Multiple Myeloma

Disease Overview

MMRF
Multiple Myeloma
Research Foundation

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Funding treatments faster. Finding a cure.

The Multiple Myeloma Research Foundation (MMRF) was founded in 1998 by identical twin sisters Kathy Giusti and Karen Andrews shortly following Kathy's diagnosis with multiple myeloma. The mission of the MMRF is **to urgently and aggressively fund research that will lead to the development of new treatments for multiple myeloma**.

As the world's number-one funder of multiple myeloma research, the MMRF has raised nearly $100 million to fund 70 laboratories worldwide. The payback on our investment has been significant:

- Four new treatments approved in four years alone when it usually takes nearly 10 years to bring a single treatment to market. These breakthrough treatments are extending the lives of myeloma patients worldwide and are now being explored in a range of other cancers
- Ten clinical trials of novel and combination treatments facilitated by our sister organization, the Multiple Myeloma Research Consortium (MMRC)
- 30 MMRF-supported compounds now in pre-clinical studies and clinical trials

www.themmrf.org

The Multiple Myeloma Research Foundation (MMRF)
383 Main Avenue, 5th Floor • Norwalk, CT 06851
Phone: 203-229-0464 • E-mail: **info@themmrf.org**

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Contents

Introduction

This booklet is designed primarily to help individuals with newly diagnosed multiple myeloma and their friends and families better understand this disease. The information provided here offers an overview of myeloma as a supplement to the information provided by your doctor. Learning as much as possible about multiple myeloma will help you be more involved in making decisions about treatment.

The booklet explains what myeloma is and how it develops within the body. Words that may be unfamiliar are **bolded** throughout the text and defined in the Glossary (page 24). 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 specific treatment choices.

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. To get copies of this booklet or the other MMRF 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.

What Is Multiple Myeloma?

Multiple myeloma (also known as myeloma or **plasma cell** myeloma) is a blood cancer that develops in the **bone marrow**. One type of cell in **bone marrow** is the plasma cell, which produces antibodies (also known as **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 cancer cells , or myeloma cells, produce large quantities of one **antibody** called **monoclonal (M) protein**. Myeloma cells crowd out and inhibit the production of normal blood cells and all other antibodies in the bone marrow, except for M protein. 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 1). These lesions are the hallmark of multiple myeloma and occur throughout much of the skeleton; however, not all individuals with myeloma will have these lesions or other signs of bone loss (Figure 2).

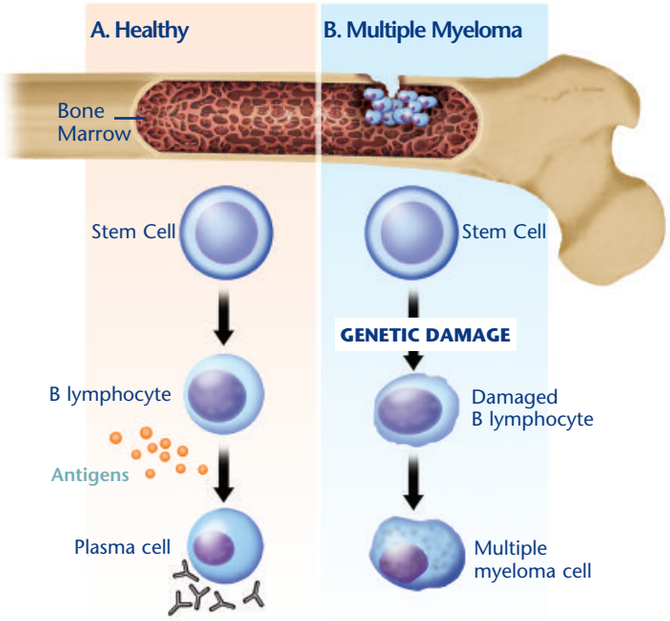

Figure 1. In healthy bone marrow (A), blood-producing **stem cells** produce all types of blood cells, including **lymphocytes**, types of **white blood cells** that help fight off infection. One type of lymphocyte is called a B-cell, which develops into normal plasma cells when foreign substances (antigens) enter the body. Normally, plasma cells make up less than 1% of the cells in the bone marrow, and these plasma cells are capable of making a large variety of different antibodies necessary to fight infection. 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.

