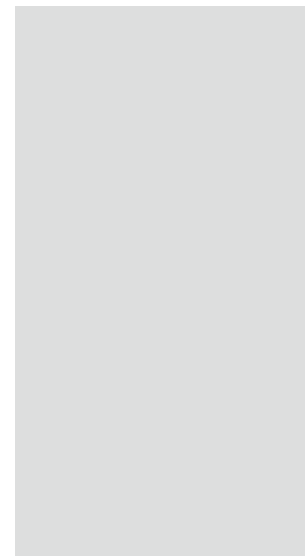




Multiple Myeloma Patient Handbook



**MYELOMA
CANADA**

MAKING MYELOMA MATTER

www.myeloma.ca



Introduction

This resource has been designed for:

1. Someone who has been newly diagnosed with myeloma and is wondering what it means and what the future will bring.
2. Those who have been living with myeloma for some time, but would like to refresh their understanding of the disease or fill in any missing pieces.
3. A person who is a family member, friend or loved one of someone with myeloma, and who wants to gain a better understanding of the disease and treatment options.

The goal of this resource is simple: to educate myeloma patients and their loved ones so they can become more active partners in their care.

If you have been searching for information on myeloma, you know how complicated this can be. This resource is an attempt to give you accurate, reliable and clear information on myeloma, its causes and effects, and how it is diagnosed, staged and treated in Canada.

There is a lot of information in this handbook and the more times you refer to it, the easier it will be for you to understand it. And don't be afraid to ask the members of your healthcare team to explain any term you don't understand. Over time, you will better understand your disease, your treatment options and what you can do to optimize your quality of life.



Myeloma Canada

Myeloma Canada is a registered non-profit organization created by, and for, people living with multiple myeloma. As the only national organization exclusively devoted to the Canadian myeloma community, Myeloma Canada has been making myeloma matter since its founding in 2005.

Working with leading myeloma researchers and clinicians as well as other cancer organizations, government agencies and local support groups across Canada, Myeloma Canada seeks to strengthen the voice of the Canadian myeloma community and improve the quality of life for myeloma patients, their caregivers and families through education, awareness, advocacy and research.

Myeloma Canada's goals are to:

- Provide educational resources to patients, families and caregivers.
- Increase awareness of the disease and its effects on the lives of patients and families.
- Advance clinical research and promote access to new drug trials in Canada.
- Facilitate access to new therapies, treatment options and healthcare resources.

Myeloma Canada is affiliated with the International Myeloma Foundation (IMF). Founded in 1990, the IMF is the oldest and largest myeloma organization, reaching more than 350,000 members in 120 countries worldwide.

This handbook is dedicated to the patients and their families who are living with myeloma and to the dedicated healthcare professionals and researchers who are working towards more effective treatments and a cure.



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Chapter 1



What is Multiple Myeloma?

In this chapter, we'll define what is meant by “multiple myeloma” and its underlying disease process. Some of this information may appear intimidating or complex at first. Don't worry – over time you will understand more and more. Refer to this resource frequently and don't be afraid to ask your healthcare team for explanations.



As early as possible, start collecting and organizing key information about your condition and your care. This should include contact information for the members of your healthcare team, copies of your lab results, your medication regimens and side effects. You'll find information on these and other issues later in this resource (Chapter 9 – How To Be Your Own Advocate). In Chapter 7, we'll also talk about how to optimize communications with the main partners in your treatment – your healthcare team.

Of Bone Marrow and Plasma Cells

You have probably heard the terms “multiple myeloma” and “myeloma”. These terms refer to the same thing: a cancer of the plasma cells. Plasma cells are part of the immune system and are a type of white blood cell normally responsible for producing antibodies. Plasma cells are found in the bone marrow, the hollow area within the bones. Because plasma cells are found in the blood, myeloma is referred to as a hematologic or blood cancer. The word “multiple” is often used because the malignant cells usually affect multiple areas of the bone marrow. In this resource, we'll use the term “myeloma” to keep things simple.

Myeloma vs. Melanoma

It's not uncommon for people to confuse "myeloma" with "melanoma". Myeloma is a cancer of the plasma cells in the bone marrow. Melanoma refers to a form of cancer that usually occurs in the skin, but can also occur in the eye and mucous membranes.

Your bone marrow is a sort of "blood factory" where three kinds of blood cells are made:

1. Red blood cells that carry oxygen.
2. Cells called platelets (or thrombocytes) that help the blood to clot whenever you cut yourself.
3. A variety of white blood cells including lymphocytes that play important roles in the functioning of your immune system. There are two types of lymphocytes: T cells and B cells. Another variety of white blood cell you may hear of is the neutrophil. This type of cell plays an important role in protection from infection. If you have a low neutrophil level you are more susceptible to infection.

With regard to lymphocytes:

- The abbreviation "T", in T cell (or T lymphocyte), stands for thymus since it is the principal organ for their development.
- B cells (or B lymphocytes) are found in the bone marrow. As they mature, B cells turn into plasma cells.

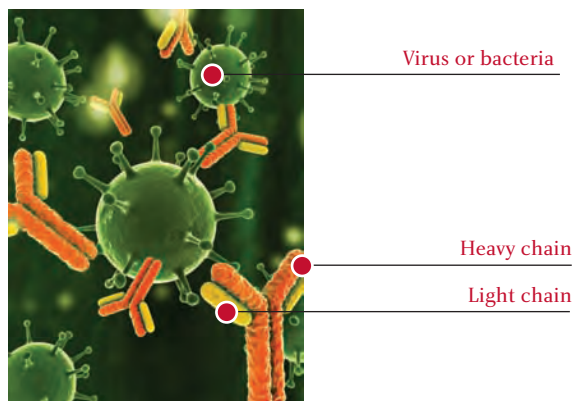
When plasma cells are exposed to foreign substances (antigens), they produce different antibodies. These antibodies are called immunoglobulins (the short form is Ig).

Immunoglobulins are proteins made up of two types of chains:

- heavy chains (G, A, M, D or E) and
- light chains (kappa, κ , or lambda, λ)

Normally, the most common immunoglobulin in the blood is IgG, followed by IgA and IgM. IgD and IgE are usually present in the blood in only very small amounts.

What happens when you have myeloma? In myeloma, the B lymphocyte (the cell that matures into a plasma cell) is damaged. It begins to reproduce plasma cells uncontrollably. We commonly refer to this "good cell gone bad" as being malignant.



Immunoglobulins (antibodies) are Y-shaped molecules. The heavy and light chains of the antibody contain specific binding sites that attach to bacteria or viruses, ultimately leading to their destruction thereby protecting against disease.



When plasma cells reproduce uncontrollably, two things happen.

- Too many plasma cells are produced. In healthy people, plasma cells make up 2-3 % of the cells in the bone marrow. In someone who has myeloma, plasma cells make up at least 10 % of the cells – or even more. The abnormally high number of plasma cells can “crowd” out other types of cells you need to be healthy, such as red blood cells or platelets.
- Too much of the same immunoglobulin is produced, such as too much IgG or IgA. This is referred to as the monoclonal protein (M-protein), monoclonal spike (M-spike), monoclonal peak (M-peak), or paraprotein. For more information about the M-protein and the different types of myeloma, please refer to Chapter 2.

When myeloma cells enter the bone marrow, they attach to other, structural cells of the bone marrow known as stromal cells. Once attached to stromal cells, interactions occur that stimulate the myeloma cells to continue reproducing.

- Chemical messengers called cytokines are produced that stimulate the growth of myeloma cells and prevent the cells from dying naturally. Interleukin 6 (IL-6) is one of these chemical messengers.
- The myeloma cells secrete chemicals called growth factors that promote the creation of new blood vessels that usually accompanies the growth of malignant cells (a process called angiogenesis). One of the most important of these growth factors is vascular endothelial growth factor (VEGF).
- The immune system begins to fail. Ordinarily your immune system would try to clear out or stop the growth of abnormal cells. But as the immune system weakens, it is unable to battle the abnormal cells.



As the myeloma cells invade the bone, they may cause multiple areas of damage that weaken the bone. These areas are known as osteolytic lesions, or lytic lesions for short.

Sometimes, the myeloma cells collect in a single bone and form a tumour called a plasmacytoma. Occasionally, a plasmacytoma can even affect areas of soft tissue outside of bone.

History of Myeloma Research

The first medical descriptions of myeloma date back to the 1840s. By the early 1900s, the role of plasma cells in the development of myeloma had been described and X-rays were being used to find areas of bone involvement (lytic lesions). It was not until 1962 that the first modern treatment of myeloma emerged, with the use of the chemotherapy drug melphalan. The use of this drug together with prednisone was first described by Dr. Daniel Bergsagel from the University of Toronto. For many years, melphalan and the steroid prednisone, the “MP” regimen, was the only available treatment for myeloma.

In the 1970s, various combinations of chemotherapy agents were developed, such as VAD (vincristine, Adriamycin® and dexamethasone). Bone marrow transplants for myeloma patients began in the 1980s. It was not until 1996, however, that a randomized controlled trial was able to show a clear benefit for high dose chemotherapy using melphalan followed by a bone marrow transplant.

Over the past decade, the increasing use of novel therapies (thalidomide (Thalomid®), bortezomib (Velcade®) lenalidomide (Revlimid®) and most recently pomalidomide (Pomalyst®) has resulted in new treatment combinations that have extended the lives of many myeloma patients.

Research has been able to increase both our understanding of the genetics of myeloma and the underlying disease process. This has resulted in the development of new approaches to treating myeloma.

Although there is still no absolute “cure” for myeloma, a growing number of patients with active myeloma are living ten or more years after diagnosis. We are also getting better at treating the complications of myeloma, giving people with the disease the best possible quality of life for the longest time possible.





Incidence and Prevalence in Canada

There are approximately 7,500 Canadians living with myeloma. According to the 2014 Canadian Cancer Statistics report released by the Canadian Cancer Society, the total new cases of multiple myeloma diagnosed annually in Canada are estimated at 2,550 (1,450 men and 1,100 women), representing an incidence of 5 in 100,000 people. This corresponds to 1.5% of total new cases of cancer in men and 1.2% of total new cases of cancer in women. The total number of deaths from multiple myeloma were estimated at 1,380 (750 men and 630 women.) Myeloma accounts for 1.8% of all cancer deaths.



Myeloma is fairly rare before age 40, and most people are in their 60s when they are diagnosed. Given that the population is ageing and patients are living longer, the prevalence of myeloma is increasing.

We know that the incidence of myeloma varies from country to country, from a low of less than one per 100,000 people in China to a high of about four or five per 100,000 in most Western industrialized countries. In the United States, myeloma is more common in African Americans than Caucasians.

