# A SCIENCE WRITER'S GUIDE TO BLOOD CANCERS AND RELATED DISORDERS

## MODULE TWO

MULTIPLE MYELOMA

# MODULE 2 – MULTIPLE MYELOMA

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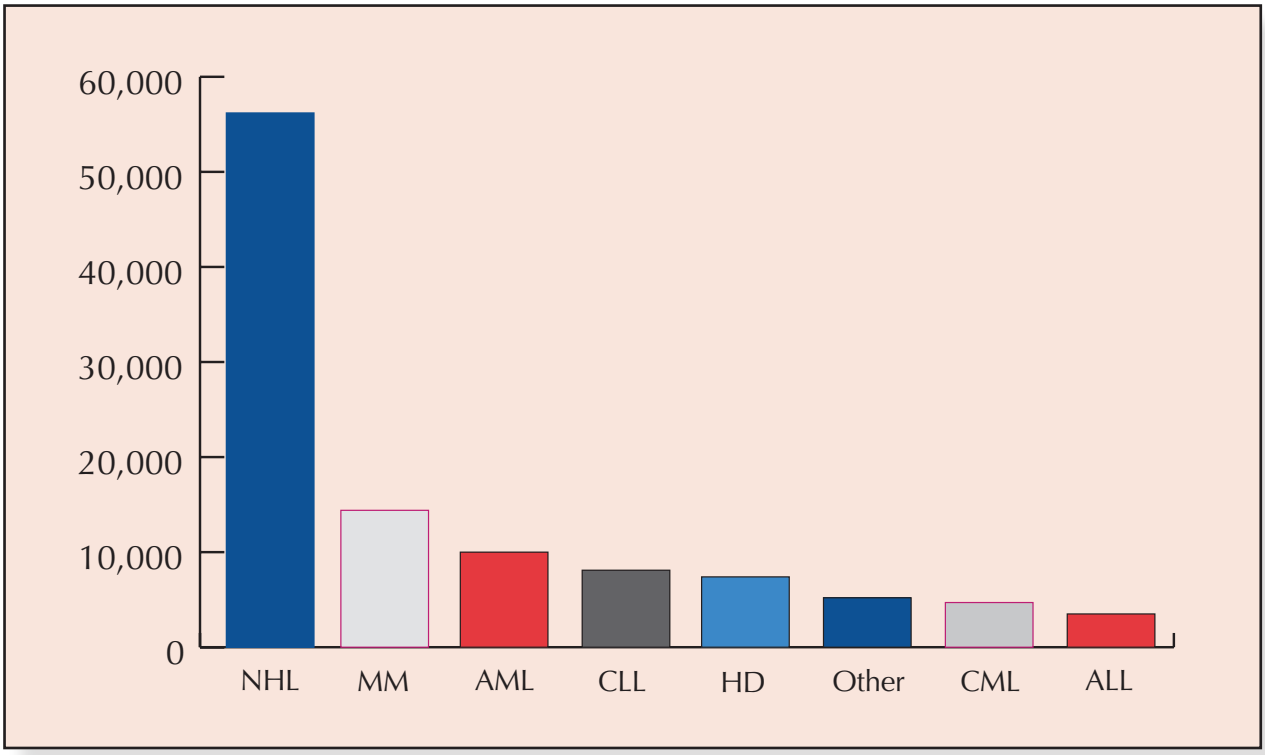
## OVERVIEW OF MULTIPLE MYELOMA

Multiple myeloma, also known as myeloma or plasma cell dyscrasia, is a blood cancer in which plasma cells – important components of the immune system – replicate uncontrollably and accumulate in the bone marrow. Multiple myeloma (MM) is the second most commonly diagnosed blood cancer after non-Hodgkin's lymphoma, with an annual incidence of 15,000 cases in the United States (Figure 1).[1] Approximately 50,000 Americans currently have MM (Figure 2), and an estimated 11,000 die from the disease each year.[1, 2]

### MM at a Glance

- Primarily affects older adults.[3]
- The median age of diagnosis is approximately 65 years.[3]
- An estimated 15,000 new cases are diagnosed each year in the U.S.[1]
- 50,000 Americans currently have MM.[2]
- Approximately 11,000 Americans die from MM every year.[1]
- The five-year survival rate of patients ranges from 10% to 50%.[4]
- Approximately 80% of patients have bone lesions, fractures and/or osteoporosis upon diagnosis.[5]
- About 40% of patients will develop kidney failure.[6]

*Figure 1. Incidence of blood cancers in 2001*




*NHL = non-Hodgkin's lymphoma; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; HD = Hodgkin's disease; CML = chronic myeloid leukemia; ALL = acute lymphocytic leukemia*

Adapted from 1.

Plasma cells are white blood cells that develop from B lymphocytes (B cells) in the bone marrow (Figure 3). Their normal function is to produce and secrete antibodies that help fight infection. Plasma cells that become malignant escape the normal growth controls, generating more and more cancerous cells and accumulating in the bone marrow. In some areas, the cancerous cells may grow rapidly and form a tumor called a plasmacytoma. Occasionally, these tumors occur in only one area and are called solitary plasmacytomas. In most cases, however, multiple plasmacytomas are found, hence the name "multiple myeloma."