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 common blood cancer, after non-Hodgkin's lymphoma, occurring in more individuals than acute leukemia or Hodgkin's disease. It makes up approximately 1% of all cancers and 2% of all cancer deaths. The American Cancer Society estimates that about 19,900 new cases of multiple myeloma will be diagnosed during 2008. The prevalence of disease 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 (Figure 3).

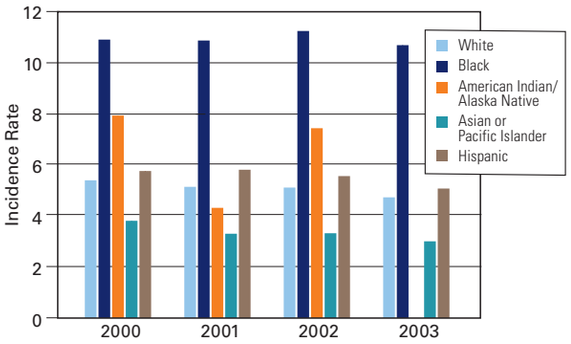

Figure 3. The prevalence of multiple myeloma varies according to race/ethnicity, with the highest rate in the black population and the lowest rate in the Asian or Pacific Islander population.

What Causes Myeloma?

To date, no cause for myeloma has been identified. Research suggests possible associations with a decline in the immune system, 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 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 4).

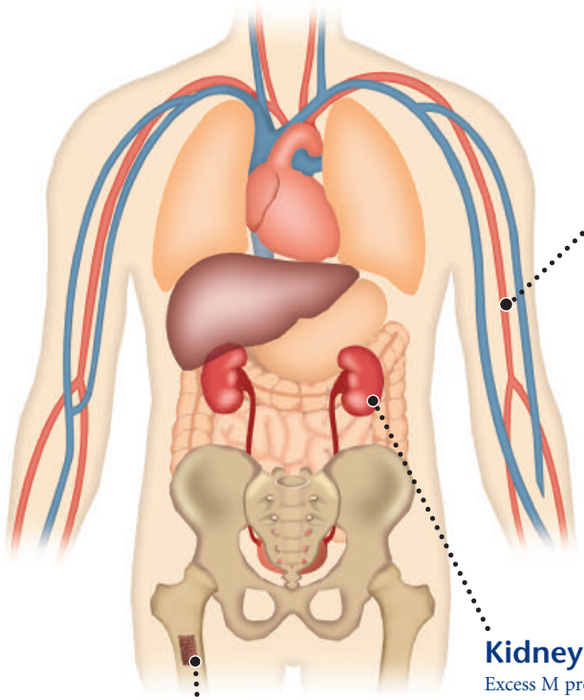

Figure 4. Effect of myeloma on major organs in the body.

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 Ig molecules, also known as **Bence Jones proteins**), crowd out normal functioning Igs 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, rib cage, skull, shoulders, hips, and upper arms. 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 the following:

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

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

- 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?

Once your doctor has 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) under "Other Resources."

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.

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
Blood Specimen		
Complete blood count (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 (see Table 2 for normal values)
Chemistry profile (albumin, calcium, lactate dehydrogenase [LDH], blood urea nitrogen [BUN], and creatinine)	Assess general health status and the extent of disease	Abnormal levels may indicate kidney damage and increased size/number of tumors
Beta-2 microglobulin (ß2-M) 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
C-reactive protein	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 electrophoresis	Detect the presence and level of various proteins, including M protein	Higher levels indicate more extensive disease; aids in classification of disease
Immunofixation electrophoresis (IFE) or immunelectrophoresis	Identify the type of abnormal antibody proteins in the blood	Aids in classification of disease
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
Urine Specimen		
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 and immunoelectrophoresis	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