Although we know that genetic changes are present in myeloma cells, there is little evidence to suggest that myeloma is a hereditary disease. Factors that may be associated with an increased risk of myeloma include exposure to toxic chemicals, radiation and possibly some viruses. There is still much to learn about what causes myeloma.

Incidence vs. Prevalence

Incidence refers to the total number of new myeloma cases diagnosed in a given year.

Prevalence describes the total number of people living with myeloma at a specific time.



Chapter 2

Types of Myeloma

Myeloma is not really one disease. In this chapter we will look at the different types of myeloma. The chart at the end of the chapter also summarizes the different criteria for each type.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

This is a benign condition in which the M protein or paraprotein is present but there is no underlying disease. MGUS can, however, be a precursor of myeloma. In someone with MGUS:

- There may be more plasma cells than normal in the bone marrow, but it is still less than 10 % of all blood cells (part of the definition of myeloma includes 10 % or more plasma cells).
- Monoclonal (M) protein level in the blood is usually less than 30 g/L.
- There is no anemia (low blood hemoglobin), renal failure (kidney disease), hypercalcemia (high levels of calcium in the blood) or bone damage (lytic lesions).

MGUS is one of the most common premalignant disorders in Western countries, with a prevalence of 3.2% in the general population 50 years of age or older.

Why is MGUS important? It is important because about 1 % of people with MGUS per year will go on to develop active myeloma. Currently, there is no clear way to predict who will progress to active myeloma. MGUS is usually monitored but not treated.





Asymptomatic or Smouldering Myeloma

In some patients, there is a transitional state, called asymptomatic myeloma, (also known as smouldering or indolent myeloma), that lies between MGUS and symptomatic or active myeloma. In asymptomatic myeloma there are few signs of active disease or the myeloma remains unchanged or stable.

In asymptomatic myeloma, plasma cells may make up 10% or more of the bone marrow and/or there is an M protein (M-spike or M-peak) greater than 30 g/L. However, there is still no anemia, renal failure, hypercalcemia or bone lesions. Because the disease is not yet active, asymptomatic myeloma is usually observed but not treated. Clinical trials are presently studying whether patients with high-risk asymptomatic myeloma should be treated before the onset of active myeloma.



Symptomatic or Active Myeloma

Symptomatic myeloma is characterized by the presence of myeloma protein in the blood or urine and an increased number of plasma cells in the bone marrow. Another possible sign of symptomatic myeloma is the growth of a plasmacytoma or tumour in the bone or soft tissue.

People with symptomatic or active myeloma can develop complications such as anemia, kidney failure, or excessive levels of calcium (hypercalcemia) in the blood. Soft spots (lytic lesions) can appear on X-rays of the bone. These lesions weaken the bone, causing pain and increasing the risk of fractures. People with symptomatic or active myeloma require treatment.

Myeloma is often referred to by the type of heavy chain immunoglobulin (monoclonal protein) or light chain (kappa or lambda) that is over-produced by the cancerous plasma cells. The excessive level of one type of immunoglobulin is referred to as the M-protein, M-spike, M-peak or paraprotein.

For a diagnosis of active myeloma, one or more of the following **CRAB** criteria must be present;

- [C] Elevated blood serum **CALCIUM**
- [R] **RENAL** insufficiency (reduced kidney function)
- [A] **ANEMIA** (low hemoglobin)
- [B] Lytic **BONE** lesions or osteoporosis

■ M proteins

In the previous chapter, we saw that immunoglobulins can be defined by the type of heavy chain they contain (G, A, M, D or E). About 60 - 65 % of all cases of myeloma involve the overproduction of IgG. In about 20 % of cases, it is the IgA protein that is involved. Myeloma can also involve IgM, IgD or IgE but these forms occur less frequently.

Uncontrolled production of IgM can also be a rare form of plasma cell cancer known as Waldenstrom's macroglobulinemia. Excessive amounts of IgM cause the blood to thicken (hyperviscosity). Symptoms can include enlarged lymph nodes, spleen or liver, fatigue due to anemia, headaches, weight loss, a tendency to bleed easily (due to too few platelets in the blood), visual problems, confusion or dizziness. In extreme cases, the increased concentration of IgM in the blood can lead to heart failure.



■ Light Chain Myeloma

Although a high level of M protein in the blood is a hallmark of myeloma, about 15 - 20% of patients produce only the light chain portion of the immunoglobulin. These are referred to as free light chains because they lack the heavy chain portion of the M protein. Light chain proteins are also referred to as Bence-Jones proteins, after the physician and chemist who discovered them in the urine of myeloma patients.

When free light chain proteins are in the urine, they can accumulate in the kidney and damage it. A 24-hour urine collection is usually required to measure and monitor the light chain proteins. Some laboratories, however, now use the Serum Free Light Chain Assay (Freelite®) to detect and measure free light chains in the blood.

When very small amounts of M protein are produced by the malignant plasma cells, it is called oligosecretory myeloma. Sensitive measurement of the M protein with Freelite® testing may be available in some centres and be useful in monitoring this type of myeloma.

Approximately 30% of patients produce light chains in the urine as well as heavy and light chains in the blood.

■ Nonsecretory Myeloma

Nonsecretory myeloma is characterized by the absence of an M protein in both the serum and urine. It occurs in approximately 2% of all patients with myeloma. Patients with nonsecretory myeloma are treated in the same fashion as multiple myeloma; however kidney problems associated with myeloma are much less common in patients with nonsecretory myeloma. The diagnosis and monitoring of patients with nonsecretory myeloma depends on an excess of monoclonal (kappa or lambda) plasma cells in the bone marrow and testing of the bones for lytic lesions.

■ Genetic Sub-Types

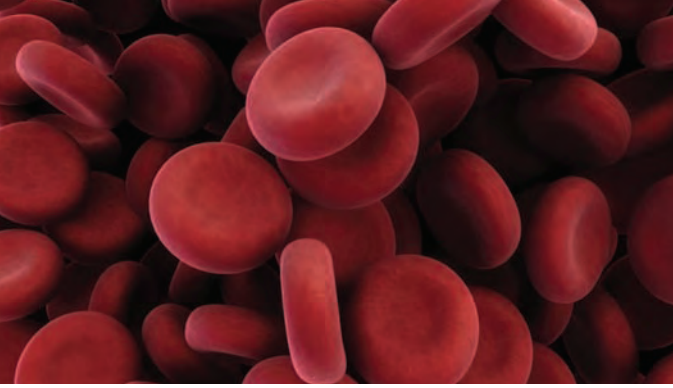
It is now known that there are multiple different genetic (DNA) abnormalities associated with myeloma. Having one of these genetic abnormalities affects how your disease will respond to different treatments. In the future, genetic profiling will play an increasingly important role in the customization of myeloma treatments.

■ Amyloidosis

About 10 - 15 % of people with myeloma will have or develop amyloidosis. In amyloidosis, the myeloma light chains (Bence-Jones proteins) form protein deposits called amyloid. The amyloid can collect in one or more organs causing the organ to malfunction. The heart, kidneys, nervous system and gastrointestinal tract are most often affected.

Criteria for Myeloma

Type of Myeloma	Criteria
MGUS (Monoclonal Gammopathy of Undetermined Significance)	<ol style="list-style-type: none"> 1. Serum monoclonal protein and/or urine M protein level low and stable over time. 2. Monoclonal bone marrow plasma cells less than 10 %. 3. No underlying disease state.
Asymptomatic or Smouldering Myeloma	<ol style="list-style-type: none"> 1. Monoclonal protein present in serum and/or urine. 2. Monoclonal plasma cells present in bone marrow and/or tissue biopsy. 3. Higher level of disease than MGUS, but still no symptoms or organ damage.
Symptomatic or Active Myeloma	<ol style="list-style-type: none"> 1. Monoclonal plasma cells in the bone marrow equal to or greater than 10 % and/or the presence of biopsy-proven plasmacytoma. 2. Monoclonal protein present in the serum and/or urine. 3. Myeloma-related organ dysfunction (1 or more of the following): <ul style="list-style-type: none"> • [C] Calcium elevation in the blood, • [R] Renal insufficiency (serum creatinine greater than 173 mmol/L), • [A] Anemia (hemoglobin less than 100 g/L), • [B] Bone disease (lytic lesions or osteoporosis).



Chapter 3

Diagnosing Myeloma

During the early stages of myeloma, there may be no symptoms. Most people first go to their doctor because of vague symptoms that can be difficult to diagnose, such as fatigue, recurrent infections or back pain.

Common symptoms of myeloma can include any of the following:

Symptom	Why It Occurs
Pain in the lower back, ribs or sternum	Osteolytic lesions weaken the bone, resulting in tiny fractures or even the collapse of a vertebra in the spine. About 70% of myeloma patients seek medical attention because of pain.
Fatigue	The increased number of myeloma cells can decrease the production of red blood cells in the bone marrow, leading to anemia.
Recurrent infections	Due to crowding in the bone marrow, the production of a variety of infection-fighting white blood cells is reduced. The immune system is unable to fight off infections and illnesses.
Tiredness accompanied by other symptoms such as thirst, frequent urination, nausea or muscle weakness	The breakdown of bone releases excess amounts of calcium into the blood (hypercalcemia). Hypercalcemia can result in a number of symptoms, such as loss of appetite, fatigue, muscle weakness, restlessness, difficulty in thinking, confusion, constipation, increased thirst, increased urine production, and nausea and vomiting.
Kidney problems	Excessive protein in the blood (which is filtered through the kidneys), excessive light chains in the urine or high levels of calcium in the blood can cause kidney damage.

How Myeloma is Diagnosed

Diagnostic lab tests help to:

- Establish whether there are monoclonal proteins (M proteins) in the blood or urine.
- Confirm the presence of abnormal numbers of malignant plasma cells in the bone marrow.
- Determine whether or not there is organ damage as a result of the myeloma (for example, bone damage or kidney dysfunction).

In short, diagnostic testing will tell you whether you have myeloma and what stage your disease is in.

Prognostic lab tests will:

- Determine the tumour burden (the severity of your disease).
- Suggest how aggressive the cancer is.

Some prognostic tests can even characterize the genetic abnormalities of the cancerous plasma cell. Prognostic tests help you and your doctor determine the best course of treatment.

Whether diagnostic or prognostic, lab tests for myeloma involve testing the blood, urine and bone. How frequently you will undergo testing will depend upon:

- How rapidly the myeloma is advancing.
- What symptoms you are experiencing.
- What treatment you are undergoing.

