 110-210 U/L                                |
| Chromosome analysis (cytogenetic testing, by either karyotyping or FISH)     | Presence of specific abnormalities may indicate poor prognosis   | Absence of abnormalities  |
| Freelite™ serum free light chain assay                                       | Abnormal results indicate risk of progression of MGUS and smoldering myeloma (SMM); as well as poorer prognosis in myeloma | Free light chain ratio<br>MGUS: 0.26-1.65<br>SMM: 0.125-8.0<br>Myeloma: 0.03-32 |
| <b>Gene expression profiling</b> (Myeloma Prognostic Risk Signature™ MyPRS™) | Presence of specific groups of genes can predict low or high risk of early relapse   | Personalized risk score   |

<sup>a</sup>Note that these values are often different at other stages of the disease process, such as before or after stem cell transplantation. These values may also be defined differently at different medical laboratories.

## HOW DO YOU DECIDE WHICH TREATMENT IS APPROPRIATE?

Deciding on a particular treatment plan for myeloma is a complex process. Treatment is tailored to each individual based on a number of things, including:

- Results of the physical exam
- Results of laboratory tests
- The specific classification and stage of disease
- Age and general health
- Symptoms
- Presence of disease complications
- Prior myeloma treatment
- The individual's lifestyle, goals, and views on quality of life

**TABLE 6. TREATMENT GOALS**

| Goal   | Intervention/Requirement   |
|--|--|
| Destroy all evidence of disease  | May require use of aggressive treatment that might have more severe side effects                               |
| Prevent damage to other organs of the body by controlling disease activity                             | Typically achieved with commonly used treatments that have side effects, but they are acceptable and tolerable |
| Preserve normal performance and quality of life for as long as possible                                | May be possible with minimal treatment   |
| Provide lasting relief of pain and other disease symptoms, as well as manage side effects of treatment | Involves use of supportive therapies that help you feel better and manage complications                        |
| Manage myeloma that is in <b>remission</b>   | May involve long-term therapy  |

**TABLE 7. THERAPIES FOR MYELOMA<sup>a</sup>**

| Therapy  | Description  |
|--|--|
| Velcade® (bortezomib, Millennium: The Takeda Oncology Company) for Injection | <b>Proteasome</b> inhibitor approved for use across the entire spectrum of myeloma disease   |
| Revlimid® (lenalidomide, Celgene)  | Oral agent that is an improvement over Thalomid and is effective across the spectrum of myeloma disease; approved for use in combination with dexamethasone in individuals who previously received treatment   |
| Thalomid® (thalidomide, Celgene)   | Oral agent shown to be effective across the spectrum of myeloma disease; approved in combination with dexamethasone as front-line therapy  |
| Doxil® (doxorubicin HCl liposome injection, Ortho Biotech)                   | Chemotherapy agent approved for use in combination with Velcade for individuals who previously received therapy other than Velcade   |
| Steroids ( <b>corticosteroids</b> ) (dexamethasone and prednisone)           | Drugs used for decades to treat myeloma throughout the spectrum of disease; may be used alone or in combination with other therapies   |
| Conventional (standard dose) chemotherapy                                    | The use of drug(s), administered alone or in combination, to kill cancer cells; some examples are melphalan (Alkeran®, GlaxoSmithKline) and cyclophosphamide   |
| High-dose chemotherapy and stem cell transplantation                         | The use of higher doses of chemotherapy drugs followed by transplantation of <b>hematopoietic stem cells</b> to replace healthy cells damaged by the chemotherapy.   |
| Radiation therapy  | The use of high-energy rays to damage cancer cells and prevent them from growing   |
| Supportive therapy   | Therapies that alleviate symptoms and manage complications of the disease and its treatment, such as bisphosphonates for bone disease, low-dose radiation therapy and analgesics for pain relief, <b>growth factors</b> , antibiotics, intravenous immunoglobulin, orthopedic interventions, drugs (primarily <b>anticoagulants</b> ) to prevent and reduce the severity of <b>deep vein thrombosis (DVT; blood clots)</b> , <b>antiemetics</b> , and drugs to prevent and reduce the severity of <b>neuropathy</b> (nerve damage) |

<sup>a</sup>Approved indications listed are those for the United States.