Table 1 continued on next page

Table 1 continued from previous page

Diagnostic Test	Purpose	Results
Bone/Bone Marrow Specimen		
Imaging studies (bone [skeletal] survey, x-ray, magnetic resonance imaging [MRI], computerized tomography [CT], positron emission tomography [PET]*)	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., fluorescence in situ hybridization [FISH])	Assess the number and normalcy of chromosomes 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.*

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 and plasma cell labeling index (PCLI) are not routinely done for individuals with newly diagnosed myeloma, but these tests are being performed more frequently at some medical institutions that specialize in the treatment of multiple myeloma. How the results of these tests affect the selection of newer treatment agents is still evolving. 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 option.

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.*

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 3). Individuals in the first two categories are considered asymptomatic and do not have to receive treatment immediately. In these cases, delaying treatment until disease progression may allow the person's own immune system to control the disease, avoid side effects and the risk of complications associated with treatment, and delay development of resistance to currently available therapeutic regimens. However, clinical trials are being conducted to determine if newer agents can delay disease progression and improve survival for this group of patients.

Monoclonal gammopathy of undetermined significance (MGUS) is not a malignant condition but is considered to be a precursor to myeloma, with myeloma subsequently developing in about 1% of patients per year or about 20% to 25% of individuals during

their lifetime. No immediate treatment is necessary for MGUS. Immediate treatment is needed, however, for individuals with symptomatic myeloma, which is associated with 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 individuals with multiple myeloma. More information about clinical trials is provided in the MMRF booklet *Multiple Myeloma: Treatment Overview*.

Table 3. Classification of Multiple Myeloma

Classification	Characteristics	Management
Monoclonal gammopathy of undetermined significance (MGUS)	•Blood M protein < 3 g/dL and • Bone marrow plasma cells <10% *and* • No evidence of other B-cell disorders • No related organ or tissue impairmenta • Risk of progression to malignancy: 1% per year	• Close follow-up (also known as "observation")
Asymptomatic, or smoldering, myeloma	• Blood M protein 3 g/dL and/or • Bone marrow plasma cells 10% • No related organ or tissue impairment or symptoms • Risk of progression to malignancy: 10% per year	• Observation, with treatment beginning at disease progression • Participation in a clinical trial • Treatment with **bisphosphonates** for patients with **osteoporosis**, or **osteopenia**
Symptomatic myeloma	• M protein in blood and/or urine • Bone marrow plasma cells or **plasmacytoma** • Related organ or tissue impairment	• Immediate treatment • Treatment with bisphosphonates for patients with osteolytic lesions, osteoporosis, or osteopenia • Participation in a clinical trial

[a]Myeloma-related organ or tissue impairment (end-organ damage) includes hypercalcemia (increased blood calcium levels), impaired kidney function (noted by increased level of blood creatinine), 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. 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 blood's ability to provide oxygen to cells in the body), 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 [normal] or B [abnormal]) (Table 4).

Table 4. The Durie-Salmon Staging System

Stage	Criteria	Myeloma Cell Mass[a]
I (low cell mass)	*All of the following:* • Hemoglobin value >10 g/dL • Blood calcium value normal or < 12 mg/dL • Bone x-ray, normal bone structure or solitary bone plasmacytoma only • Low M-protein production rate (IgG value < 5 g/dL; IgA value < 3 g/dL; Bence Jones protein < 4 g/24 hr.)	< 0.6
II (intermediate cell mass)	*Fitting neither stage I nor stage III*	0.6 -1.2
III (high cell mass)	*One or more of the following:* • Hemoglobin value < 8.5 g/dL • Blood calcium value > 12 mg/dL • Advanced lytic bone lesions • High M-protein production rate (IgG value > 7 g/dL; IgA value > 5 g/dL; Bence Jones protein > 12 g/24 hr.)	> 1.2

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)

[a]The myeloma cell mass is expressed as the number of myeloma cells per body surface area.