*Figure 2. Prevalence of blood cancers*

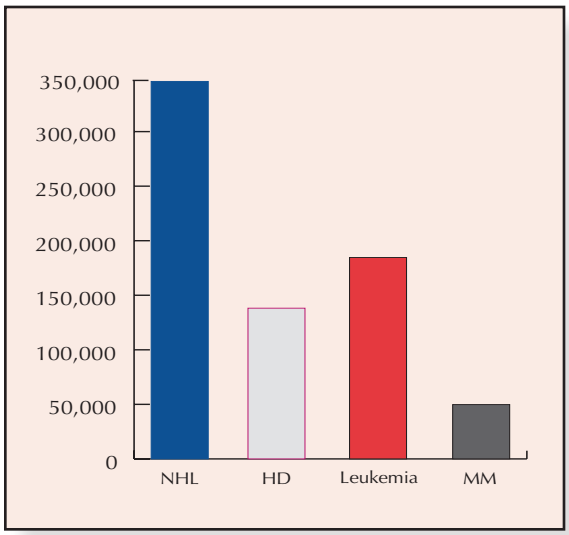



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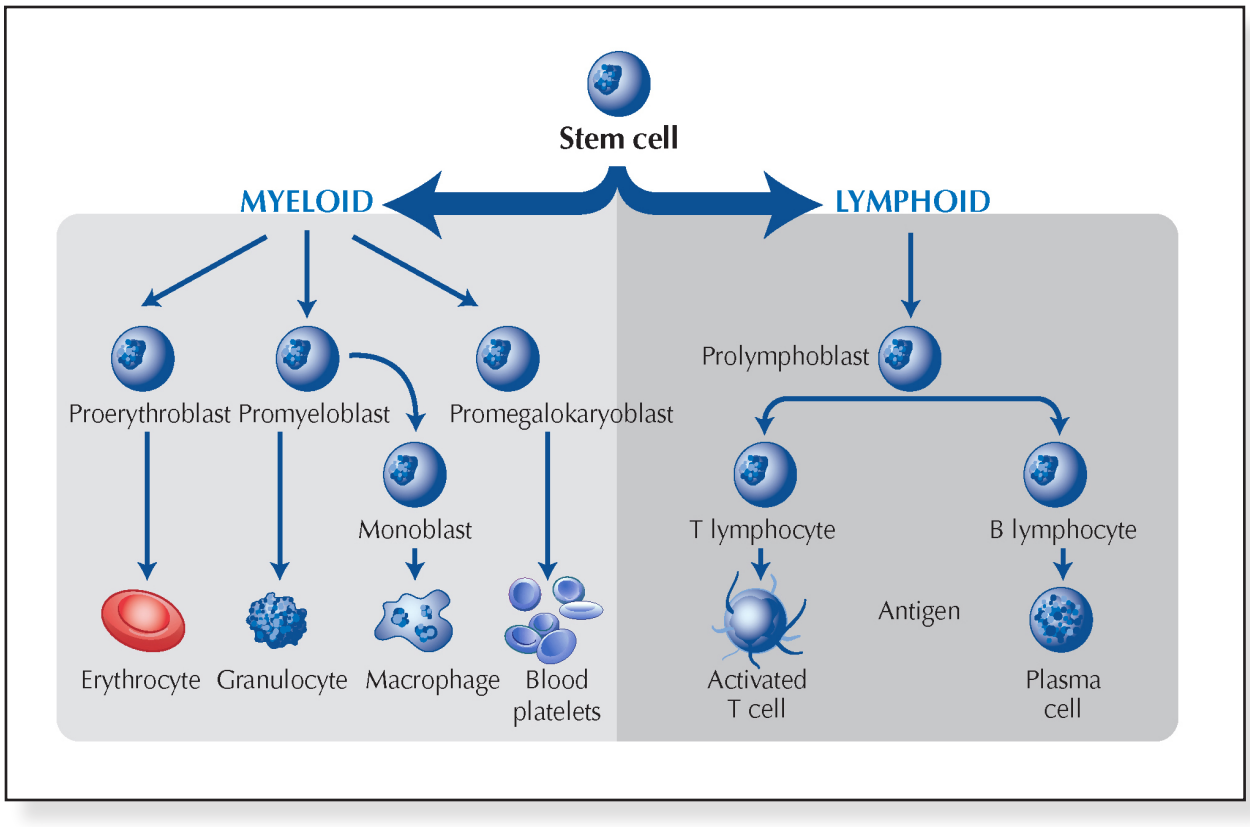
*Figure 3. Origin of plasma cells*




*Hematopoietic stem cells can develop into two types of lymphocytes: B lymphocytes (B cells) and T lymphocytes (T cells). When foreign substances (antigens) such as bacteria enter the body, B cells develop into plasma cells that produce proteins called immunoglobulins (Ig), also known as antibodies, to help fight infection.*

The overabundance of myeloma cells in the bone marrow can have many effects on the body, including bone destruction, anemia, kidney failure and elevated blood calcium levels (hypercalcemia). Many people with MM experience debilitating bone pain and fractures that require radiation or surgery.[7,8] Bone fractures can be particularly dangerous when they occur in the spinal column, and the vertebrae compress or damage nerves. In some cases, paralysis can occur.[9]

MM is sensitive to both chemotherapy and radiation therapy and is therefore treatable, yet it remains incurable.[10] However, important treatment advances have resulted in higher rates of remission and longer survival than were seen in the past.[11] And, as researchers gain a greater understanding of the development and progression of MM, alternative treatment modalities could yield further benefits.

## CAUSES, RISK FACTORS AND EPIDEMIOLOGY

The exact cause of MM is unknown, but several risk factors may increase a person's chance of developing the disease. In some patients, occupational risk factors have been suggested, including repeated exposure to chemicals such as pesticides, benzene and paint sprays.[12–23] Exposure to radioactivity is thought to account for a very small number of cases.[24, 25] Several studies have linked viral infections such as human immunodeficiency virus (HIV) to the development of MM; patients with HIV are 4.5 times more likely to develop the disease than the general population.[26] Persons with Gaucher disease, a hereditary metabolic disorder, are also at significantly higher risk of developing MM than those who do not have the disease.[27] Although MM does not appear to be an inherited disorder, it is more common in some families.[28]

The development of MM is associated with various chromosomal (cytogenetic) abnormalities, including extra or missing copies of particular chromosomes, and deletions or rearrangements of chromosome segments. The most common rearrangements involve genes that encode antibody proteins and genes that regulate cell growth (oncogenes). Some common deletions involve genes that inhibit abnormal cell growth (tumor suppressors).[6]