When undergoing treatment, some people may undergo testing monthly or even weekly; at other periods you may not require testing for much longer periods of time. There is no one “schedule” for testing – everyone’s condition must be assessed individually.



	Diagnostic Testing	Prognostic Testing
Objective	To determine whether you have myeloma.	To stage your disease, determine how aggressive it is and see whether it is responding to treatment.
When Performed	When being diagnosed.	Whenever required, depending upon your individual condition and treatments.
Types of Tests	<ul style="list-style-type: none"> • Blood tests • Urine tests • Skeletal X-rays or other imaging • Bone marrow aspiration and biopsy 	<ul style="list-style-type: none"> • Blood tests • Urine tests • Skeletal X-rays or other imaging • Bone marrow aspiration (biopsies may be repeated if required)

■ Blood Tests

A Complete Blood Count (CBC) measures the number of white and red blood cells in your blood as well as the number of platelets. When studying the results of a CBC, your doctor will look for:

- a decreased level of hemoglobin (an indication of anemia)
- a decreased platelet count that can cause bleeding problems (referred to as thrombocytopenia)
- a decreased level of white blood cells which causes the immune system to weaken (referred to as granulocytopenia)

Although values can vary, normal CBC results are summarized in the following chart. Values that are significantly outside of the normal range will raise questions and may lead to other tests.



To find out more about your blood, please read the Myeloma Canada InfoGuide *Understanding Your Blood and Blood Tests*.

Count	Definition
Erythrocytes (RBCs)	Erythrocytes are also known as red blood cells or red corpuscles. Erythrocytes transport oxygen and carbon dioxide between the lungs and all the tissues of the body. A circulating erythrocyte is little more than a container for hemoglobin. Low numbers of red blood cells or low hemoglobin or hematocrit indicate anemia, which can cause physical and mental fatigue.
Hemoglobin (Hb)	The iron-containing oxygen-transport substance in the red blood cells.
Hematocrit (HCT)	Measures of the proportion of the blood volume that is occupied by red blood cells.
Leukocytes (WBCs)	<p>White blood cells or leukocytes are cells of the immune system that defend the body against both infectious disease and foreign materials. A low number of white cells can increase the possibility of infection.</p> <p>Neutrophils defend against bacterial infection and other very small inflammatory processes and are usually first responders to bacterial infection.</p> <p>Lymphocytes are responsible for immune responses. There are two main types of lymphocytes: B cells and T cells.</p> <p>Monocytes are large white blood cells that ingest microbes or other cells and foreign particles.</p> <p>Basophils are involved in immediate hypersensitivity reactions, such as allergic reactions to wasp stings, and are also involved in some delayed hypersensitivity reactions.</p> <p>Eosinophils are responsible for combatting infection by parasites; they also control mechanisms associated with allergy and asthma.</p>
Platelets	Platelets (or thrombocytes) are involved in the formation of blood clots. Low levels of platelets predispose to bleeding, while high levels may increase the risk of clotting (thrombosis).

***Please note that normal values may vary from lab to lab. The ranges are for reference only.**

	Normal Range * (Canadian values)	Normal Range * (American values)
	F: 4.1 - 5.1 x 10 ¹² /L M: 4.5 - 5.3 x 10 ¹² /L	F: 4.1 - 5.1 x 10 ¹² /L M: 4.5 - 5.3 x 10 ¹² /L
	F: 120 - 160 g/L M: 130 - 180 g/L	F: 12 - 16 g/dL M: 13 - 18 g/dL
	F: 36 - 46 % M: 37 - 49 %	F: 36 - 46 % M: 37 - 49 %
	Total WBC: 3.5 - 10.5 x 10 ⁹ /L Neutrophils: 1.7 - 7.0 Lymphocytes: 0.9 - 2.9 Monocytes: 0.3 - 0.9 Basophils: 0.0 - 0.3 Eosinophils: 0.0 - 0.5	Total WBC: 3.5 - 10.5 x 10 ⁹ /L Neutrophils: 1.7 - 7.0 Lymphocytes: 0.9 - 2.9 Monocytes: 0.3 - 0.9 Basophils: 0.0 - 0.3 Eosinophils: 0.0 - 0.5
	150 - 450 x 10 ⁹ /L	150 - 450 x 10 ⁹ /L



Blood chemistry tests will also be conducted. These tests look for indications of:

- Increased levels of total protein in the blood
- Poor kidney function (renal dysfunction). Indicators include:
 - abnormal blood urea
 - increased creatinine
- Decreased albumin
- An elevated level of lactate dehydrogenase (LD or LDH)
- More bone breakdown than normal. Indicators are:
 - hypercalcemia, an elevated calcium level in the blood that occurs when calcium is released from the bone
 - in some cases, there may be elevated levels of alkaline phosphatase (ALP); in other cases, lytic lesions can occur without any increase in ALP levels

Other tests that may be performed include measuring the level of:

- Beta-2 microglobulin (β 2-M), an indicator to help evaluate the severity and prognosis of the myeloma
- C-reactive protein (CRP), an indicator for interleukin-6 (IL-6), a growth factor for myeloma cells.

Once the diagnosis of myeloma is made, even more specialized blood tests may be ordered to confirm the diagnosis and determine what type of myeloma you have.

- Serum protein electrophoresis (SPE or SPEP) gives a picture of the level of various proteins in the blood. SPE shows if there is a monoclonal peak or abnormal level of a particular immunoglobulin, as well as kappa and lambda free light chains. Electrophoresis can also be conducted on urine (UPE or UPEP).
- Immunofixation is the test used to identify the monoclonal paraprotein or M-spike seen by SPE. Immunofixation can also be conducted on urine.
- A quantitative immunoglobulin (QIG) test measures the levels of different types of immunoglobulins or antibodies in the blood (IgG, IgA and IgM).
- The Serum Free Light Chain Assay (Freelite[®]) can be used to measure the level of free light chains in the blood.

■ Urine Tests

When myeloma is suspected, urine tests may be ordered. Urine tests can be used to:

- Measure the amount of protein in the urine
- Look for free light chains
- Test for creatinine, a waste product excreted by the kidneys
- Look for bilirubin, a breakdown product of hemoglobin

A 24-hour urine test may be conducted to measure the amount of protein in the urine over a day. Urine protein electrophoresis (UPE or UPEP) may be done to look for free light chains in the urine and to assess kidney function. If they are present, your doctor may follow up with urine immunofixation or blood tests.

These tests can help to determine what stage of the disease you are in or how the disease is responding to treatment.

■ Tests Conducted on the Bone

X-rays can be used to check for changes in the bone structure and to determine if there are osteolytic or lytic lesions in the bone (weak spots). A bone (skeletal) survey consists of a series of X-rays of the skull, spine, arms, ribs, pelvis and legs. Less frequently, other imaging techniques may also be used, such as Magnetic Resonance Imaging (MRI), Computerized Axial Tomography (CAT or CT-scan) or Positron Emission Tomography (PET scan).

Samples of the bone marrow may also be taken to check the number of plasma cells. There are two bone marrow sampling techniques. In both cases, samples are usually taken from either the hip or breast bone (aspiration only).

- **Bone marrow aspiration** — a needle with a syringe attached is used to draw a sample of liquid bone marrow. As well as examining the sample under a microscope, the cytogenetics of the plasma cells can be studied.
- **Bone marrow biopsy** — a biopsy needle is inserted into the bone and rotated to force a tiny sample of solid bone tissue into the needle. A biopsy is usually performed when you are first diagnosed and may not need to be repeated.



Getting A Second Opinion

Once your doctor has provided you with your diagnosis and a treatment plan, you may wish to have another specialist review the plan. This is called getting a second opinion. While you may have complete confidence in your doctor, it is sometimes helpful to have another expert opinion. You may feel uncomfortable asking for a second opinion, but you have a right to do so. This is one of the most important decisions you will ever make. It can have a significant impact on both the quality of your life and the chances of a positive outcome.



Cytogenetics – the study of the structure of chromosomes (the ribbons of DNA that make up our genes). The two techniques most commonly used in the cytogenetics of myeloma are karyotyping and Fluorescence In Situ Hybridization (FISH).

Karyotyping – a means of looking at the chromosomes of an individual cell arranged in pairs and sorted by size. This test can detect large genetic changes, such as the existence of an extra chromosome.

FISH – a powerful molecular technique that uses a fluorescent-labelled probe to determine the presence or absence of a particular segment of DNA. It can detect even small changes, such as the translocation or rearrangement of chromosome segments.

Genome sequencing - a powerful scientific tool that can be used to better understand the mechanisms underlying the development of multiple myeloma. In genome sequencing, the makeup of a patient's genetic information can be determined. By comparing the genomic sequence of a healthy cell to the sequence of a cancerous cell, different mutations can be identified and studied.



Chapter 4

Staging Myeloma

In the last chapter, we discussed how some tests are considered “prognostic”. Prognostic tests are not conducted in order to tell you whether or not you have active myeloma, but to figure out more about the disease and how advanced it is (known as its “stage”). Prognostic testing will help to determine what sort of care is appropriate for you.

There are two main systems used to “stage” symptomatic myeloma: the International Staging System (ISS) and the Durie-Salmon Staging System.

The ISS system is based upon two blood test results:

- **Beta-2 microglobulin (β 2M)** — β 2M is a protein that is normally found on the surface of cells. A higher-than-normal level of this protein indicates inflammation somewhere in the body. It may also indicate some types of white blood cell (lymphocyte) disorders.

A normal level of β 2M in the blood is usually less than 2.5 μ g/mL, **depending on the laboratory.**

- **Albumin** — The most common form of protein in the blood plasma is albumin. The normal range for albumin is between 35 to 50 g/L (in American units, 3.5 to 5.0 g/dL). Lower levels may be an indicator of kidney dysfunction.

The Durie-Salmon Staging System requires a number of other blood tests.





They include:

- **Hemoglobin (Hb)** — This is the protein in the red blood cell that carries and releases oxygen. Normal hemoglobin levels are 120 to 160 g/L for adult women and 130 to 180 g/L for men (equivalent American values are 12 to 16 g/dL for women and 13 to 18 g/dL for males). Abnormally low values may indicate anemia.
- **Serum calcium** — Although calcium is an important electrolyte in the body, too much calcium in the blood can be an indicator of bone disease. Normal value ranges may vary slightly among different laboratories but are usually between 2.10 to 2.65 mmol/L (in American units, from 8.5 to 10.2 mg/dL).
- **Serum monoclonal proteins** — This refers to the level of individual M-proteins, such as IgG, IgA, etc., or free light chains.
- **Serum creatinine** — Creatinine is a byproduct produced when creatinine phosphate is broken down, an important part of muscle. If kidney function is abnormal, creatinine levels may be elevated. Because they typically have more muscle mass, men usually have higher creatinine levels than women. A normal value of creatinine is usually 50 to 100 $\mu\text{mol/L}$ for women and 70 to 120 $\mu\text{mol/L}$ for men (roughly equivalent to the American values of 0.8 to 1.4 mg/dL).