Clinical staging systems that may be able to determine prognosis better than the Durie-Salmon system are now being used more frequently. One such system is the International Staging System (ISS), which was developed based on responses to **front-line therapy** with conventional and/or high-dose **chemotherapy** and **stem cell transplant**. The ISS is based on the assessment of two blood results, beta 2-microglobulin (b2-M) and albumin (Table 5). 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).

Table 5. International Staging System for Myeloma

Stage	Criteria
I	β_2-M < 3.5 mg/dL and albumin ≥ 3.5 g/dL
II	β_2-M < 3.5 and albumin < 3.5 g/dL *or* β_2-M 3.5 – 5.5 mg/dL
III	β_2-M > 5.5 mg/dL

b_2-M = beta-2 microglobulin.

Can Outcome Be Predicted?

Several clinical and laboratory findings provide important information about prognosis (Table 6). Many tests can be performed routinely in any laboratory, whereas others are performed only in specialized laboratories or a research setting. 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 doctors 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 the doctor decide when treatment should begin.

Table 6. Prognostic Indicators

Test	Indication	Values indicating a more favorable prognosis (at diagnosis)[a]
β_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
Plasma cell labeling index (PCLI)	Higher index may indicate poorer prognosis	≥ 1%
C-reactive protein level	Higher levels may indicate poorer prognosis	< 6 µg/mL
Lactate dehydrogenase (LDH) level	Higher levels indicate more extensive disease	Age ≤ 60 y: 100-190 U/L Age > 60 y: 110-210 U/L
Plasmablastic morphology[b]	Increased number of immature plasma cells (plasmablasts) indicates poor prognosis	
Chromosome analysis (cytogenetic testing)	Presence of specific abnormalities may indicate poor prognosis	Absence of abnormalities

[a]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.

[b]The number of plasmablasts in the bone marrow.

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
- Health status, including other medical conditions
- Presence of symptoms and complications
- Whether the individual 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. In addition to treatment of the disease, supportive care is provided to alleviate symptoms related to both the disease and its treatment.

Table 7. Therapies for Myeloma[a]

Therapy	Description
Thalomid® (thalidomide, Celgene)	Oral agent shown to be effective across the spectrum of myeloma disease; approved in combination with dexamethasone as front-line therapy
Velcade® (bortezomib, Millennium)	Proteasome inhibitor approved for use in individuals who have received at least one prior therapy; also an appropriate option as part of front-line combination therapy
Revlimid® (lenalidomide, Celgene)	Oral agent that is an improvement over Thalomid, which is approved for use in combination with dexamethasone in individuals who have received at least one prior therapy; also an appropriate option as part of front-line combination therapy
Doxil® (doxorubicin HCl liposome injection, Ortho Biotech)	Chemotherapy agent approved for use in combination with Velcade for individuals who have not previously received Velcade and have received at least one prior therapy
Steroids (corticosteroids) (dexamethasone and prednisone)	Drugs similar to steroid hormones; may be used alone or in combination with other therapies
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 [Alkeran®, Celgene, GlaxoSmithKline] is a chemotherapy agent used frequently for the treatment of myeloma)
High-dose chemotherapy and stem cell transplantation	The use of higher doses of chemotherapy drugs followed by transplantation of stem cells to replace those damaged by the chemotherapy. Autologous transplants are the type of stem cell transplant most commonly performed
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, growth factors, antibiotics, intravenous immunoglobulin, orthopedic interventions, anticoagulants, antiemetics, and drugs to prevent and reduce the severity of neuropathy (nerve damage)

[a]*Approved indications listed are those for the United States.*

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 high-dose chemotherapy and autologous stem cell transplantation (Figure 5). As shown in the treatment pathway, 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, 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 agents (such as erythropoietin) to treat 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.

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

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. At one time, the most common initial treatment was the combination of melphalan and the corticosteroid prednisone (a combination referred to as MP). In addition, Thalomid and newer agents approved for use as second-line therapy, such as Velcade (bortezomib, Millennium) and Revlimid (lenalidomide, Celgene), are being combined with MP and other agents for use as front-line therapy. These drug combinations have been shown to offer improved response rates compared with standard MP. However, the increased efficacy must be balanced against a potential increase in side effects.