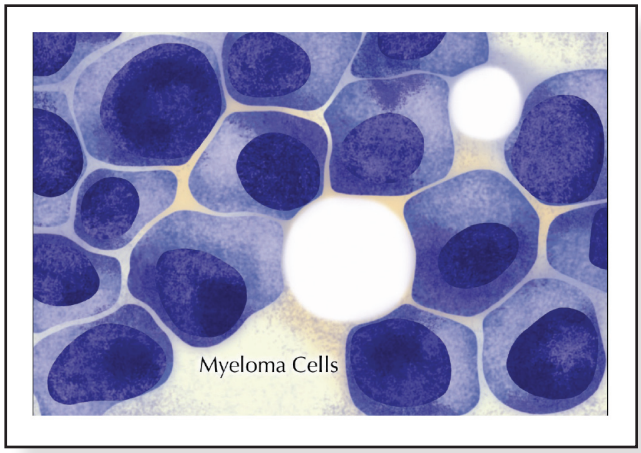
Most people with MM have no known risk factors other than age.[29] The majority of the approximately 50,000 cases of MM in the United States are in individuals over the age of 40, with a slightly higher incidence in males. MM is twice as common in African Americans as in Caucasians.[1, 3, 11] The median age of patients at the time of diagnosis is approximately 65 years.[3]

## PATHOLOGY OF MULTIPLE MYELOMA

The pathogenesis of MM is thought to begin with genetic abnormalities that allow plasma cells to replicate uncontrollably and accumulate in the bone marrow (Figure 4). In the marrow, the malignant cells adhere to and interact with surrounding cells called stromal cells – collectively referred to as the bone marrow microenvironment. Various interactions with these cells and proteins contribute to the spread of the cancer:

- Myeloma cells stimulate stromal cells to produce cytokines, such as interleukin 6 (IL-6), which stimulate the growth of the myeloma cells and inhibit a normal cell-death process known as apoptosis.[30]
- Stromal cells, in turn, stimulate myeloma cells to produce growth factors that promote the development of new blood vessels, or angiogenesis. Vascular endothelial growth factor (VEGF) appears to play a key role in angiogenesis in MM.[31]

*Figure 4.Myeloma cells*




Interactions between myeloma cells and the bone marrow microenvironment also lead to the increased production of cytokines and other factors that activate bone-destroying cells called osteoclasts. Normally, the activity of osteoclasts – known as bone resorption – is counterbalanced by the activity of osteoblasts, which create new bone. In MM, however, osteoblast activity is blocked. The combination of accelerated bone resorption and reduced bone formation results in "osteolytic" lesions and bone loss (osteoporosis).[8, 32]

Normal plasma cells make antibodies, or immunoglobulins (Ig), that help to fight disease. Immunoglobulins are composed of four protein chains, two long "heavy" chains and two shorter "light" chains. Myeloma cells also secrete immunoglobulins, but since the cells are monoclonal (i.e., derived from a single plasma cell), they all produce the same immunoglobulin protein (IgG, IgA, IgD or IgE) in large amounts. The monoclonal (M) protein does not help protect the body from infection. In addition, M protein can build up in organs such as the kidneys, causing serious damage over time. In some cases, myeloma cells secrete immunoglobulins that contain only the light chains.[33] These are known as Bence Jones proteins. In less than 5 percent of cases of MM, myeloma cells do not secrete detectable levels of M protein. These patients are considered to have "nonsecretory" disease.[6]

## SIGNS AND SYMPTOMS

MM can cause many complications, including Calcium elevation (hypercalcemia), Renal (kidney) dysfunction, Anemia and Bone disease. This constellation of signs and symptoms is commonly referred to as "CRAB".[34] These and other complications (see Table 1) are described below.

### Calcium elevation

The destruction of bone results in the release of calcium into the blood (hypercalcemia), which can contribute to fatigue, weakness, loss of appetite, nausea and confusion. Hypercalcemia is a medical emergency because it can result in renal failure.

### Renal dysfunction

Excess proteins and high blood calcium levels associated with MM can damage the kidneys. Impaired renal function is a common complication in MM patients, with about 20 percent presenting with renal failure at diagnosis and another 20 percent developing renal failure in later stages of the illness.[6, 35]

### Anemia

The accumulation of myeloma cells in the bone marrow can interfere with the normal production of healthy blood cells, leading to a shortage of red blood cells (anemia), white blood cells (leukopenia) and platelets (thrombocytopenia). These deficiencies can cause chronic anemia, increased susceptibility to infections and excessive bleeding, respectively.

### Bone disease

The most troubling symptom of MM is bone pain, which is experienced by two-thirds of patients at the time of diagnosis.[7] Osteolytic lesions and inhibition of new bone formation make bones highly susceptible to fractures, which can lead to pain.[8, 32] Fractures of the vertebrae can result in increased pressure on the spinal nerves, causing numbness, tingling, pain or muscle weakness in the lower extremities. Occasionally, myeloma cells grow within the spinal canal and compress the spinal cord. Symptoms of spinal cord compression may include severe back pain, muscle weakness or paralysis, especially of the legs, numbness or tingling and incontinence. Spinal cord compression is a medical emergency and requires immediate treatment to prevent permanent damage.

### Other complications

The excessive production of proteins by myeloma cells can cause a thickening of the blood called hyperviscosity syndrome. Symptoms may include bleeding from the nose and mouth, blurred vision, stroke-like symptoms and congestive heart failure. Hyperviscosity syndrome can be treated by plasmapheresis, a procedure that removes the excess proteins from the blood.[35, 36]

*Table 1. Effects of myeloma*

| Sign or symptom | Impact on patient |
|---|---|
| **Anemia** | Fatigue, weakness, shortness of breath, dizziness, headaches |
| **Thrombocytopenia** | Excessive bleeding |
| **Leukopenia** | Increase in infections |
| **High protein level in the serum and/or urine** | Abnormal thickening of blood, stroke, possible kidney damage |
| **Bone damage** | Bone pain, bone swelling, fracture of bone, collapse of vertebrae, spinal cord compression |
| **High blood calcium** | Mental confusion, dehydration, constipation, fatigue, weakness, loss of appetite, restlessness |
| **Renal failure** | Fatigue, confusion, nausea, vomiting, seizures, decrease in urine output |