The following table summarizes the ISS and Durie-Salmon systems.

Staging Systems for Symptomatic Myeloma

Stage	ISS	Durie-Salmon
I	<p>$\beta 2$ microglobulin is less than 3.5 $\mu\text{g}/\text{mL}$</p> <p>AND</p> <p>Albumin is equal to or greater than 35 g/L</p>	<p>All of the following must be present:</p> <ol style="list-style-type: none"> Hemoglobin ≥ 100 g/L Normal serum calcium (< 2.88 mmol/L) Low levels of monoclonal protein: <ul style="list-style-type: none"> IgG < 50 g/L IgA < 30 g/L Urine light chain < 4 g per 24 hrs. Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only
II	<p>$\beta 2$ microglobulin is less than 3.5 $\mu\text{g}/\text{mL}$, but albumin is less than 35 g/L</p> <p>OR</p> <p>$\beta 2$ microglobulin is between 3.5 and 5.5 $\mu\text{g}/\text{mL}$, irrespective of albumin</p>	<p>Fitting neither Stage I nor Stage III</p>
III	<p>$\beta 2$ microglobulin is equal to or greater than 5.5 $\mu\text{g}/\text{mL}$</p>	<p>One or more of the following must be present:</p> <ol style="list-style-type: none"> Hemoglobin < 85 g/L Elevated serum calcium (> 2.88 mmol/L) High M-protein production rates <ul style="list-style-type: none"> IgG > 70 g/L IgA > 50 g/L Urine light chain > 12 g per 24 hrs. Advanced lytic bone lesions on skeletal survey <p>Subclassification:</p> <ol style="list-style-type: none"> Relatively normal renal function (serum creatinine less than 180 $\mu\text{mol}/\text{L}$) Abnormal renal function (serum creatinine equal to or greater than 180 $\mu\text{mol}/\text{L}$)

Other Factors

A number of factors can affect your prognosis. Some of the most commonly recognized factors are summarized in the following chart. In general, higher or abnormal test results indicate more active myeloma and possibly less likelihood of having a long response with treatment.

Test	Significance
<ul style="list-style-type: none">• β2M• Serum albumin• Lactate dehydrogenase (LD or LDH)• C-reactive Protein (CRP)• Abnormal chromosomes on bone marrow cytogenetics and FISH (Fluorescent In Situ Hybridization)	<ul style="list-style-type: none">• The higher ($> 3 \mu\text{g/mL}$) the level the more advanced the stage• The lower ($< 35 \text{ g/L}$) the level the higher the stage• Increased with active disease• Increased with active disease• Several chromosome deletions or translocations; can be associated with shorter duration of remission



Chapter 5

Your Treatment Options

How your myeloma is treated will depend upon a number of factors, including:

- The results of your physical exam and diagnostic testing (blood, urine and bone tests).
- The stage of your disease.
- What sort of prognostic indicators you may have (e.g., whether a chromosome mutation is identified, and if so, which type).
- Your age and general state of health.
- The symptoms you are experiencing, such as bone pain or fractures.
- What type of complications of the disease you may be experiencing (e.g., kidney disease, anemia or infections).
- What sort of treatments you have had before and how your myeloma responded to them.
- What new treatments are becoming available, such as those accessed by participating in clinical trials.

Each patient is assessed individually. What works for one patient may not work for someone else. Whatever treatment you are given, the goals of therapy are similar:

- Stop the production of abnormal plasma (myeloma) cells.
- Strengthen the bone and prevent fractures.
- Increase the hemoglobin count and reduce fatigue.
- Reduce the risk of infections.
- Promote your well-being and quality of life.

Response to Treatment

When reading about myeloma – particularly myeloma research – you may hear terms such as “Complete Response” (CR) or “Partial Response” (PR). Different studies may use different definitions, so check the study for what it is using. The International Myeloma Working Group response categories are:

sCR (Stringent Complete Response): Complete Response (see below) plus normal free light chain ratio and an absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence.

CR (Complete Response): Negative immunofixation in the serum and urine, disappearance of any soft tissue plasmacytomas and 5 % or less of plasma cells in the bone marrow.

VGPR (Very Good Partial Response): Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90 % or greater reduction in serum M-protein plus urine M-protein less than 100 mg per 24 hours.

PR (Partial Response): 50 % or greater reduction in the serum M-protein and a reduction in the 24-hour urinary M-protein of 90 % or more, or to less than 200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a 50 % or greater decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable and serum free light assay is also unmeasurable, a 50 % or greater reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was 30 % or greater. In addition to these criteria, if present at baseline, a 50 % or greater reduction in the size of soft tissue plasmacytomas is also required.

SD (Stable Disease): Not meeting the criteria for CR, VGPR, PR or progressive disease. SD is not recommended for use as an indicator of response, as the stability of disease is best described by estimating the time to progression.

PD (Progressive Disease): Requires one or more of the following:

- Increase of 25 % or more from baseline in:
 - serum M component and/or urine M component and/or bone marrow plasma cell percentage (the absolute percentage must be equal to or greater than 10 %)
 - development of new bone lesions or plasmacytomas
 - development of hypercalcemia attributable to the plasma cell disorder

Since relapses are common in myeloma, you and your healthcare team have to think about not only your immediate needs – but also what you might want to do in the future. Talk with your doctor and your healthcare team about how you can keep your options for future treatments as open as possible.

The Three Rs: Remission, Relapse and Refractory

Remission: Complete or partial disappearance of the signs and symptoms of myeloma.

Relapse: The reappearance of signs and symptoms of myeloma after a period of improvement.

Refractory: Myeloma that is unresponsive to a treatment.

At this point, the standard treatments for myeloma are:

- Observation
- Radiotherapy
- Standard chemotherapy (intravenous or oral)
- Steroids (dexamethasone or prednisone)
- High dose chemotherapy with stem cell transplantation
- Thalidomide (Thalomid®)
- Bortezomib (Velcade®)
- Lenalidomide (Revlimid®)
- Pomalidomide (Pomalyst®)
- Clinical trials

Treatments or drugs are commonly used in different combinations, such as lenalidomide and dexamethasone or melphalan and prednisone with bortezomib. A number of new and emerging treatment therapies are becoming available.

Observation

Sometimes, the best treatment is no treatment at all. If your myeloma is stable (that is to say, is not progressing or getting worse), the best option may be to simply monitor your condition. Currently, there is no evidence that treatment is beneficial for people who have MGUS or asymptomatic myeloma (smouldering or indolent myeloma). Research on the role of ongoing or maintenance therapy is being conducted and approaches may change in the future.



First Line and Second Line Therapies

You may have heard these terms, but what do they mean? A first line treatment is a form of therapy that is used on people who have not had any previous treatment for their myeloma. If the myeloma does not respond (the disease is said to be refractory) or if it progresses after the first line therapy has been completed (i.e., there is a relapse), the subsequent therapy is referred to as second line treatment.

Radiotherapy

High-energy radiation may be used to damage the myeloma cells and prevent them from growing. Radiation therapy is typically used on specific parts of the body to treat bone pain and plasmacytomas, usually in combination with some form of chemotherapy.

Total body irradiation was used in the preparation for autologous stem cell transplantation in the past. Clinical trials have shown that radiotherapy does not improve outcomes for autologous stem cell transplantation and adds to side effects. It is usually not used in conjunction with autologous transplantation anymore.

Chemotherapy

The goal of chemotherapy is to reduce the number of plasma cells in the bone marrow and the proteins they produce. Chemotherapy cannot “cure” myeloma but it may put the disease into remission (that is to say, stop it from progressing or getting worse). It must be tailored individually to each patient.

There are many forms and combinations of chemotherapy regimens. Some of the most common in Canada are:

- Melphalan, either in combination with bortezomib (Velcade®) and prednisone (VMP) or thalidomide and prednisone (MPT)
- Cyclophosphamide or cyclophosphamide and prednisone (CP)
- CyBorD (cyclophosphamide, bortezomib and dexamethasone) or CyBorP (cyclophosphamide, bortezomib and prednisone)



People with myeloma may receive their chemotherapy intravenously, in cycles of alternating treatment and rest periods. The rest periods allow patients to recover from chemotherapy-related side effects. They also increase the chances that tumour cells that are dividing will be exposed to treatment. The length and type of chemotherapy will depend in part upon whether there are plans to perform a stem cell transplant in the future.

Central Lines

When you are receiving chemotherapy, you may be given a central line or catheter. You may hear it referred to as a Port-a-Cath®, PICC line or Hickman®. A central line is a long, hollow tube made from silicone rubber which is inserted or tunneled under the skin of your chest into a vein. The line can be left in for weeks or months and makes it possible for you to have your treatment without having to have needles inserted at each visit. When it is time for your chemotherapy, the nurse or doctor connects the line to a syringe or intravenous drip. When you no longer need chemotherapy, the line may be removed.

Steroids

Steroids (corticosteroids) are chemicals naturally produced by the adrenal gland to help prevent inflammation. The synthetic or man-made steroids most commonly used to treat myeloma are prednisone and dexamethasone. Steroids can be used alone or in combination with other drugs, such as chemotherapy drugs.





High-Dose Chemotherapy and Stem Cell Transplantation

Stem cells are a class of undifferentiated cells that are able to differentiate into specialized cell types. They are normally found in the bone marrow and in the blood and can be used to “repopulate” the bone marrow after a high-dose chemotherapy treatment. There are several types of stem cell transplantation approaches that may be used to treat myeloma.

- **Autologous stem cell transplantation (ASCT)** is the most common. It is referred to as an “autograft” because it uses your own stem cells. Stem cells can be obtained from blood in the veins (a peripheral blood stem cell or PBSCT) or your bone marrow. A transplant consists of the following steps:

1. To prepare for the ASCT, the number of myeloma cells needs to be reduced. This is done with an **induction regimen** most often using bortezomib (Velcade®) in combination with a steroid and cyclophosphamide.

If the stem cells are being harvested from the peripheral blood, drugs are used to “coax” or mobilize them out of the bone marrow and into the blood. By using a medication called a Granulocyte-Colony Stimulating Factor (G-CSF) (e.g. Neupogen®) with or without chemotherapy, the bone marrow is stimulated to increase the number of stem cells in the blood. A process called pheresis is then used to collect the stem cells from the blood.