Among the drug combinations that may be used for individuals who are not candidates for a transplant are the following:

- MP
- Melphalan, prednisone, and Thalomid (MP-Thal)
- Velcade, melphalan, and prednisone (Velcade-MP)
- Revlimid and low-dose dexamethasone (Revlimid-low-dose dex)
- Revlimid, melphalan, and prednisone (Revlimid-MP)
- Thalomid-dex (Thal-dex)

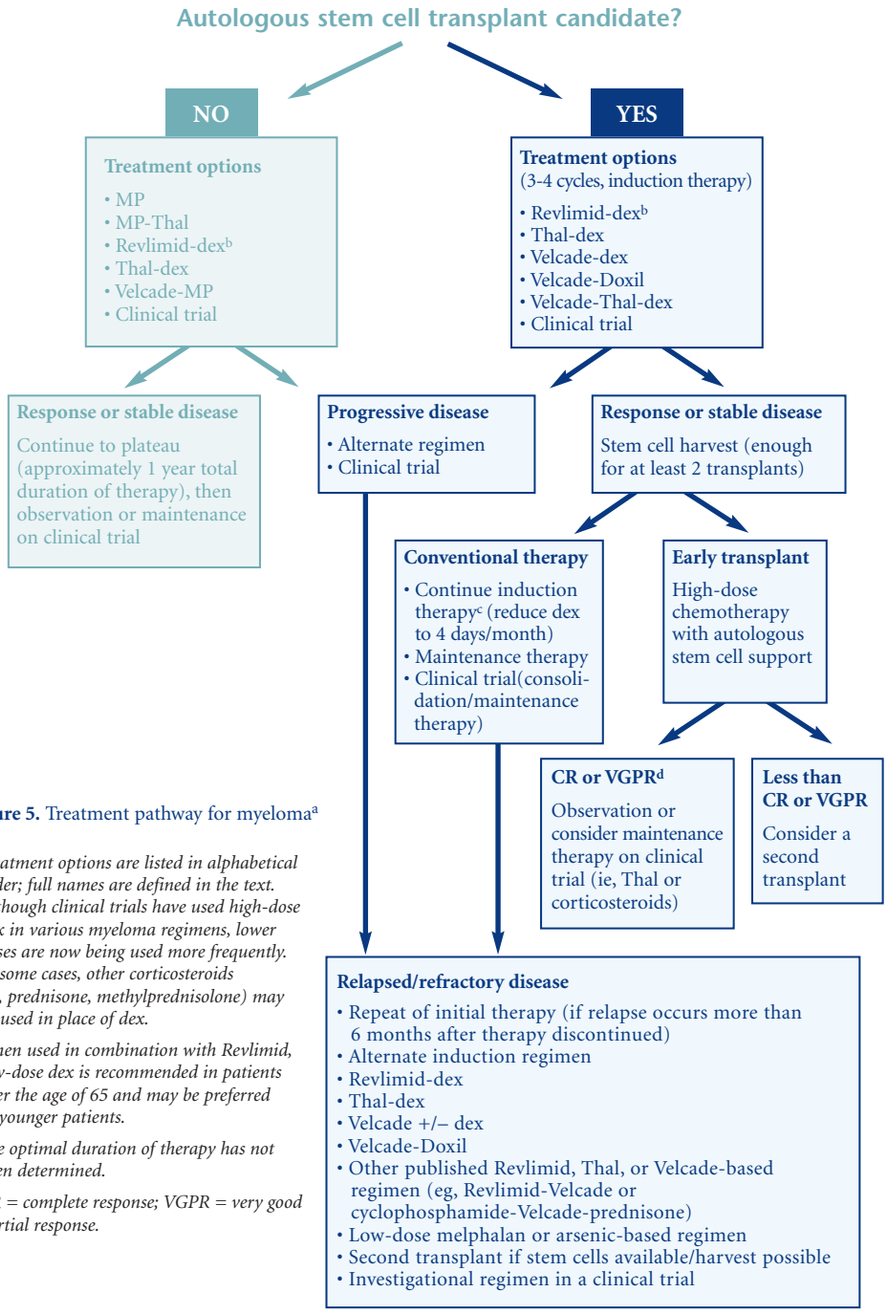

Figure 5. Treatment pathway for myeloma[a]

