MULTIPLE MYELOMA

A SCIENCE WRITER'S GUIDE

PREFACE

Blood cancers and related disorders – a serious health risk

In a 2003 address to the U.S. Senate Committee on Appropriations of Funding, George Dahlman, vice president of the Leukemia and Lymphoma Society, called blood cancers "a serious health risk to all Americans." Although recent progress has been made in the diagnosis and treatment of blood-related malignancies, their incidence is on the rise, and they collectively cause more deaths than all other cancers, except for cancer of the lungs.

The World Health Organization has classified more than 20 cancers that affect one or more components of the blood. Leukemias (all types combined) and non-Hodgkin's lymphoma are the most common and the most familiar hematologic malignancies, with a combined annual rate of approximately 110,000 new cases per year in the United States.

Lesser known forms of blood cancer such as multiple myeloma (MM) and myelodysplastic syndromes (MDS) represent a significant cause of cancer-related morbidity and mortality in the United States (Figure 1). MM, which ranks as the third most prevalent blood cancer after non-Hodgkin's lymphoma and the combined leukemias, is responsible for approximately 10,700 U.S. deaths each year. MDS is as prevalent as chronic lymphocytic leukemia, one of the most common forms of leukemia. In its most aggressive form, MDS can be fatal within one year of diagnosis.

With greater understanding of the underlying pathology of blood cancers and related disorders and the introduction of new therapeutic options, the outlook for some of these diseases has improved over the past several decades. Still, as George Dahlman emphasized in his speech to the Senate, research into new and improved treatments must remain a priority.

This guide has been developed to help health and science writers prepare to cover important news about blood cancers, particularly MM.

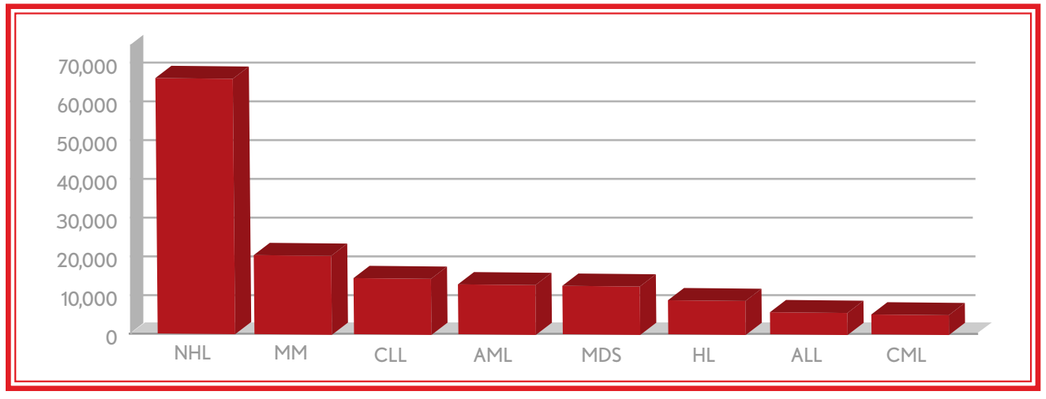

Figure 1. Incidence of blood cancers in the United States, 2011. NHL = non-Hodgkin's lymphoma; MM = multiple myeloma; CLL = chronic lymphocytic leukemia; AML = acute myeloid leukemia; MDS = myelodysplastic syndromes; HL = Hodgkin's lymphoma; ALL = acute lymphocytic leukemia; CML = chronic myeloid leukemia

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WHAT IS BLOOD CANCER?

To understand the underlying pathology and clinical course of blood cancers, it is important to first understand the process of blood cell production and the roles different blood cells play in maintaining health.

COMPONENTS OF BLOOD

Blood is composed of several types of specialized cells that circulate in plasma, a straw-colored fluid. Major functions of blood include delivering oxygen and nutrients to tissues throughout the body, fighting infection and clotting to heal wounds. The blood cells responsible for transporting oxygen are called erythrocytes, or red blood cells. Leukocytes, or white blood cells, make up the infection-fighting or immune component, of blood and comprise many different cell types, including neutrophils. Platelets (thrombocytes) form blood clots.

BLOOD CELL PRODUCTION

Blood cells are produced in the bone marrow through a process referred to as hematopoiesis. The bone marrow contains hematopoietic stem cells, which are precursors to all blood cells in the body. Hormone-like proteins called cytokines cause hematopoietic stem cells to proliferate and differentiate through a series of steps into mature red or white blood cells or platelets (Figure 2).