Prior to collection, be sure to talk with your physician about the number of stem cells that will be collected. By ensuring that enough stem cells are harvested and frozen to support two or more transplants, you can increase your treatment options for the future.

In situations where there is difficulty in collecting the required number of stem cells, another drug called plerixafor (Mozobil®) can be added to improve the release of stem cells.

2. The stem cells that are collected are frozen and stored until it is time for them to be reinfused following the high-dose chemotherapy.
3. You then undergo a **conditioning regimen** of high-dose chemotherapy with melphalan. This regimen will destroy the cancer cells in the bone marrow. In the process, it will also destroy the blood-producing cells in your bone marrow.
4. Within a few days of completing the high-dose chemotherapy, the stored stem cells are thawed and infused back into you. In time, the transplanted stem cells begin to produce new blood cells. You may or may not stay in the hospital following your transplant.

All treatments have both their risks and benefits. However, studies have shown that on average, people who undergo ASCT live longer than those who receive standard chemotherapy alone.

- **Allogeneic transplant** involves collecting stem cells from someone else, usually a brother or sister. The donor’s cells must match the recipient’s tissue type – note that this is different from blood type and requires special blood testing. The transplanted donor stem cells may also help attack any myeloma cells remaining in the patient’s bone marrow. This is referred to as the graft-versus-myeloma effect.

Few patients are good candidates for allogeneic transplant. It is difficult to find good donor matches and the procedure has a greater risk of complications, including infections, graft-versus-host disease

(GVHD, a potentially life-threatening condition in which the donor's bone marrow attacks and destroys the patient's own tissue) and death. For these reasons, allogeneic transplant is not a standard therapy for myeloma.

There are two types of allogeneic transplant:

- **Ablative or “full”** – high-dose chemotherapy is used to condition the bone marrow before transplant, which destroys the patient's own bone marrow cells.
 - **“Mini” or non-myeloablative** – a moderately high-dose chemotherapy conditioning regimen is used that does not destroy the patient's bone marrow cells but rather causes enough immunosuppression to allow the donor cells to grow in the patient's bone marrow.
- A **syngeneic** cell transplant refers to a transplant using stem cells taken from an identical twin. The prognosis for syngeneic transplants is better than that of allogeneic transplants; however, this is an option for only a small number of patients.
 - A **matched unrelated donor (MUD)** transplant refers to a transplant using stem cells taken from a donor who is not a relative but has the same tissue type.
 - **Tandem (double) autologous transplants** are performed in some centres. For a tandem transplant, the plan is to conduct a second transplant within six months of the first one. This approach may be beneficial for people who do not have a full response to the first transplant or who have “high risk” disease, as indicated by age or cytogenetics.
 - An experimental approach is **ASCT followed by a mini-allogeneic** transplant. In this version, a patient first undergoes high-dose chemotherapy to reduce the overall number of myeloma cells, followed by an autologous transplant. Next there is a second course of moderately high-dose chemotherapy with an allogeneic transplant of donor stem cells. The second course of therapy – in combination with the help of the allogeneic transplant – should reduce the number of myeloma cells.

Maintenance Therapy

Maintenance therapy is a prolonged, and often low-dose, form of treatment given to myeloma patients after their initial therapy. The goal of maintenance therapy is to prevent disease progression for as long as possible while maintaining a favourable quality of life.

Data from clinical trials suggest that maintenance therapy following a stem cell transplant delays time to disease progression and improves overall survival.

Consolidation Therapy

Consolidation therapy is different from maintenance therapy since it usually involves a shorter course of treatment with the goal of deepening patients' responses to the initial therapy. Clinical trials have demonstrated that some patients had a longer median progression-free survival than those who did not receive consolidation therapy after transplantation.

Is there an age cut-off for stem cell transplant?

Many myeloma centres have a general rule that ASCT is not routinely offered to people above a certain age, such as 65 or 70 years. These are not hard-and-fast rules. The important thing is not your chronological age but rather your biological age – how generally healthy you are. An otherwise healthy 70-year-old may be a good candidate for ASCT, whereas a 64-year-old with multiple health problems may be a poor candidate.

Thalidomide (Thalomid®)

Thalidomide is an immunomodulatory agent (IMiD). Instead of destroying myeloma cells (like chemotherapy drugs), thalidomide interferes with the underlying processes that promote the growth and reproduction of myeloma cells. Thalidomide:

- inhibits factors that promote the growth of blood vessels (Vascular Endothelial Growth Factor or VEGF and basic Fibroblast Growth Factor or bFGF) that help to feed tumours
- modulates the level of several chemicals (called cytokines) that the cancer cells use to communicate with one another and orchestrate growth and reproduction (e.g., Tumour Necrosis Factor – alpha or TNF- α , interleukin 6 or IL-6, interleukin 2 or IL-2, and interferon-gamma or IFN- γ)
- alters the expression of chemicals involved in acute rejection, such as cytokine secretion and cell growth

Thalidomide has been used to treat cases in which the myeloma has not responded to treatment (refractory myeloma) or has returned after treatment (relapsed myeloma). In Canada, thalidomide is approved for use in combination with melphalan and prednisone (MPT) as a front-line treatment for patients who are not eligible for a stem cell transplant.



Bortezomib (Velcade®)

Bortezomib is a proteasome inhibitor, one type of the new generation of “biological treatments”. It works by acting on the myeloma cells and the cells with which they interact to inhibit plasma cell growth and reproduction and to promote cell death.

Bortezomib is usually given subcutaneously (under the skin) once a week.

Bortezomib can be used in combination with melphalan and prednisone (VMP) as a front-line treatment for patients who are not eligible for stem cell transplantation. Patients who have relapsed after their first treatment may also be given bortezomib either alone or with other medications, such as dexamethasone and pegylated liposomal doxorubicin (Doxil® or Caelyx®).

For patients undergoing an autologous stem cell transplant (ASCT), bortezomib is used in a medically recognized combination (e.g. in combination with cyclophosphamide and prednisone) for four to six cycles as induction therapy.

Lenalidomide (Revlimid®)

Like thalidomide, lenalidomide is an immunomodulatory agent (IMiD) but is more potent and has a different side effect profile from thalidomide. Lenalidomide has multiple mechanisms of action that affect both the cancer cell and its microenvironment.

Lenalidomide can be used as a second-line treatment in combination with dexamethasone as a treatment for patients who have received at least one prior therapy.

Clinical trials have also shown that lenalidomide in combination with low-dose dexamethasone is effective as a maintenance treatment following an autologous stem cell transplant.

Pomalidomide (Pomalyst®)

Pomalidomide is a third-generation IMiD that is used in combination with dexamethasone for patients for whom both lenalidomide and bortezomib have failed and have received at least two prior treatment regimens and have demonstrated disease progression on their last treatment.

New and Emerging Therapies

A number of new therapies are in development. At the time this handbook was printed, among the new promising therapies being evaluated were second and third generation proteasome inhibitors (carfilzomib, ixazomib and oprozomib); monoclonal antibodies (daratumumab, elotuzumab and SAR650984); a histone deacetylase inhibitor (panobinostat); an XPO1 inhibitor (selinexor); and new immunotherapeutic approaches such as the measles vaccine.

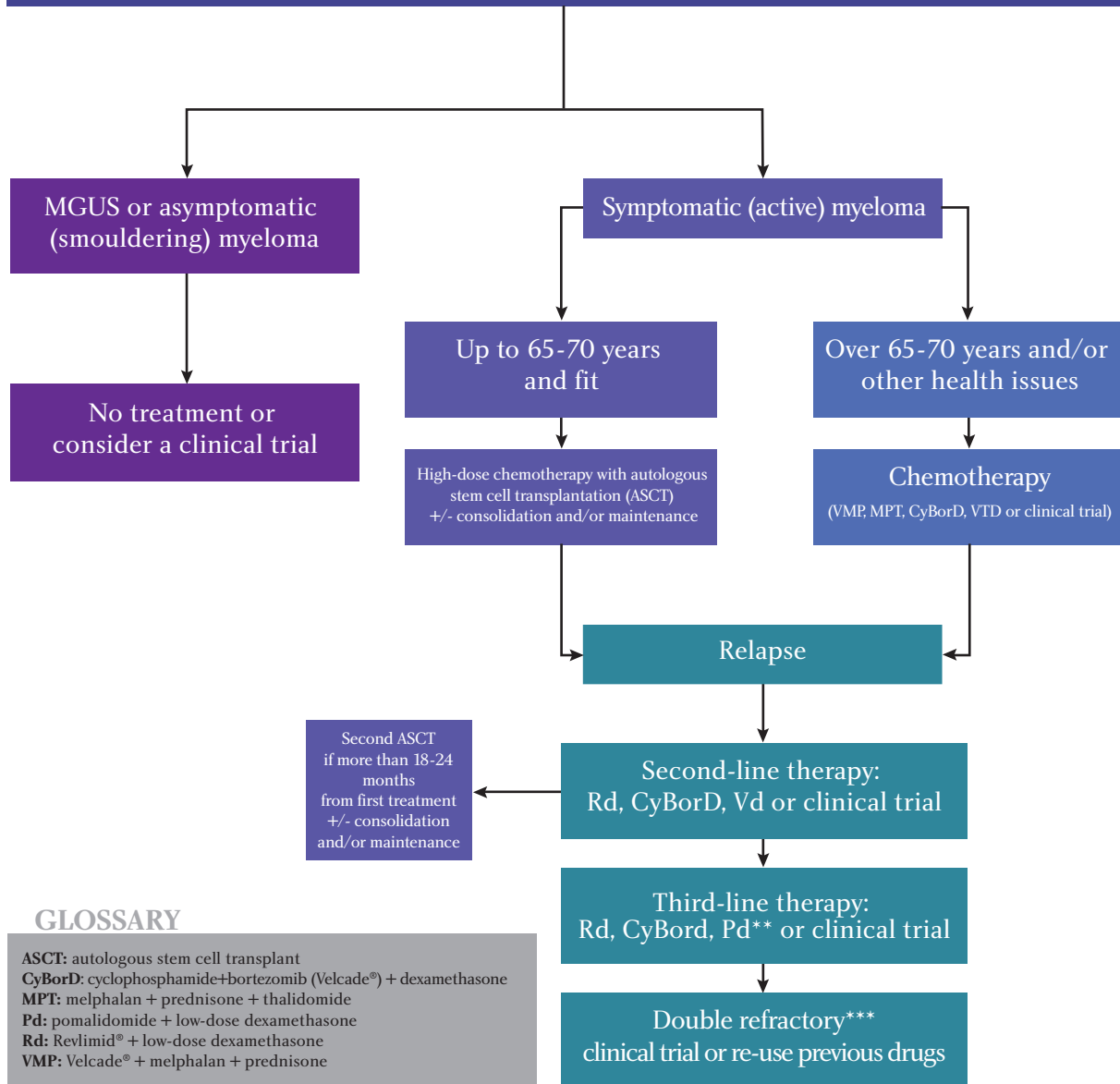
One of the most exciting aspects of current research is the insights that are being made into the genetics of the disease. In the future, knowing more about the genetics of myeloma will make it possible to more closely individualize and tailor treatment.