[a] *Treatment options are listed in alphabetical order; full names are defined in the text. Although clinical trials have used high-dose dex in various myeloma regimens, lower doses are now being used more frequently. In some cases, other corticosteroids (ie, prednisone, methylprednisolone) may be used in place of dex.*

[b] *When used in combination with Revlimid, low-dose dex is recommended in patients over the age of 65 and may be preferred in younger patients.*

[c] *The optimal duration of therapy has not been determined.*

[d] *CR = complete response; VGPR = very good partial response.*

Initial therapy for myeloma is continued for about a year or until the response of the disease to the treatment reaches a plateau. 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 be also 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.

Induction Therapy

Before the transplant is done, initial treatment, referred to as **induction therapy**, is given in three or four cycles to reduce the amount of myeloma cells. The drugs used in induction therapy may differ from those used for individuals who do not have a transplant or who are not candidates for transplant, as the prolonged use of some chemotherapy agents, such as high-dose melphalan, may impair the ability to collect stem cells for use in a transplant.

One of the most commonly used induction therapies has been Thal-dex. Recently, newer agents, such as Revlimid and Velcade, in combination with dexamethasone and other agents, have also been added to the list of options for induction therapy. For example, Revlimid and low-dose dexamethasone (known as Revlimid-low-dose dex) has been found to be a highly effective induction regimen and is associated with better outcomes than Revlimid and high-dose dexamethasone; it may also be better tolerated. Velcade-based regimens, such as Velcade and dexamethasone (Velcade-dex); Velcade, Thalomid, and dexamethasone (Velcade-Thal-dex); and Velcade and Doxil, may also be options for individuals who are candidates for a transplant.

Participation in a clinical trial, such as one evaluating an investigational induction regimen that includes Velcade, Revlimid, Thalomid, or Doxil, 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. The individual's stem cells are collected (also called "harvested") following administration of growth factors with or without chemotherapy, and are reintroduced during the transplant. This type of transplant is called an autologous stem cell transplant. 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. More specific information on stem cell transplants can be found in the MMRF booklet *Multiple Myeloma: Stem Cell Transplantation.*

Treatment Options for Relapsed or Refractory Disease

Individuals who have an initial response to therapy, however, eventually have relapse, as no curative therapies are available yet. Disease that relapses within six months after the completion of initial therapy or that does not respond to initial therapy is known as **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 six months after discontinuing therapy
- Revlimid-dex
- Velcade-melphalan
- Thalomid with dex, melphalan, or prednisone
- Velcade-cyclophosphamide-dex
- Velcade-Doxil
- Velcade with or without dex
- Second transplant if stem cells available/collection possible
- Investigational regimen in a clinical trial

Participating in a clinical trial offers access to the very latest advances in treatment. Therefore, you should always talk to your doctor about what clinical trials may be appropriate. The MMRF Navigator Program was recently developed to help match individuals with appropriate clinical trials. To take advantage of this program, you (or your caregiver or family member) can visit www.myelomatrials.org and complete a simple questionnaire. Or, you can call **866-603-MMCT (6682)** 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.

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 for individuals with multiple myeloma.

If you want to learn more about current and emerging treatment options in myeloma, please read the MMRF booklet *Multiple Myeloma: Treatment Overview.*

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? 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 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 fails, what are my options?

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James R. Berenson, MD
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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 immunoglobulins (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 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 (b2-microglobulin or 2-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.

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.

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.

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.

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.

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 initial therapies.

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: 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 transplant: 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.

Notes

MMRF

Multiple Myeloma Research Foundation

Funding treatments faster. Finding a cure.

Multiple Myeloma Research Foundation
383 Main Avenue, 5th Floor
Norwalk, CT 06851

www.themmrf.org • email: info@themmrf.org

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