## HOW DO YOU KNOW IF A TREATMENT IS WORKING?

During and after treatment, your doctor will monitor your levels of M protein and your symptoms. Your doctor may also perform some of the same laboratory tests and medical procedures that were done when you were diagnosed with myeloma, such as blood tests, x-rays, or bone marrow biopsy. All of these results show how well the treatment is working and whether you are experiencing any side effects. These tests also help determine if, after an initial response to treatment, your myeloma relapses.

In clinical trials, the outcome of treatment in myeloma is defined using very specific standards, or criteria. These “response criteria” allow the relative effectiveness of one treatment to be compared with other treatments.

## WHAT THERAPIES ARE USED IN MYELOMA?

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 may be more potent against disease but cause more side effects. In addition to

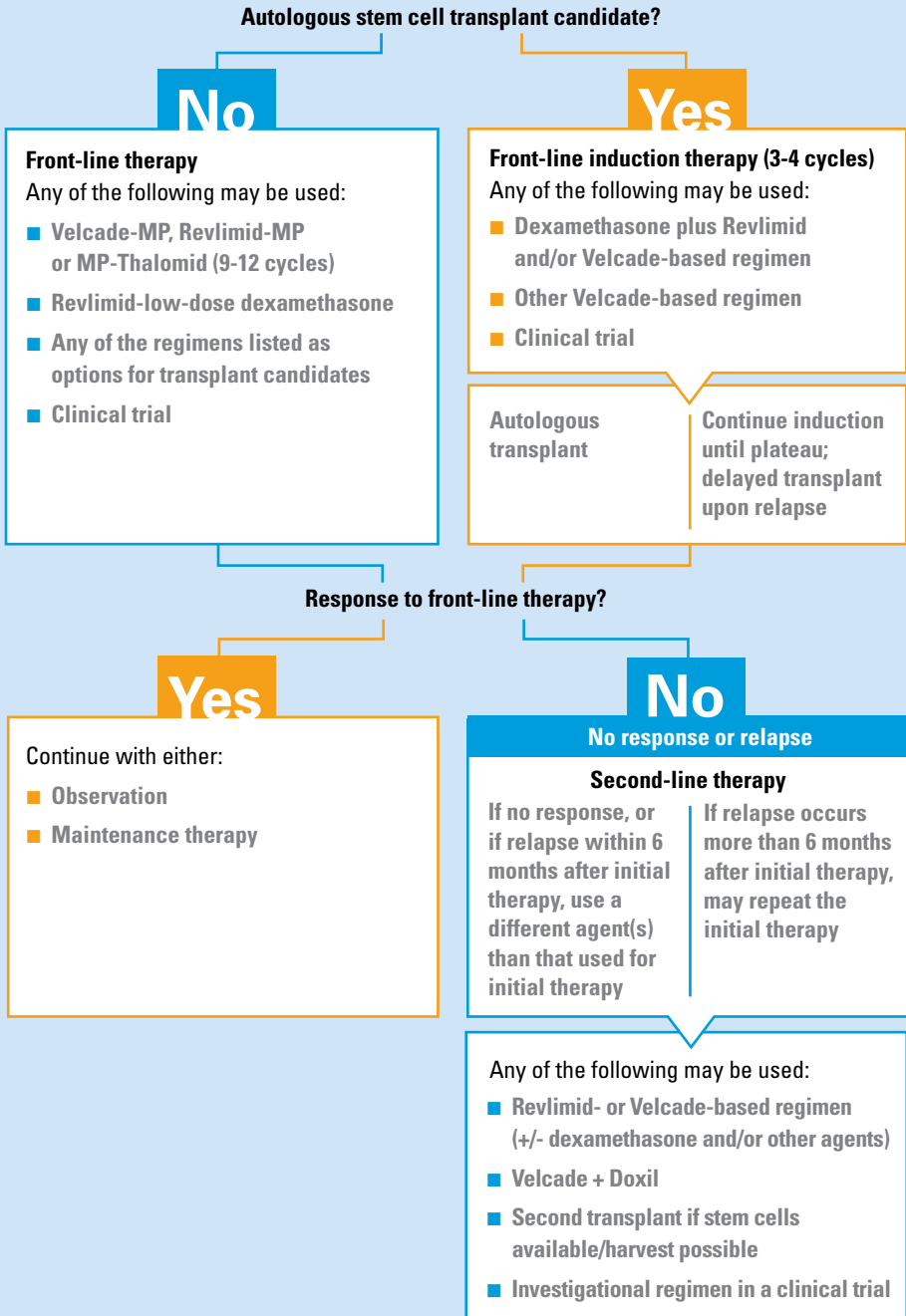
treatment of the disease, supportive care is provided to alleviate symptoms related to both the disease and its treatment.