Another exciting area of research is the measurement of minimal residual disease (MRD) using very sensitive and sophisticated techniques to identify trace amounts of myeloma cells that remain after treatment. MRD will be an important tool in identifying possible curative approaches to treatment.

For more information about new and emerging therapies, please refer to the Myeloma Canada website (www.myeloma.ca), the Myeloma Matrix on the International Myeloma Foundation (IMF) website (www.myeloma.org), Cancer View Canada (www.canadiancancertrials.ca) and the US National Institutes of Health (www.clinicaltrials.gov).



Treatment Options and Approaches*



GLOSSARY

ASCT: autologous stem cell transplant
CyBorD: cyclophosphamide+bortezomib (Velcade®) + dexamethasone
MPT: melphalan + prednisone + thalidomide
Pd: pomalidomide + low-dose dexamethasone
Rd: Revlimid® + low-dose dexamethasone
VMP: Velcade® + melphalan + prednisone

* NOTE: These treatment options may vary because of restricted access in some provinces and/or individual circumstances. Always ask about clinical trials that may be available. Other drug combinations or options may also be considered.

** If both bortezomib and lenalidomide have been used previously

*** To lenalidomide and bortezomib



Chapter 6

Managing Complications and Side Effects

The build-up of myeloma proteins in the bone marrow can cause a number of medical problems. It is important that such problems be identified, monitored and treated.

Complications of the bone

Healthy bones are continually breaking down (referred to as resorption) so new bone can be laid down. There are two types of cells that are important for bone:

- **Osteoclasts** — cells that break bone down. If you are replacing the roof on your house, one of the first things you should do is tear off the old roof. Osteoclasts breaks down old bone so there is room for new bone.
- **Osteoblasts** — cells that lay down new bone. These are the cells that follow behind the osteoclasts and strengthen the bone by laying down fresh, new bone.

Myeloma cells stimulate the **osteoclasts** – the cells that break bone down – while inhibiting the **osteoblasts**, the cells that make new bone. If there is more bone breakdown than creation, there can be:

- areas of damage or “holes” in the bone, known as osteolytic or lytic lesions
- progressive bone thinning, called osteoporosis

To learn more about bone complications, read the Myeloma Canada InfoGuide *Myeloma Bone Disease*.



When bone thins or there are lytic lesions:

- You are at increased risk of fractures. Sometimes, even everyday activities can cause bones to break. Myeloma patients with bone disease can experience fractures in the ribs or compression fractures of the vertebrae in the spine.
- You may experience bone pain. The majority of myeloma patients experience bone pain at some point. Words commonly used to describe bone pain in myeloma include “constant”, “aching”, “deep” and “sharp”. The pain is often localized and worse when you move or shift positions. Compression fractures of the vertebrae can occur, which in turn can cause nerve damage and pain.

What is done for bone disease in myeloma?

- Skeletal X-rays and bone density tests (a form of special X-ray) are used to monitor bone loss and to check for specific areas of damage.
- People with myeloma are routinely prescribed bisphosphonate drugs that strengthen the bone, such as clodronate (Bonafos®), pamidronate (Aredia®) or zoledronic acid (Zometa®).
- Radiation therapy can be used to treat specific bone lesions and help relieve pain. Extensive radiation of the spine or the long bones should be avoided, however, as it can lead to prolonged suppression of the bone marrow.
- Vertebral fractures (fractures in the spine) have traditionally been treated by a procedure called vertebroplasty, in which cement is injected into the affected vertebrae to stabilize it. A newer alternative is kyphoplasty. In kyphoplasty, a balloon is inserted into the compressed vertebra and inflated to raise up the collapsed section. The cavity is then filled with a bone cement, stabilizing the vertebrae and preserving the reestablished height.

Is exercise safe?

Unless there are reasons why you cannot exercise, mild to moderate exercise such as walking or swimming may be physically and emotionally beneficial. It is important to avoid contact sports or activities that could result in falls. Talk with a physical therapist or your healthcare team about activities that would be suitable for you.

Anemia

By crowding the bone marrow, myeloma can result in a reduced red blood cell count. Red blood cells are important because they contain hemoglobin. Hemoglobin carries oxygen from the lungs to the cells of your body, giving you energy and stamina.

If the hemoglobin count is less than 120 g/L in a woman or less than 130 g/L in a man, it is called anemia. Whether anemia requires treatment will depend upon its level, how quickly the level is changing, and how well you are feeling and functioning.

Symptoms of anemia include:

- feeling very tired even though you are getting enough rest
- looking pale
- becoming short of breath after even mild exertion
- finding it hard to do daily chores, to concentrate or to remember things
- feeling lightheaded or dizzy

Different people react differently to having a low hemoglobin count. Some people also report headaches, leg pains or feeling cold.

Why treat anemia? Studies have shown that in people with cancer, treating anemia can help relieve fatigue, make it easier to do everyday activities, reduce the need for blood transfusion, improve the quality of daily life and make it more likely they will be able to complete their cancer therapy.

There are a number of treatment options for anemia, and it is important to discuss all of them with your healthcare team.

- If your anemia is due to a change in your diet, eating a healthier diet or taking iron, vitamin B12 or folic acid (folate) supplements may help. **Always check with your doctor or pharmacist before taking any non-prescription, over-the-counter iron or vitamin supplement, or any herbal remedy.** Some supplements or remedies can interact with prescription medications.



- Blood transfusions can be used to treat severe anemia and can quickly increase the hemoglobin level on a short-term basis.
- A medication can be prescribed that stimulates the body to make more red blood cells. Epoetin alfa (Eprex®) and darbepoetin alfa (Aranesp®) contain versions of the human hormone erythropoietin, which tells the bone marrow to make more red blood cells. Both drugs are given by subcutaneous injection (an injection just under the skin).



Infections

Myeloma and some of its treatments can affect the normal production of antibodies and reduce the white blood cell counts. This can leave a person susceptible to infections. Someone with this problem may get repeated infections or illness, especially respiratory infections, or take a long time to recover from them.

Many infections cannot be prevented, so it is important that they be treated as soon as they develop. Fever or other signs of infection or disease should be reported promptly to your healthcare team. Antibiotics may be required.

It is important to have a complete dental examination before you begin any treatment therapy. Because of the increased risk of infection, myeloma patients may require antibiotics before any dental work.

Reduce your risk

To reduce the risk of infections and illnesses, remember to practice good hand-washing techniques. When in public places, wash your hands frequently or use a hand sanitizer (the small containers can easily fit into your pocket or purse). Avoid situations where you may come into contact with people who are ill.

Kidney damage

The M-proteins produced by myeloma are cleared from the body in the kidneys. Over time, the elevated levels of abnormal M-proteins in the blood and urine can damage the kidneys. This is why renal function is assessed regularly by creatinine testing of the blood.

The best way of preventing kidney damage (renal disease) is to treat the myeloma and keep the M-protein levels as low as possible. Sometimes – but infrequently – if the renal dysfunction is severe, dialysis may be required.



Drink up!

Drinking lots of fluids can help to flush medications and toxins from your body, maintain normal blood volume and pressure, lubricate the joints, limit fatigue and help prevent kidney damage. The best single fluid to drink is water. Gradually increase your intake until you are drinking 6 to 8 glasses of water a day. Try to limit drinks that contain caffeine, such as coffee, tea and soft drinks. Caffeine and alcohol increase your urine output and can lead to dehydration and fatigue.

High blood calcium

As bone is broken down, it releases calcium into the blood stream. If the myeloma is causing a lot of bone damage, the blood can develop excessively high levels of calcium. This condition is called hypercalcemia.

Hypercalcemia is a complication of myeloma and is treatable. Symptoms can include constipation, increased frequency of urination, weakness and in extreme cases, confusion.

Hold off on calcium supplements

In people without myeloma, calcium supplements are often recommended for bone health. But if you have myeloma, never take a calcium supplement without checking with your doctor. Too much calcium in the blood can be unhealthy.

Other blood complications

Myeloma can result in other complications of the blood, although most are relatively rare. If the number of platelets in the blood drops below a healthy level, normal clotting will be affected. This can lead to bruising or excessive bleeding.

When combined with steroids, some medications, such as thalidomide and lenalidomide (Revlimid®) can also increase the risk of blood clots in the veins, such as in the legs. Known as deep vein thrombosis (DVT), this can be a potentially dangerous complication. Blood-thinning medications can be prescribed to reduce this risk.

In a small number of people, a high M-protein level can cause the blood to thicken (known as hyperviscosity). If this occurs, blood flow to the skin, fingers, toes, nose, kidneys or brain can be affected.

Bone pain, nerve pain and neuropathy



There are three main causes of pain for myeloma patients:

- bone pain
- nerve damage, often due to compression fractures
- peripheral neuropathy

The sort of treatment you require will depend upon the cause of the pain, its severity, and how you respond to different therapies. Other treatments may be helpful. For example, bone pain may be relieved by radiation or bisphosphonates, and nerve damage due to compression fractures by vertebroplasty or kyphoplasty.

There are several categories of painkillers that can help with your pain:

- Painkillers for mild pain, such as acetaminophen (Tylenol®)
- Painkillers for moderate pain, such as dihydrocodeine
- Painkillers for severe pain, such as morphine and fentanyl (Duragesic®)
- Drugs for pain involving the nerves (neuropathic pain), such as gabapentin (Neurontin®), amitriptyline (Elavil®) and pregabalin (Lyrica®)

You and your doctor can work together to find the right painkiller for you – no two people are alike, so it might take some trial and error. Your doctor will usually start you on a low-dose or milder painkiller and increase to the dose or type of painkiller that controls your pain best and gives you the least number of side effects. You may find that you get the most relief from a combination of painkillers. If your usual combination of painkillers ever becomes less effective, contact your doctor or nurse.

Painkillers come in a variety of forms – tablets, injections and patches that allow medication to be absorbed through the skin. Although non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin® or Advil®), naproxen (Naprosyn® or Aleve®) and diclofenac (Voltaren®) are common and effective painkillers, people with myeloma should avoid them, particularly if they have kidney damage.