## STAGING OF MULTIPLE MYELOMA

Proper staging of MM helps determine the extent of the cancer and the type of treatment a patient will receive. Since 1975, the Durie-Salmon Staging System has been used to categorize MM (Table 2). In this system, the staging of MM is based on several measurements, including levels of M protein, the number of bone lesions, serum calcium levels, hemoglobin levels and renal function.[37]

*Table 2. Durie-Salmon Staging System criteria*

| Stage | Impact on patient |
|---|---|
| **Stage I (low cell mass)** | All of the following:<br>• Hemoglobin value >10 g/dL<br>• Serum calcium value normal or ≤12 mg/dL<br>• Bone X-ray, normal bone structure or solitary bone plasmacytoma<br>• ≤1 bone lesion<br>• Low M-protein production rates<br>  o IgG <5g/dL<br>  o IgA <3g/dL<br>  o Urine M protein <4g/24h<br>• Myeloma cell concentration <0.6 x $10^{12}$ cells/$m^2$ |
| **Stage II (intermediate cell mass)** | • Fitting neither Stage I nor III<br>• Myeloma cell concentration 0.6–1.2 x $10^{12}$ cells/$m^2$ |
| **Stage III (high cell mass)** | One or more of the following:<br>• Hemoglobin value <8.5 g/dL<br>• Serum calcium value >12 mg/dL<br>• Advanced osteolytic bone lesions (>3 bone lesions)<br>• High M-protein production rates<br>  o IgG >7g/dL<br>  o IgA >5g/dL<br>  o Urine M protein >12g/24h<br>• Myeloma cell concentration >1.2 x $10^{12}$ cells/$m^2$ |
| **Sub-classification (either A or B)**<br>• A: relatively normal renal function (serum creatinine value <2 mg/dL)<br>• B: abnormal renal function (serum creatinine value ≥2 mg/dL) | |

Adapted from 37

Due to its complexity and challenges with accuracy, the Durie-Salmon System may soon be replaced with the recently introduced International Staging System (ISS) (Table 3). The ISS is based on only two parameters: serum levels of the proteins albumin and ß2-microglobulin (ß2-M).[38] High levels of ß2-M, a protein normally found on the surface of cells, are a reliable indicator that many myeloma cells are present in the body.[39]

*Table 3. International Staging System (ISS) criteria*

| Stage | Criteria | Definition | Median survival (months) |
|---|---|---|---|
| I | Low ß2-M and normal albumin | ß2-M <3.5 mg/L and albumin ≥3.5 g/dL | 62 |
| II | Patients not meeting criteria for Stage I or III | ß2-M <3.5 mg/L and albumin <3.5 g/dL or ß2-M 3.5 to <5.5 mg/L | 44 |
| III | High ß2-M | ß2-M ≥5.5 mg/L | 29 |

Adapted from 38

## CATEGORIES OF MULTIPLE MYELOMA

Patients with MM are classified into one of several categories, which help to determine treatment options (Table 4).

Monoclonal gammopathy of undetermined significance (MGUS) is a benign condition that is characterized by slightly elevated levels of M protein with no underlying disease.[40] MGUS is 80 to 100 times more common than MM; approximately 75 percent of people with MGUS remain asymptomatic and do not progress to MM.[41]

*Table 4. Categories of MM*

| Category | Characteristics | Management |
|---|---|---|
| **MGUS** | • Serum M protein <3g/dL<br>• Bone marrow plasma cells <10%<br>• Absence of anemia, renal failure, hypercalcemia and osteolytic bone lesions | Observation |
| **Smoldering MM (asymptomatic MM)** | • Serum M protein >3 g/dL *and/or* bone marrow plasma cells ≥10%<br>• Absence of anemia, renal failure, hypercalcemia and osteolytic bone lesions | • Observation with treatment beginning at disease progression<br>• Bisphosphonates<br>• Supportive care<br>• Participation in a clinical trial |
| **Indolent MM (asymptomatic MM)** | • Stable serum/urine M protein<br>• Bone marrow plasmacytosis<br>• Mild anemia or few small osteolytic bone lesions<br>• Absence of symptoms | • Monitoring every three months, with treatment beginning at disease progression<br>• Bisphosphonates<br>• Supportive care<br>• Participation in a clinical trial |
| **Symptomatic MM** | • Presence of serum/urine M protein<br>• Bone marrow plasmacytosis (>30%)<br>• Anemia, renal failure, hypercalcemia or osteolytic bone lesions | Immediate treatment (see Treatment) |

Adapted from 42

## DIAGNOSIS

The signs and symptoms of MM can mimic many other diseases; therefore, a series of evaluations is required to rule out other conditions. Recommendations for the initial diagnostic work-up are outlined below:[10]