## INITIAL THERAPY FOR NEWLY DIAGNOSED SYMPTOMATIC 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, or interested in, high-dose chemotherapy and **autologous stem cell transplantation** (see Figure 4 on next page). In general, individuals in good physical condition with adequate kidney, lung, and heart function are potential candidates for transplant. In addition to specific treatment aimed at stopping the progression of disease, individuals with myeloma may receive supportive care, such as intravenously administered bisphosphonates to relieve bone pain and reduce the risk of fracture, blood transfusions or treatments (such as **erythropoietin**) to treat anemia due to chemotherapy, drugs to strengthen immunity, and antibiotics to treat infection. Participation in a clinical trial is an option at virtually every stage of the disease.

It is important to note that the order of treatment options listed here does not imply degree of effectiveness.

Figure 4. Treatment options for myeloma



## Individuals Who Are Not Candidates for a Transplant

Advances in myeloma research have expanded the treatment options for individuals who are not candidates for stem cell transplantation. For these individuals, drugs are given at standard doses to avoid damage to normal cells.

In the past, the most common initial treatment was the combination of melphalan and the corticosteroid prednisone (a combination referred to as MP). However, clinical studies with Velcade® (bortezomib), Thalomid® (thalidomide), and Revlimid® (lenalidomide) have shown that adding one of these agents to MP improves response rates. The combinations of Velcade plus MP and Thalomid plus MP have also been shown to offer improved survival compared with MP alone. Thus, the use of MP in combination with any one of the newer agents is a recommended option for initial therapy in patients who are not eligible for transplant. The increased effectiveness of these new drug combinations must be balanced against a potential increase in side effects that is natural with additional drugs.

Other recommended treatment options for non-transplant candidates include:

- Revlimid and low-dose dexamethasone (Revlimid-low-dose dex), which appears to be active and well tolerated in older individuals

- Velcade and dexamethasone (Velcade-dex), which may offer response rates similar to that seen with Velcade-MP

Initial therapy for myeloma is continued for about a year or until the response of the disease to the treatment reaches a plateau, or levels off. At that time, the individual may be followed-up closely with no therapy (often referred to as “observation”) or the doctor may ask the individual to consider maintenance therapy, which may also be done with the patient participating in a clinical trial.

## Individuals Who Are Candidates for a Transplant

Stem cell transplantation involves the use of higher than conventional doses of chemotherapy, 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 the individual must be able to tolerate the side effects of the higher doses of chemotherapy. Therefore, potential candidates must be in good physical condition, with adequate kidney, lung, and heart function.

## THE EVOLVING ROLE OF TRANSPLANTATION IN MYELOMA

The improved response rates that have been found with use of newer agents as initial therapy have raised questions about the role of transplantation in the treatment of myeloma.

Preliminary results from several studies appear to indicate that transplantation remains a standard therapy and may improve outcomes when compared to standard therapy with newer agents. However, longer follow-up is needed in order to compare survival, and the potential toxicities associated with transplantation must be balanced with the benefits.

Until then, people with myeloma should carefully discuss the benefits and risks of all treatment options with their doctors. All individuals who are eligible for transplantation are encouraged to have stem cells obtained (also known as “harvested”) so that the cells are available if the individual later chooses to undergo transplantation.

## Induction Therapy

Before the transplant is done, initial treatment, referred to as induction therapy, is given to reduce the amount of myeloma cells. Because prolonged use of melphalan may impair the ability to collect stem cells for use in a transplant, other agents are typically used as initial induction therapy. Dexamethasone (dex), once commonly used for induction therapy, is now used more frequently, especially at lower doses, in combination with newer agents such as Revlimid and Velcade.