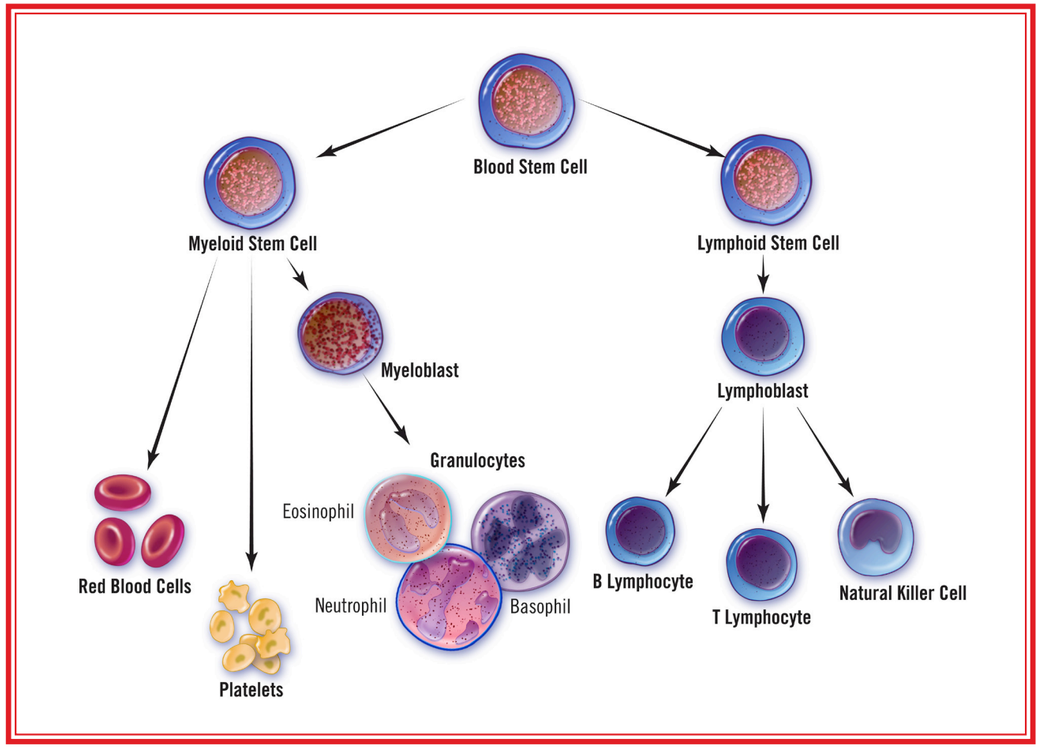

Figure 2. Hematopoiesis. Hematopoietic stem cells undergo step-wise changes that lead them down different maturation pathways. Eventually, the stem cells become erythrocytes (red blood cells), platelets (clotting factors), or any number of infection-fighting white blood cells (such as T and B cells, neutrophils, or macrophages).

Blood cancer is characterized by the uncontrolled growth of abnormal cells within the blood or bone marrow (the soft blood-forming tissue that fills the cavities of bones). Blood cancer begins when a blood cell becomes malignant (cancerous), usually due to abnormalities in the cell's genetic material (chromosomes). As the cell replicates and more cancerous cells are produced, they accumulate and crowd out healthy blood cells, impairing the body's immune response. The accumulation of cancerous cells can also leave the body vulnerable to a variety of debilitating and dangerous conditions such as anemia (too few red blood cells), neutropenia (too few white blood cells) and thrombocytopenia (too few platelets, or blood-clotting cells) (Table 1). If untreated, blood cancer eventually can invade other organs, such as the lymph nodes and spleen.

Table 1. Signs and symptoms associated with blood cancers

Anemia	Neutropenia	Thrombocytopenia
• Fatigue • Shortness of breath • Dizziness • Headaches • Palior (paleness) • Heart palpitations	• Frequent infections • Infections that do not resolve • Mouth sores • Fevers	• Excessive bleeding (nose bleeds, bleeding while brushing teeth) • Bruising • Petechiae (tiny, rash-like bruises on the skin)

As shown in Table 2, the type of cell affected and location of the malignancy determines the type of blood cancer or blood disorder.

Table 2. Type of cell affected and location of the malignancy

Type	Affected cell	Description
Leukemia	Lymphocyte	Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of white blood cells to be produced and enter the bloodstream.
Lymphoma	Lymphocyte	Cancer that originates in the lymphatic system – a network that distributes immune cells throughout the body via a fluid called lymph – and is characterized by the over-production of white blood cells, which can lead to tumors in the lymph nodes.
Multiple myeloma	Plasma cell	Cancer that causes the excessive proliferation of antibody-producing white blood cells, which can result in the formation of tumors in the bone marrow called myelomas.
Myelodysplastic syndromes	Stem cell	Blood cancer in which the cells that give rise to red blood cells, white blood cells and platelets fail to develop normally, resulting in low numbers of mature blood cells.
Myelofibrosis	Fibroblast	Blood disorder that is caused by the over-production of connective tissue by cells called fibroblasts, which disrupts the normal production of blood cells and causes scarring of the bone marrow.
Amyloidosis	Plasma cell	Blood disorder that originates in the bone marrow and occurs when plasma cells overproduce the amyloid protein, which accumulates in tissues and can cause organ malfunction.

WHAT IS MULTIPLE MYELOMA?

Multiple myeloma, also known as myeloma, is a blood cancer in which plasma cells – important components of the immune system – replicate uncontrollably and accumulate in the bone marrow. Rather than making normal antibodies, myeloma cells tend to overproduce a useless antibody known as M protein.