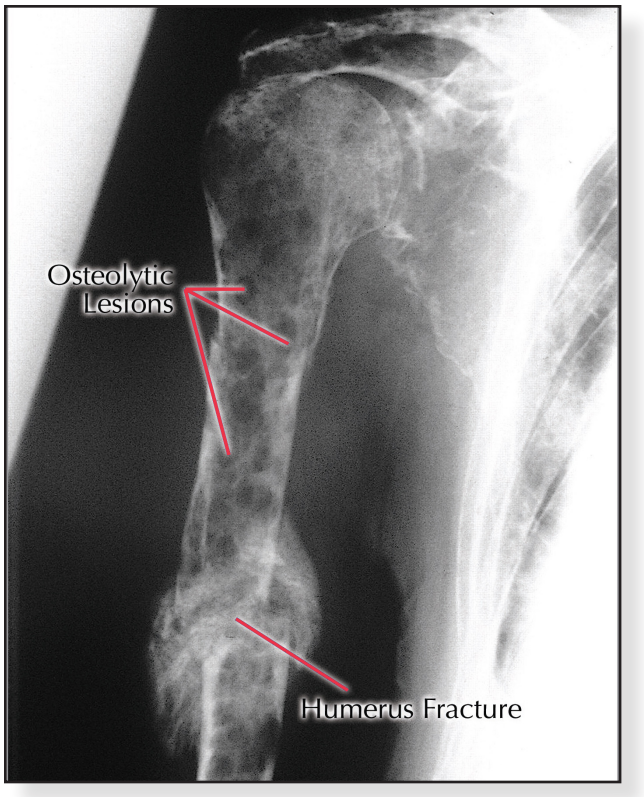
### Blood and urine tests

- A complete blood count (CBC) measures the number and proportions of blood cells.
- A chemistry profile measures the levels of various blood components such as blood urea nitrogen (BUN), calcium, creatinine, lactate dehydrogenase (LDH) and ß2-M.
- A C-reactive protein test determines whether acute inflammation is present.
- Electrophoresis measures the levels of various proteins, particularly M protein, in the blood and urine.
- Immunoelectrophoresis (immunofixation) is used to provide more specific information about the type(s) and proportions of abnormal immunoglobulins that are present (see Immunoelectrophoresis).
- Quantitative immunoglobulins measure the quantity of IgM, IgG and IgA immunoglobulins present in the blood.

### Tests conducted on the bone

- A bone marrow biopsy and bone marrow aspiration – the single most critical test in an MM evaluation – detects an increase in the number of plasma cells in the bone marrow.[34]
- X-rays and other imaging tests (magnetic resonance imaging, computed tomography scan, positron emission tomography scan) are used to evaluate changes in bone structure and determine the number and size of bone tumors (Figure 5).
- A bone density analysis may help assess the severity of diffuse bone loss.

*Figure 5. X-ray of osteolytic lesions and fractured humerus in an MM patient*



## MM Diagnostic Checklist

- **Patient history and physical examination**
- **Blood work-up**
  - CBC with differential and platelet counts
  - BUN, creatinine
  - Electrolytes, calcium, albumin, LDH
  - Quantitative immunoglobulins
  - Serum protein electrophoresis (SPEP) and immunofixation
  - ß2-microglobulin, C-reactive protein (CRP)
  - Serum free light chain assay
- **Urine**
  - Bence Jones quantitation (24-hour urine)
  - 24-hour urine protein electrophoresis (UPEP) and immunofixation
- **Other**
  - Skeletal survey
  - Unilateral bone marrow evaluation with cytogenetics

According to the International Myeloma Working Group, the diagnosis of MM requires the presence of all three of the following criteria:[43]

- Monoclonal plasma cells in the bone marrow ≥10 percent and/or presence of a biopsy-proven plasmacytoma.

- M protein present in the serum and/or urine. If no M protein is detected, then ≥30 percent monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma is required.

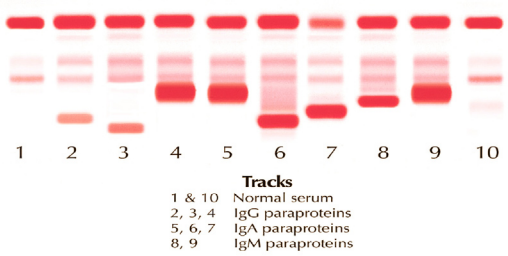
- Signs of one or more MM-related organ dysfunctions:

  - **C**alcium elevation = serum calcium >10.5 mg/L or upper limit of normal
  - **R**enal dysfunction = serum creatinine >2 mg/dL
  - **A**nemia = hemoglobin <10 g/dL or 2 g/dL below normal
  - **B**one disease (osteolytic lesions or osteoporosis)

### Immunoelectrophoresis

Immunoelectrophoresis detects the presence and relative quantity of immunoglobulins such as M protein in the blood. A sample of blood or urine is placed in a small slot cut into a flat sheet of gel. An electric current is then passed through the gel. Since immunoglobulins carry an electric charge, they migrate through the gel, leaving streaks and bands varying in length and intensity depending on the size and amount of the molecule (see Figure 6).

*Figure 6. Protein electrophoresis gel*



## DETERMINING PROGNOSIS

The prognosis of individuals with MM is dependent on a variety of factors including the patient's age and the stage of disease.

A number of laboratory tests have prognostic value and help determine how fast the myeloma cells are growing and specific properties of the cells (Table 5). For example, various genetic abnormalities are associated with low- or high-risk MM. Patients with a deletion of part of chromosome 13, or loss of one copy of this chromosome, typically require aggressive treatment.[44,45]

*Table 5. Prognostic indicators*

| Test | Description |
|---|---|
| **ß2-M** | Serum levels reflect extent of disease |
| **Plasma cell labeling index (PCLI)** | Relative percentage of plasma cells actively growing; a low PCLI may indicate longer survival |
| **C-reactive protein (CRP)** | Increased levels of CRP may indicate poorer prognosis |
| **Lactate dehydrogenase (LDH)** | LDH may reflect tumor-cell burden |
| **Albumin** | Serum levels often indicate general health status; higher levels may indicate a better prognosis |
| **Chromosome analysis, including fluorescence in situ hybridization (cytogenetic testing)** | Assesses the number and composition of chromosomes; some abnormalities, such as loss of chromosome 13, are associated with poor prognosis |

Adapted from 44-49

### Treatment response

Prognosis can also be determined based on treatment response (Table 6). For example, patients who have had a prior response to chemotherapy may also respond to treatment with the same or another chemotherapy if the disease relapses.[50] In general, individuals who achieve a complete response and those who have a longer duration of response between treatments will have a more favorable outcome.[51, 52, 53]

*Table 6. European Group for Blood and Marrow Transplant (EBMT) or Blade criteria for determination of response to therapy**

| Response | Serum M protein | % plasma cells in bone marrow | Skeletal disease (on X-ray) |
|---|---|---|---|
| **Complete response** | 100% decrease and immunofixation electrophoresis negative | <5% | Stable |
| **Partial response** | ≥50% decrease | N/A | Stable |
| **Minimal response** | 25–49% decrease | N/A | Stable |
| **Stable disease** | Not meeting criteria for minimal response or progressive disease | | |
| **Progressive disease** | >25% increase | >25% increase | Increase in number of new bone lesions or increase in size of existing lesions |

* Includes two assessments performed six weeks apart. Responses must have lasted at least six weeks.
Adapted from 54

## Survival rates

Because MM is incurable, disease is often discussed in terms of survival rates, which are based on the percentage of people who are alive for a given period of time after diagnosis. This is commonly expressed as the five-year survival rate and does not account for people dying from another cause, such as heart disease. The five-year survival rate of people with MM ranges from 10 to 50 percent, depending on the stage of the cancer at diagnosis and the patient's response to treatment.[4] These rates are not predictive in any single case; rather they represent statistics from a general population.