Among the recommended options for initial induction therapy for individuals eligible for transplant are the following:

- Velcade-based regimens, such as Velcade-Dex; Velcade, Thalomid, and dexamethasone (Velcade-Thal-dex), Velcade, Revlimid, and dexamethasone (RVD); Velcade and Doxil®; and Velcade, cyclophosphamide, and dexamethasone (VCD or CyBorD)
- Revlimid-low-dose dex

Participation in a clinical trial, such as one evaluating an investigational induction regimen, is also an appropriate option for patients considering a transplant.

## Stem Cell Transplantation

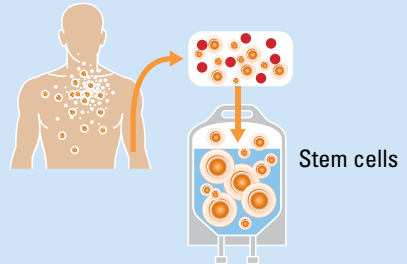
Stem cells are normally found in the bone marrow and in the peripheral blood (blood found in the arteries or veins). Virtually all transplants in myeloma are now obtained from the peripheral blood and are referred to as peripheral blood stem cell (PBSC) transplants.

Stem cell transplantation is done after completion of induction therapy. With an autologous transplant, the individual's stem cells are collected (also called "harvested") and are reintroduced following high-dose chemotherapy (Figure 5). An **allogeneic transplant** involves collecting stem cells from a donor (usually a relative of the individual with myeloma) and infusing them into the individual after high-dose therapy. This type of transplant is infrequently performed today because of the high risk of complications. A mini (nonmyeloablative) allogeneic transplant is a modified form of allogeneic transplant in which a lower dose of chemotherapy is used.

Figure 5. **Stem cell transplantation**

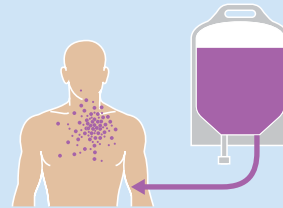
### 1. Collection

*In stem cell transplantation, peripheral blood stem cells (PBSCs) are collected (also called "harvested") from the individual with myeloma following administration of growth factors with or without chemotherapy, or from a donor.*



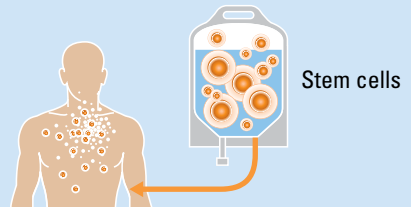
### 2. High-dose chemo

*The cells are processed in the laboratory, frozen, and stored until needed. The person receives high-dose chemotherapy.*



### 3. Infusion

*The stem cells are then thawed and infused into the individual with myeloma.*



*Transplanted stem cells begin to produce new blood cells.*

## SHOULD I RECEIVE MAINTENANCE THERAPY?

There is increasing evidence supporting the role of maintenance therapy after the completion of front-line therapy alone or after front-line therapy and transplantation. Because myeloma is not curable, it will recur even in individuals who initially respond to treatment. The overall goal of maintenance therapy is to maintain the response for as long as possible, thus improving survival.

The results of studies are now showing that maintenance therapy may improve survival and help to keep myeloma in remission after transplantation and suggest it also provides benefit for patients who have not received a transplant. Two large trials showed that Revlimid provides significant benefit as maintenance therapy after transplantation, with one study demonstrating improved survival. Researchers are evaluating other regimens, including Thalomid (alone or in combination with dex or prednisone) or Velcade (alone or with Thalomid). While more data are needed to *definitively* determine the survival benefit of maintenance therapy, more doctors are likely to discuss the benefit and risk of maintenance therapy with their patients based on these promising results.

## TREATMENT OPTIONS FOR RELAPSED OR REFRACTORY MYELOMA

If relapse occurs more than six months after the completion of initial therapy, the initial therapy may be repeated. Alternatively, another regimen commonly used as initial therapy may be given. Participation in a clinical trial is also an option.