Pain medication dependency and addiction

Some myeloma patients hesitate to take opioid medications because they are afraid of addiction. Most healthcare professionals agree that in someone with no history of dependency or addictions, there is little chance of developing a true addiction. Physical and psychological dependency can occur and can be handled by decreasing the dose gradually.

It may take some time to find the right treatment for your pain. Extreme cases may require treatment by a pain specialist.

Peripheral neuropathy appears to be a side-effect of certain drugs used to treat myeloma, such as thalidomide, bortezomib (Velcade®) and vincristine. It usually occurs in the feet, legs, hands or arms and is very different from bone pain. Characteristics of neuropathic pain include:

- a painful sensitivity to touch (known as allodynia)
- the sensation of “electric jolts” or that the pain travels
- a burning, tight or pulling sensation
- numbness or a “pins and needles” feeling

These sensations may come on spontaneously without movement or get worse at night.

Drug-induced neuropathy must be treated differently from bone pain or nerve damage resulting from spinal compression. First, in some cases it can be reversed by changing the frequency of drug administration or reducing the dose of the drug causing the neuropathy. In some cases, it may be necessary to stop the treatment. Second, the sorts of medications used for neuropathic pain are different. Drugs used to treat neuropathic pain include gabapentin (Neurontin®), amitriptyline (Elavil®) and pregabalin (Lyrica®).

A number of unconventional and alternative approaches have been proposed for treating neuropathy but to date there is no evidence that they are effective. Some patients have reported that acupuncture has provided some relief from the pain of neuropathy.



Alternative Therapies

Many vitamins, supplements and herbal therapies can interact with your cancer medications. Before taking any vitamin, supplement or herbal therapy, talk with your physician and/or your pharmacist.



Osteonecrosis of the jaw (ONJ)

Dental health is very important for myeloma patients. Encourage your dentist to talk with your oncologist to discuss any special precautions you may require, especially when receiving treatment. Check to see if your cancer centre has a dental clinic. Before starting any therapy, have a complete dental examination.

Osteonecrosis of the jaw (ONJ) is a relatively rare side-effect of long-term bisphosphonate use in which there is abnormal death (necrosis) of the jaw bone. A review of patients at one of Canada's largest myeloma centres, the Princess Margaret Hospital in Toronto, found that 2% of patients taking pamidronate developed osteonecrosis. It can occur spontaneously but appears to be more likely following dental work, particularly traumatic work such as extractions. The risk of osteonecrosis appears to be higher among those taking zoledronic acid (Zometa®), compared to pamidronate (Aredia®).

If you think you may take bisphosphonates in the future, be sure to have a complete dental examination and all corrective work completed. Once you start taking bisphosphonates, it is recommended that you:

- practice good oral hygiene to reduce the odds of needing dental care
- see your dentist regularly to catch problems when they are small
- avoid extractions and periodontal surgery if possible
- do not have dental implants

Restorative work such as fillings, bridges and crown and root canals are probably safe, provided wounds are as small as possible and all rough edges are carefully smoothed.

To reduce the risk of osteonecrosis of the jaw, many cancer centres are changing the way they prescribe bisphosphonates, either reducing the dose or the length of time for which they are taken.

Medication side effects

All prescription medications have intended effects and others that you may not want, commonly known as side effects. Your healthcare team, particularly your pharmacist and nurse educator, can explain what side effects you can expect from the medications you are prescribed, which ones to report right away, and what can be done to relieve them.

Common side effects of chemotherapy are:

- **Nausea and vomiting** — anti-nausea (anti-emetic) drugs can help to prevent and control nausea and vomiting. Avoiding strong smells and getting lots of fresh air may also help. Vomiting can dehydrate you, so it is important to try and keep taking sips of cool drinks.
- **Hair loss (alopecia)** is common with some – but not all – kinds of chemotherapy. If it occurs, remember that your hair will grow back once your treatment has finished.
- **Changes in the mouth** — depending upon the type of chemotherapy you are receiving, you may experience mouth sores, or a sore or dry mouth. Medicines or a special mouthwash can help to prevent or treat mouth ulcers. When undergoing high-dose intravenous chemotherapy (e.g., with melphalan), sucking on ice chips may help to prevent mouth sores. Keep your teeth clean by regularly using a soft toothbrush, and try to avoid things that might irritate your mouth, such as spicy, salty or tangy foods. If you have a sore or dry mouth, avoid food that sticks to the roof of your mouth (e.g., peanut butter or chocolate) and mouthwashes that contain alcohol. Moisten your food with gravy or sauces and try drinking through a straw or sucking ice cubes or frozen treats.
- **Loss of appetite** — at times over the course of your treatment, you may have no appetite or feel you cannot face food. To avoid losing weight, try to eat small amounts of food – particularly fresh fruits and vegetables – frequently throughout the day. Or if you feel hungry at some parts of the day and not at others, eat your larger meal when you are hungry. No matter what you eat, be sure to always drink plenty of fluids.



Corticosteroids (steroids) such as dexamethasone and prednisone are frequently used to treat myeloma. Side effects can include:

- Fluid retention and swelling, particularly if you also have congestive heart failure
- An increase in blood sugar, which is of concern to people with diabetes or at risk of diabetes
- Insomnia
- Increased appetite
- Indigestion or heartburn – speak to your physician about medication to prevent this problem
- Hiccups
- Blurred vision
- Mood or emotional changes, such as depression, mood swings, agitation, anxiety, or even psychosis

Other effects that can develop after long-term use of high-dose steroids include the Cushingoid appearance (weight gain with a “moon face”), osteoporosis or bone loss, and muscle weakness and/or wasting. Fatigue, depression and cataracts are other potential side effects.

Coping with “Roid Rage”

Dealing with the diagnosis of cancer is hard – for you and your loved ones. The mood changes brought about by steroids can add to that burden. It is important that you talk with your loved ones and explain the effects steroids can have on your mood and activity levels. Give them a “heads up” when you will be going on and off your medication. Family members and friends can help by being supportive and understanding that sometimes “it’s the ‘roids talking”.

Depression

Some studies suggest that up to 40% of cancer patients experience depression or anxiety. As you deal with your disease, periods of feeling “blue” or “down” are not unusual. After all, you are going through a lot of changes. You may sometimes feel that you are no longer the person you used to be. Physical and mental changes may threaten your feeling of self-esteem.

If the depression lasts for many weeks without relief or is severe enough to interfere with everyday life, you may need some help. Talk about your feelings with your doctor, nurse or counsellor. Sometimes just talking with someone is enough to help. In other cases, medication can be given to help relieve depression.



Speak with a health professional if you experience five or more of the following symptoms for more than two weeks:

- Feeling sad, anxious, irritable, nervous and/or guilty
- Feelings of worthlessness or hopelessness
- Changes in your usual sleep patterns (either having trouble sleeping or sleeping more than normal)
- Changes in your appetite; gaining or losing weight without trying
- Loss of interest in activities you used to enjoy
- Restless or slowed behaviour
- Persistent or recurring headaches, digestive disorders, or chronic pain
- Difficulty concentrating, remembering or making decisions
- Fatigue, loss of energy
- Change in work style or productivity
- Thoughts of suicide – **if these occur, seek immediate professional help**

Chapter 7



Your Healthcare Team

When you were told you have myeloma, you may have felt like you were alone in the battle of your life. But in reality, there is a whole team of dedicated professionals who are behind you and ready to help you. They are the members of your healthcare team. In this section, we'll begin by looking at the roles played by the different members of your team. Then we'll discuss how you can optimize your communications with your team members and become a more informed and active participant in your care.



Family Doctor

When you first became ill, probably the first person you saw was your family doctor. Your family doctor helped to narrow down the possibilities of what might be wrong and provided referrals to specialists. Most family doctors see only a few, if any, myeloma patients in their practices.



Oncologist

A medical oncologist is a physician who specializes in the diagnosis and treatment of cancer. This doctor may be the key member of your health care team. He or she will determine your exact diagnosis and, in consultation with you and other specialists, design your treatment plan.

Hematologist

Because myeloma is a cancer of the blood, you may be referred to a hematologist. A hematologist is a physician who studies, diagnoses and treats diseases and disorders of the blood. Some hematologists specialize in blood cancers, whereas others may specialize in other blood problems such as clotting disorders. This doctor may be the key member of your healthcare team.



Radiation Oncologist

If you require radiation therapy, you will be referred to a radiation oncologist. As the name implies, a radiation oncologist is a physician who specializes in treating cancer with radiation therapy.



Surgical Oncologist

A surgical oncologist is a surgeon who specializes in cancer operations. For example, if a tumour must be removed, you may be referred to a surgical oncologist.



Nurse or Nurse Practitioner

Nurses may fill several important roles in your healthcare team. An oncology nurse is a specially-trained nurse who works closely with your medical oncologist, hematologist or radiation oncologist to coordinate your care, oversee your therapy and keep your physicians informed of any problems you may encounter. Other nurses may specialize as cancer educators. Nurse practitioners are nurses who have undertaken additional training in diagnosis and treatment of medical conditions.



Orthopedic Surgeon

If you require surgery on your bones, muscle or joints, you may be referred to an orthopedic surgeon.





Pharmacist

Your treatment for myeloma will involve many medications, some of which may be oral and others which may be delivered through an intravenous line. Whether working in the hospital or the community, pharmacists are valuable sources of information for patients and care providers. Pharmacists can help you to understand what different medications are designed to do, how to take them, what effects and side effects to expect, and what to do if side effects occur.



Dentist

Your dentist is an important but often overlooked member of your healthcare team. Good oral health is important at all times, and even more so when you are undergoing myeloma treatment. Infections from the teeth can drain into the lymph glands in the neck, and if your teeth and gums are not kept clean large quantities and varieties of bacteria can colonize the gums. These types of infections are an important and preventable source of problems.

If possible, it is best to identify and treat dental problems before you start chemotherapy, undergo stem cell transplant, or start taking bisphosphonates. Generally, the best time to be treated is when your hemoglobin count is 100 or more, platelet count 80 or more, and your neutrophil count 2.0 or more. Special precautions such as prophylactic antibiotics are probably required if you have a central line or catheter in place.

Dentists who work at cancer centres are familiar with the special requirements of myeloma patients, but some community dentists may not be. Speak with your dentist and clearly outline what drugs you are taking (including intravenous therapies), where you are in your therapy and what the plans may be for the future. Encourage him or her to talk with a cancer centre specialist.