# TREATMENT OF MULTIPLE MYELOMA

There is no one standard treatment for MM, and choice of therapy depends on many factors, including physical exam and laboratory test results, the specific stage or classification of the disease, age and general health, symptoms, presence of complications and prior treatment.[10]

Key objectives for MM treatment include:

- Kill myeloma cells and control the disease to prevent damage to various organs
- Control tumor growth, extend disease-free survival time and prolong life
- Control pain and other disease-related symptoms
- Allow patients to have an active and good quality of life

## Newly diagnosed patients

Newly diagnosed MM is managed based on the clinical features of the disease. Patients with a solitary plasmacytoma, for example, are usually treated with radiation therapy and/or surgery. According to the National Comprehensive Care Network (NCCN), patients with inactive (i.e., asymptomatic) MM should be observed but should not receive initial treatment outside of a clinical trial, since they can go for months or even years without disease progression.[10]

Patients with symptomatic MM typically receive some form of initial therapy along with bisphosphonates (drugs that counter the ill effects of MM on the bones) and other supportive therapies (see below). The main goal of initial therapy is to bring the cancer into remission. Commonly used regimens for initial therapy include traditional agents such as corticosteroids (e.g., dexamethasone), combination regimens such as VAD (vincristine, doxorubicin and dexamethasone) and alkylating agents such as melphalan. The selection of initial therapies is now more varied with the introduction of novel immunomodulatory agents, which are sometimes used in combination with traditional agents.[10]

The choice of initial treatment depends on whether the patient and his or her physician want to pursue high-dose chemotherapy and autologous stem cell transplant (SCT), which involves the collection and transplantation of stem cells from the patient's own blood (see below), as a consolidation therapy. Treatments used prior to high-dose chemotherapy and SCT are also known as induction therapies. Agents that are less toxic to bone marrow are preferred for induction therapy because they result in a greater yield of stem cells, which are frozen prior to the administration of high-dose chemotherapy.[55]

## Stem cell transplantation

SCT is performed after a patient receives high-dose chemotherapy, which destroys cancerous cells more effectively than conventional therapy, but also kills the normal precursors of new blood cells. SCT replaces these blood-forming cells. The procedure is generally more common in patients under the age of 65 in good physical condition and older patients in very good health.[10]

High-dose chemotherapy followed by autologous SCT, which uses the patient's own stem cells, is associated with higher response rates, longer time to disease progression, longer event-free survival and longer overall survival than standard therapies.[10, 56] Side effects of the procedure are related to the toxicities of high-dose chemotherapy and include nausea, vomiting, diarrhea, mouth sores, skin rash and hair loss. Patients are also susceptible to infection, anemia and bleeding due to the destruction of blood-forming cells. Treatment-related mortality is approximately 15 percent.[56] On average, it takes two to three months to recover after an autologous SCT; however, patients may not be able to return to their normal routine for as long as a year.[57]

Allogeneic SCT, which involves the use of stem cells harvested from a healthy donor, is another form of transplantation that can be used to regenerate blood cells following high-dose chemotherapy. However, allogeneic SCT has varying degrees of success due to a higher rate of complications, a higher incidence of treatment-related mortality (30 to 50 percent), and a longer recovery time than autologous SCT.[56, 57] For these reasons, this form of treatment is usually only performed in clinical trials. In order to overcome the high mortality rate associated with allogeneic SCT, investigators are using lower doses of chemotherapeutic agents that do not destroy the bone marrow completely. This is called a "non-myeloablative" or "mini" allogeneic transplant.[57]

## Maintenance therapy

The goal of maintenance therapy is to maintain remission and quality of life for the patient. Several drugs may increase the duration of the initial remission to varying degrees, although evidence for a survival benefit has been variable.[10] Drugs that have been or are being studied as maintenance therapies include corticosteroids (dexamethasone and prednisone), immunomodulatory drugs and alpha interferon.[58]

## Refractory or relapsing MM

Approximately 10 to 30 percent of patients with newly diagnosed MM do not respond to chemotherapy (i.e., are refractory to treatment, defined as a less than 50 percent decrease in the M protein in serum and/or new bone disease or hypercalcemia). Moreover, nearly all MM patients who achieve an initial response will relapse.[6, 10] The goal for these patients is to keep the cancer under control for a longer period of time without progression of the disease.

For chemotherapy-refractory patients, various conventional therapies are used to induce a response. Novel agents, including proteasome inhibitors (bortezomib) and immunomodulatory drugs, have been shown to be superior to conventional therapies in patients with refractory MM.[10, 58]

Among patients who have experienced a relapse, up to 60 percent will respond to the same regimen that induced the first remission.[6] For the remainder, conventional and/or novel agents are often used to induce another remission. Patients who relapse after autologous SCT may be treated with allogeneic SCT, a second autologous SCT or novel therapies.[10]

## Supportive care

Supportive care strategies are an important aspect of the treatment of MM because they address the symptoms and complications of the disease, such as bone pain, anemia and increased infections.

- Bisphosphonates, a class of drugs that inhibit osteoclast activity, significantly reduce the number of skeletal-related events in MM patients, such as the formation of new osteolytic lesions, fractures, bone pain and hypercalcemia.

- Surgery may be used to relieve pressure from an isolated plasmacytoma on the spine, and bone cement can be injected within vertebrae to relieve pain and strengthen the spine.