Individuals who relapse shortly following completion of initial therapy may no longer respond to the initial medications used. These individuals, as well as those who do not respond to initial therapy, are said to have **refractory disease**. As with the primary treatment of myeloma, recent advances in research have created more options for treating relapsed/refractory disease. These options include:

- A variety of approved agents, including Revlimid-dex, Velcade (with or without dex), Velcade-Doxil, Thal-dex, and conventional chemotherapy agents such as melphalan and cyclophosphamide
- Various published multi-drug combination regimens based on novel therapies with or without steroids and/or chemotherapy, such as Velcade-Revlimid-dex
- Stem cell transplant (if possible)
- Participation in a clinical trial

Participating in a clinical trial offers access to the very latest advances in treatment. The MMRF Patient Navigator Program matches individuals with appropriate clinical trials. To take advantage of this program, you (or your caregiver or family member) can complete a simple questionnaire online.

### **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 new 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 improve survival and quality of life.

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You can call 866.603.MMCT (6628) to speak with a Clinical Trials Specialist who will ask you questions and talk to you about clinical trials that will be appropriate for you. The Specialist can also help you become enrolled in a trial if that is your choice.

Weblinks: Clinical Trial Information  
MMRF Patient Navigator Program  
[www.myelomatrials.org](http://www.myelomatrials.org)

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## QUESTIONS TO ASK YOUR DOCTOR

- 1** Should I be treated now or should therapy be delayed?
- 2** What is the expected outcome of the treatment? What are the goals of this therapy (is it given primarily to treat the disease 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 long is treatment given? How will I be monitored?
- 4** Am I a candidate for stem cell transplantation? If so, what kind—autologous or 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 kinds of side effects might I expect? 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? Is there any follow-up or maintenance therapy?
- 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 side effects?
- 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 fails, what are my options?

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contributions to this brochure.**

## GLOSSARY

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

**Allogeneic transplant** Stem cell transplant in which cells are collected from another person.

**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).

**Anticoagulant** Drug that prevents blood from clotting.

**Antiemetic** Drug that prevents or alleviates nausea and vomiting.

**Autologous transplant** Stem cell transplant in which cells are collected from the individual being treated.

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

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

**Beta<sub>2</sub>-microglobulin (β<sub>2</sub>-microglobulin or β<sub>2</sub>-M)** A protein normally found on the surface of various cells in the body. Increased blood levels occur in inflammatory conditions and certain lymphocyte disorders, such as myeloma.

**Bisphosphonate** Type of drug used to treat osteoporosis and bone disease in individuals with cancer. Bisphosphonates work by inhibiting the activity of bone-destroying cells (osteoclasts).

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

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

**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 kill rapidly dividing cancer cells.

**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).

**Corticosteroids** A potent class of drugs that have 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.

**Front-line therapy** The initial treatment given (also known as first-line therapy).

**Fluorescence 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.

**Gene expression profiling** A test that provides a genetic “fingerprint” of a cancer. The genetic fingerprint can provide an estimate on the risk of relapse.

**Growth factor** Substance that stimulates cells to multiply.

**Hematocrit** Proportion of blood that consists of red blood cells.

**Hemoglobin** Oxygen-carrying substance in red blood cells.

**Hematopoietic 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. (Hematopoietic stem cells are different from embryonic stem cells.) *See also stem cell transplantation.*

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

**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.

**Induction therapy** Treatment used as a first step in shrinking the cancer and in evaluating response to drugs and other therapeutic agents.

**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.

**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.

**Neuropathy** Disorder of the nerves that can result in abnormal or decreased sensation, or burning/tingling. When the hands and feet are affected, it is referred to as peripheral neuropathy.

**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** Antibody-secreting immune cell that develops from a B 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.

**Prognosis** The predicted course of a disease and the outcome after treatment.

**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.

**Red blood cell** Oxygen-transporting blood cell.

**Refractory disease** Disease that is not responsive to therapy.

**Relapse** Return of disease or disease progression.

**Second-line therapy** Treatment that is given after failure of front-line therapy (disease is refractory) or after disease relapses.

**Stem cell transplantation** Therapeutic procedure in which bone marrow or peripheral blood stem cells are collected, stored, and infused into an individual 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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