Multiple myeloma (MM) is the second most commonly diagnosed blood cancer after non-Hodgkin's lymphoma, with an annual incidence of more than 20,500 cases in the United States (Figure 1). Nearly 74,800 Americans currently have MM, and an estimated 10,700 will die from the disease in 2012.

MM at a Glance

- Primarily affects older adults
- Median age at diagnosis is 69 years
- An estimated 74,800 Americans are living with or are in remission from MM
- An estimated 22,000 new cases will be diagnosed in the U.S. in 2012
- Approximately 10,700 Americans will die from MM in 2012
- The five-year survival rate for MM patients is about 40%
- Black Americans are more than twice as likely to have MM as white Americans. The incidence is lowest in Asian Americans
- Approximately 80% of patients have bone lesions, fractures or osteoporosis upon diagnosis
- About 40% of patients will develop kidney failure

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. 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.

MM is treatable yet currently remains incurable. Important treatment advances, however, have resulted in higher rates of remission and longer survival than were seen in the past. As researchers gain a greater understanding of the development and progression of MM, targeted treatment strategies are yielding further benefits.

CAUSES AND RISK FACTORS

The exact cause of MM is unknown, but several risk factors may increase the odds of developing this disease. Repeated exposure to chemicals such as pesticides, benzene and paint sprays have been proposed as potential causes. Several studies have linked viral infections, such as the human immunodeficiency virus (HIV), to the development of MM; patients with HIV are 4.5 times more likely than the general population to develop MM. Gaucher disease, a hereditary metabolic disorder, also significantly increases the risk of developing MM.

MM is twice as common in African Americans compared to Caucasians and is significantly more common in patients who have a close relative with the disease, suggesting that unidentified genetic factors may have a role.

Most people with MM have no known risk factors other than age. Patients' median age at the time of diagnosis is approximately 69 years, and the majority of the approximately 74,800 cases of MM in the United States are in individuals over the age of 40, with a slightly higher incidence in males.

The development of MM is associated with various chromosomal abnormalities, including extra or missing copies of particular chromosomes and deletions or rearrangements of chromosome segments.

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".

- Calcium elevation: the destruction of bone results in the release of calcium into the blood, which can contribute to fatigue, weakness, loss of appetite, nausea and confusion and can result in renal failure.
- Renal dysfunction: excess proteins and high blood calcium levels associated with MM can damage the kidneys. About 20 percent of patients with MM present with renal failure at diagnosis and another 20 percent develop renal failure in later stages of the illness.
- 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. Osteolytic lesions and inhibition of new bone formation make bones highly susceptible to painful fractures. 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, causing severe back pain, muscle weakness or paralysis, numbness or tingling, and incontinence.

Additionally, the excessive production of proteins by myeloma cells can thicken the blood, causing bleeding from the nose and mouth, blurred vision, stroke-like symptoms and congestive heart failure. Plasmapheresis, a procedure that removes the excess proteins from the blood, can be used to treat the problem.

Table 3. 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

TREATMENT

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.

Patients with MM are classified into one of several categories that help determine treatment options (Table 4). The five-year survival rate of people with MM is about 40 percent.

MM treatment aims for the following key objectives:

- Killing myeloma cells and controlling the disease to prevent damage to various organs
- Controlling tumor growth, extend disease-free survival time and prolong life
- Controlling pain and other disease-related symptoms
- Allowing patients a good, active quality of life

Newly diagnosed patients

Newly diagnosed MM is managed based on the clinical features of the disease. 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.

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 control the disease.

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 such as thalidomide. Along with bortezomib, novel agents such as these are often used in combination with traditional agents.

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, including the novel agents, 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.

Following SCT, maintenance treatment with novel agents may be used to help prevent MM from returning, as long as the patient is able to tolerate side effects.

Table 4. Categories of MM

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

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 bone-destroying cells, significantly reduce the number of skeletal-related events in MM patients, such as fractures, bone pain, hypercalcemia and the formation of new bone lesions.
- Surgery may be used to relieve pressure from an isolated tumor 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.
- 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. In patients with severe anemia, blood transfusions can be administered.
- Hormone-like substances called colony stimulating factors (CSFs), including granulocyte CSF (G-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.

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.

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. 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.

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. 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. For these reasons, this form of treatment is usually only performed in clinical trials.

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. Drugs that have been or are being studied as maintenance therapies include immunomodulatory drugs such as lenalidomide, corticosteroids (dexamethasone and prednisone), proteasome inhibitors (bortezomib), and alpha interferon.

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). Moreover, nearly all MM patients who achieve an initial response will relapse. 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 immunomodulatory drugs lenalidomide and pomalidomide and proteasome inhibitors (bortezomib, carfilzomib), have been shown to be superior to conventional therapies in patients with refractory MM.

Among patients who have experienced a relapse, up to 60 percent will respond to the same regimen that induced the first remission. 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.