- Some MM patients receive radiation therapy as palliative treatment to relieve uncontrolled pain and to help prevent or treat bone fractures or spinal cord compression.[10]

- The administration of erythropoietin, a hormone that stimulates red blood cell production and maturation, can improve red blood cell counts in patients with chronic anemia.[59] In patients with severe anemia, blood transfusions can be administered.

- Hormone-like substances called colony stimulating factors (CSF) can be used to stimulate the production and maturation of other blood cells such as neutrophils and monocytes.

- Antibiotics, pain control measures and orthopedic interventions, such as braces and corsets, are also important supportive care strategies.

## Conclusion

Although the use of high-dose chemotherapy with SCT has improved the duration of response to therapy; only 5 to 10 percent of patients with MM survive longer than 10 years. Furthermore, up to 30 percent of newly diagnosed patients do not respond to chemotherapy, and nearly all patients who do respond to any form of treatment will eventually relapse.[6] Thus, there remains a great need for new treatments and combinations of treatments based on an understanding of the underlying disease.

## EMERGING THERAPIES

A better understanding of the pathogenesis and progression of MM has led to the development of new treatments that target both the myeloma cell and the bone marrow microenvironment. Combination therapies involving established and investigational drugs also hold promise. Treatments currently under investigation for the treatment of MM are listed below.[60, 61]

- **Lenalidomide –** The mechanism of action of lenalidomide is not fully understood. It modulates the production of cytokines that inhibit inflammation and promote immune responses; induces the proliferation of T lymphocytes; augments the activity of natural killer cells; inhibits the proliferation of hematopoietic cell lines (cells that reproduce indefinitely under laboratory conditions); and inhibits the growth of new blood vessels.
- **Bevacizumab –** Bevacizumab inhibits a protein called VEGF, which is considered to play a role in growth of new blood vessels and proliferation of blood cells.
- **Tipifarnib –** Tipifarnib inhibits farnesyl transferase activity, which prevents the activation of the growth-promoting ras gene.
- **Thalidomide –** The mechanism of action of thalidomide is not fully understood but may be related to suppression of excessive TNF-alpha production and down-modulation of selected cell surface adhesion molecules involved in white blood cell migration.
- **PTK787/ZK222582 –** This drug inhibits VEGF receptor kinase and other tyrosine kinases involved in angiogenesis.
- **Depsipeptide, SAHA, PXD101 –** These drugs inhibit histone deacetylases, which help to package DNA and regulate gene expression.
- **Doxil –** Doxil interferes with the growth of cancer cells by binding to DNA and inhibiting nucleic acid synthesis.
- **Aplidin –** This drug is thought to inhibit VEGF and induce apoptosis.
- **Arsenic trioxide –** Arsenic trioxide directly inhibits the growth of cancer cells and induces apoptosis; blocks the ability of myeloma cells to "stick" to bone marrow stromal cells by inhibiting the production of adhesion molecules on the surfaces of both cell types; and inhibits the secretion of IL-6 and the production of VEGF.
- **17-AAG –** 17-AAG [17-(allylamino)-17-demethoxygeldanamycin] is an inhibitor of the heat shock protein Hsp90, which promotes myeloma cell growth and survival.
- **CHIR-258 –** CHIR-258 is an inhibitor of the fibroblast growth factor receptor 3 (FGFR3), which regulates cell growth and angiogenesis.
- **Atiprimod –** Atiprimod inhibits IL-6, which is essential for cancer cell growth; also inhibits bone erosion.
- **SCIO-469 –** SCIO-469 inhibits the protein p38 MAP kinase, which is involved in the production of IL-6 and VEGF.
- **CCI-779 –** CCI-779 inhibits the mammalian target of rapamycin (mTOR) pathway, which facilitates cell growth.

## GLOSSARY OF TERMS

**Albumin –** The most abundant protein found in blood plasma.

**Anemia –** Condition in which there are too few red blood cells in the bloodstream, resulting in insufficient oxygen to tissues and organs. Symptoms include fatigue, shortness of breath and weakness; untreated, severe anemia can lead to organ failure and death.

**Angiogenesis –** Production of new blood vessels. Certain substances in the body induce this process, which is required for normal hematopoiesis.

**Antibody –** See immunoglobulin.

**Antigen –** Substance (e.g., protein on the surface of a virus) capable of inducing an immune response.

**Apoptosis –** Programmed cell death. Within certain tissues, cells reproduce and replenish continuously; apoptosis is necessary to prevent an over-abundance of cells.

**Beta 2-microglobulin (ß2-microglobulin) –** Protein found on the surface of many cells; in active MM, increased production of myeloma cells causes ß2-microglobulin levels in the blood to increase.

**Bence Jones protein –** Characteristic protein found in the urine of many patients with MM. The protein is a fragment of a larger immunoglobulin molecule secreted by myeloma cells.

**Bisphosphonate –** Type of drug that blocks adhesion of myeloma cells to the bone and inhibits osteoclast activity, reducing the number of fractures and lesions in patients with MM.

**Blood urea nitrogen (BUN) –** Diagnostic blood test that measures the serum level of urea, the major breakdown product of protein metabolism that is ordinarily removed by the kidneys, to assess renal function. During renal failure, urea accumulates in the blood.

**B lymphocytes –** Also known as B cells. One of two main types of lymphocytes. Mature B lymphocytes known as plasma cells govern the humoral immune response by producing and secreting antibodies that destroy a specific antigen.

**Bone marrow –** Soft, spongy tissue located in the center of bones that produces hematopoietic stem cells, which differentiate and mature into red and white blood cells and platelets.

**Bone marrow aspiration –** Removal by needle of a sample of fluid and cells from the bone marrow for microscopic examination.

**Bone marrow biopsy –** Removal by needle of a sample of tissue from bone. A biopsy is often performed at the same time as a bone marrow aspiration and is especially useful when the aspiration does not yield an adequate sample. Biopsies provide the most reliable information about the bone marrow and can show if there is damage or scarring within the marrow.

**Calcium –** Mineral found mainly in the hard part of the bone.

**Chemotherapy –** The use of drugs to kill cancer cells.

**Chromosomes –** Structures contained in the nuclei of cells that are made up of strands of deoxyribonucleic acid (DNA) and the genes encoded within them.

**Complete blood count (CBC) –** Clinical laboratory test that provides information about the types and number of cells in the blood.

**C-reactive protein –** Specific protein produced by the liver that is present during episodes of acute inflammation or in disease states.

**Creatinine –** Chemical normally excreted by the kidneys. If the kidneys are damaged, the serum level of creatinine builds up.

**Cytogenetics –** Evaluation of the chromosomal and genetic characteristics of human cells.

**Cytokine –** Hormone-like proteins that govern immune reactions and mediate cell reproduction and function.

**Electophoresis –** Technique of separating electrically charged particles, particularly proteins, in a solution by passing an electric current through the solution. The rate of movement of the different components depends upon their charge, so that they gradually separate into bands. Electrophoresis is widely used in the analysis of the different proteins in blood serum.

**Erythropoietin –** Naturally occurring hormone that stimulates formation of erythroblasts and the release of maturing red blood cells from the bone marrow into the blood.

**Farnesyl transferase inhibitors –** Novel class of investigational drugs that target a gene mutation referred to as the ras proto-oncogene, which is expressed in various forms of cancer. It is also believed farnesyl transferase inhibitors act upon other, as yet unidentified pathologic mechanisms.

**Growth factors –** Substances that stimulate the bone marrow to produce mature blood cells. They are produced naturally in the body; synthetic versions of them have been developed to promote cell production in people with blood cell deficiencies due to disease or as a result of chemotherapy/radiation.

**Hemoglobin –** Iron-protein compound in red blood cells responsible for transporting oxygen from the lungs to the tissues.

**Hypercalcemia –** Abnormally high concentration of calcium in the blood. In MM, the breakdown of bone, which is rich in calcium, is the main cause of high calcium levels in the blood and urine.

**Hyperviscosity –** Thickening of blood, which can result from excess protein in blood.

**Immunoelectrophoresis –** Type of electrophoresis that uses special antibody staining techniques to identify specific types of immunoglobulins.

**Immunoglobulin –** Also known as antibodies, immunoglobulins (Ig) are proteins produced by plasma cells that help fight infection by targeting specific antigens on bacteria, viruses, toxins or tumors. They consist of heavy chains and light chains and are divided into five classes – IgA, IgD, IgE, IgG, IgM – according to their structure.

L**actate dehydrogenase –** Enzyme that at high levels indicates the presence of tissue damage.

**Leukopenia –** Abnormally low number of white blood cells in the circulating blood.

**Lymphocytes –** White blood cells that govern the body's immune responses. There are two main types – T lymphocytes and B lymphocytes.

**Monoclonal gammopathy of undetermined significance (MGUS) –** Condition related to MM in which levels of M protein are slightly elevated, but no underlying disease is noted. Most people with MGUS remain well and never have symptoms.

**Monoclonal (M) protein –** Immunoglobulin protein produced by myeloma cells.

**Morphology –** Study of cells and cell structure in body tissues.

**Myelosuppression –** Decrease in the production of red blood cells, platelets and some white blood cells in the bone marrow.

**Neutropenia –** Shortage of neutrophils in the bloodstream, making patients vulnerable to multiple infections.

**Oncogenes –** Genes that promote cell growth and replication. These genes are normally present in all cells. Oncogenes may undergo changes (mutations) that activate them, causing cells to grow uncontrollably and form tumors.

**Osteoblast –** Cell that produces the tissue and minerals that give bone its strength.

**Osteoclast –** Cell that absorbs and removes old or worn-out bone.

**Osteoporosis –** Bone disease characterized by a reduction of bone mass and a deterioration of the bone structure, leading to bone fragility.

**Plasma cell –** White blood that develops from a B lymphocyte and produces antibodies to help fight disease and infection.

**Plasma cell labeling index –** Prognostic test that measures the relative percentage of plasma cells actively growing.

**Plasmacytoma –** Collection of cancerous plasma cells found in a single location rather than diffusely throughout the bone marrow, soft tissue or bone. If there is only one such area of bone involved it is called a solitary plasmacytoma. An area outside of bone may be referred to as an extramedullary plasmacytoma.

**Plasmapheresis –** Purification of plasma in order to remove certain proteins, such as excess M protein, from the blood.

**Platelet –** Also called a thrombocyte. A small cell that has an essential role in blood clotting.

**Proliferation –** Reproduction and increase in number of cells.

**Proteasome –** Specialized structure (organelle) in cells that degrades or breaks down proteins.

**Radiation therapy –** The use of high-energy radiation from X-rays, gamma rays, neutrons or other sources to kill cancer cells and shrink tumors.

**Resorption –** Process of breaking down old or worn-out bone.

**Stem cells –** Hematopoietic stem cells in the bone marrow differentiate and mature into mature, functional red and white blood cells.

**Thrombocyte –** See platelet.

**Thrombocytopenia –** Shortage of platelets in the bloodstream associated with an increased risk of bleeding.

**Tumor necrosis factor (TNF)-alpha –** Protein that is produced by certain blood cells (monocytes and macrophages) in response to infection and other stimuli (cytokines). TNF-alpha activates white blood cells and has anti-tumor activity.

**Tumor suppressor genes –** Genes in the body that can suppress or block the development of cancer.

**Vascular-endothelial growth factor (VEGF) –** Naturally occurring substance that promotes production of new blood vessels and reproduction of stem cells.

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## APPENDIX: RESOURCES

**Patient and professional education and information**

American Cancer Society (www.cancer.gov)

American Society of Clinical Oncology (www.asco.org)

American Society of Hematology (www.hematology.org)

National Comprehensive Cancer Network (www.nccn.org)

National Cancer Institute (www.nci.nih.gov)

International Myeloma Foundation (www.myeloma.org)

Multiple Myeloma Research Foundation (www.multiplemyeloma.org)

Multiple Myeloma Association (www.webspawner.com/users/myelomaexchange)


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