Registered Dietitian/Nutritionist

Cancer and cancer treatment can make eating difficult. You may find it difficult to eat enough – or to eat the right kinds of food – to keep up your strength. Or some medications can actually increase your appetite, making it difficult to avoid overeating. The dietitian can help you maintain the healthiest diet possible throughout the different stages of your treatment. If you are struggling with nausea, vomiting, anorexia (loss of appetite) or a dry or sore mouth, your dietitian can suggest foods or drinks to help.



Psychiatrist or Psychologist

A psychiatrist is a physician trained in the diagnosis and management of mental illness. A psychologist is not a physician, but someone who has advanced training in counselling and human psychology. Both psychiatrists and psychologists can be very helpful in dealing with the psychological, emotional or behavioural problems you may encounter. In addition to “talk therapy”, psychiatrists are licensed to prescribe medication, such as antidepressants, if required.



Social Worker or Counsellor

Like a psychologist, a social worker or counsellor can help you deal with the many emotional changes being diagnosed with myeloma can bring. In addition, a social worker may be able to help you deal with some of the practical issues that arise, such as finding out more about your healthcare coverage.



Clergy or Spiritual Advisor

Some people find that talking with their clergy or spiritual advisor can be very helpful.



Optimizing Communications

As a patient, you have both rights and responsibilities when interacting with the members of your healthcare team.

Rights:

- To be treated with respect and courtesy.
- To be your own advocate or to bring an advocate with you.
- To be kept fully informed and to have things explained to you in language you can understand.
- To be informed of all possible treatment options available at your centre or other facilities, including clinical trials.
- To be allowed, and even helped, to obtain a second opinion if you want one.
- To be given the opportunity to participate in treatment decision-making, including the right to refuse any treatment you do not want.
- When you ask, to receive copies of your records, such as lab results, X-rays, and test results, at a reasonable cost (e.g., for the cost of copying).

Responsibilities:

- To tell the whole truth and nothing but the truth.
- To speak up if you aren't happy or don't understand (it helps to be tactful when doing so).
- To try and learn about your condition and treatments so you can share in decision making.
- To comply with any mutually acceptable treatment plan.
- To treat the members of your healthcare team with respect and courtesy.

As you probably know only too well, most healthcare professionals are very busy. Their time to talk is often limited. And most healthcare professionals are so used to the medical terms they use that they may forget that other people do not understand them. Here are some tips for optimizing your communications with your health care team.

- Write down any questions you have as well as any side-effects or symptoms you are experiencing. Bring these lists or documents with you to your appointment. Give the list to your doctor at the beginning of your consultation. Don't wait until the end, when the doctor is out of time.
- Take notes during your consultation of what your doctor says. Or bring someone with you to take notes for you. Some patients bring tape recorders to their appointments so that they can easily refer back to what was discussed.
- Ask your doctor if he or she has an assistant or nurse that you can talk to whenever you have questions.
- Ask if there are any brochures or other educational material you can take home with you.
- Keep your own history of your medical history and treatment. Many patients find it helpful to keep a binder in which they write down all of their appointments and treatments, who treated them, what medications they received, and their test results. In Canada, patients by law must be given access to their medical information if they request it (a reasonable fee may be charged to cover copying costs). Creating and maintaining your own binder of information will give you a better understanding of your condition, and may be helpful when dealing with healthcare professionals who are not familiar with your condition.

Not certain of what to ask? Following are some sample questions for different members of your healthcare team.

For your oncologist, hematologist or radiation oncologist:

- Who should I contact if I have problems, especially after hours or on weekends? Ask for names and telephone numbers.
- What are the results of my tests and what do they mean?
- What are all my treatment options, which one do you recommend and why do you feel this is the best approach?
- Are there clinical trials available at this centre or other centres that I could consider?
- What should I expect when undergoing treatment?
- How will we know if the treatment is working?
- Are there any warning signs or side effects that I should watch out for, and if they occur, whom should I report them to? Which ones do I need to report immediately?
- Are there foods, vitamins, supplements or herbal therapies that I should avoid?
- How often will I require testing or follow-up care?



For your **surgical oncologist or orthopedic surgeon:**

- Can you explain my surgical procedure in detail?
- What should I expect before, during and after surgery? What will my recovery be like?
- When do I need to come back for a follow-up visit?

For your **cancer nurse or educator:**

- What is your role in my cancer care? Are you the person I should contact if I have a problem or question?
- Can you help me find reliable and accurate information on myeloma?
- What advice can you give me at this stage of my cancer treatment?
- What sort of activities can you suggest so I can stay as active as possible? Which activities should I avoid?

For your **pharmacist:**

- What is the purpose of this medication? What side effects are likely to occur and which ones should I report immediately if they occur?
- Are there vitamins, supplements or herbal remedies that I should avoid while taking this drug?
- Can you help me set up a system, such as daily pill boxes or blister packs, to ensure I take all of my medications as prescribed?

For your **dentist:**

- Are there any infections or dental problems that should be taken care of before I begin my myeloma treatment?
- Are you familiar with the requirements for treating someone with myeloma and/or with a central line in place?
- What can I do to reduce the risk of requiring extractions or other traumatic dental work while undergoing treatment?

For your **dietitian**:

- I'm finding it difficult to eat. Is there anything you can recommend to help me?
- I'm going to start a new therapy soon. What do we know about this treatment's effect on appetite, digestion, etc.? Is there anything you can recommend to reduce its effects?
- Steroids have increased my appetite and I'm finding it difficult to control my eating. What should I do?

For your **psychologist, counsellor or spiritual advisor**:

- Can you help me better deal with the emotional effects of my diagnosis?
- My family and loved ones are very upset about my illness. What can I do to help them?

For your **social worker**:

- Can you help me and my family to learn ways of coping with the changes brought by my disease?
- Can you help me figure out what healthcare or other benefits I may be eligible for, such as short or long-term disability leaves?

Chapter 8



Development, Approval and Reimbursement of New and Emerging Therapies

For decades, only a very small number of therapies were available for myeloma. Today, the treatment of myeloma has entered a new and exciting phase. Research into the underlying cellular and biochemical processes of the disease is making possible a variety of innovative therapies. In this chapter, we'll look at how new therapies are developed and the approval process they must undergo. We'll also look at how new therapies are paid for.

New therapy development

Developing new therapies is a long and very expensive process. A number of phases of types of studies are required.

1. Pre-Clinical

The research that eventually leads to a new drug or treatment typically begins in a laboratory. Using the results of research into the basic genetic, cellular or biochemical processes underlying myeloma, scientists test different molecules or substances. This research may begin by using cells in a test tube (in vitro) and if promising, proceed to testing in small animals such as rats or mice (in vivo). Repeated animal trials are required to establish that a new agent is safe before it can be tested in any humans. Many molecules may be studied, but only the most promising will make the leap from pre-clinical to clinical trials.



2. Clinical Trials

Clinical trials are research studies involving people. Because people are involved, all clinical trials must be reviewed by Health Canada and shown to be safe. Clinical trials must also be approved by the Ethics Committees of all participating hospitals. These review processes are in place to protect the safety of participants. Only those studies that pass these rigorous approval processes are allowed to recruit patients.

There are four phases or types of clinical trials, and each phase is designed to answer specific questions.

■ Phase I

The primary question of a Phase I trial is: “What is the best and safest way to administer the new therapy?” A Phase I trial usually involves a small number of volunteers. The testing establishes the optimal dose for the new agent (enough that it is effective but not so much that it has toxic side effects), and perhaps the best way to administer it (e.g. orally or intravenously). A Phase I trial is an essential safety check for the new agent. Only those agents that are shown to be safe can proceed to the next phase of testing.

■ Phase II

The primary question of a Phase II trial is: “Does the new agent work in a selected group of patients?” A Phase II trial typically involves a larger group of volunteers than a Phase I trial. Volunteers are usually chosen to reflect a particular type or stage of the disease. The goal is to evaluate how effective the new therapy is in treating the disease in this type of patient. Possible side effects are also monitored.





■ Phase III

Only therapies that are effective, safe and have tolerable side effects can proceed to Phase III testing. Phase III trials are usually the largest, and can involve hundreds or even thousands of patients at cancer centres around the world. Patients in a Phase III trial are usually assigned randomly to either the new therapy (often referred to as the “treatment group”) or the existing therapy (“usual care” or “control” group). If there is no existing therapy, the new agent may be compared to a placebo (“sugar pill”) but this is seldom necessary in myeloma research. The term “Randomized Controlled Trial” is derived from the random way in which people are allocated to either the treatment or control group.

The primary question answered by a Phase III trial is: “Is the new agent effective, particularly in comparison to the best available existing treatment?” To ensure expectations don’t affect the assignment of people into groups or the interpretation of the data, Phase III trials are often “blinded”. “Blinded” means the patients do not know which agent they are getting. “Double blinding” is sometimes used so that neither the patient nor the researcher knows who is getting the new agent until the study is completed.



■ Phase IV

A Phase IV trial is sometimes referred to as “post marketing research”. It is research on a drug that has already been approved and is being used widely. Phase IV trials may be conducted to determine if the drug works as well in the “real world” as it did under the controlled conditions of a Phase III clinical trial. It may also be conducted to see if there are any significant long-term effects of the therapy or whether the drug could be used for other indications.

You can contribute to myeloma research

As a myeloma patient, you may be able to make an invaluable contribution to myeloma research and the development of new therapies. Perhaps you can donate marrow for laboratory research, or can volunteer for a clinical trial. Speak with your doctor or your healthcare team.

There are both advantages and disadvantages to participating in clinical trials. The advantages are:

- You may gain access to a new therapy that is not available outside of the trial. If the agent is effective, you will be among the first patients to benefit.
- You will be monitored even more closely and frequently than you would ordinarily.
- You will be helping other patients, now and in the future.

Among the disadvantages to consider:

- If you receive the new treatment, it may not turn out to be as effective as the existing therapy or there may be unexpected side effects.
- You may need to be tested more frequently than you would ordinarily.

It is important that you understand all potential risks and benefits before you agree to join a clinical trial. People who are asked to participate in a clinical trial must give what is called an informed consent. To do so, the clinical trial coordinator must give you a written document that explains in plain language the study protocol or written plan, as well as all potential risks, benefits and requirements.





If you are considering a clinical trial, don't be afraid to ask a lot of questions. The more you know about a study, the more informed your decision will be. Some questions you may want to ask include:

- What is the purpose of this study?
 - Is it a Phase I, Phase II, Phase III or Phase IV study?
 - Has the treatment or therapy been tested before? If so, what were the results? Were there side effects I should know about?
 - Who has reviewed and approved this clinical trial?
 - How long will the study last? How long will I be involved?
-
- Who will be in charge of my care? Will I be cared for by my own doctor?
 - Where will my treatment take place?
 - How will my safety be monitored during the study?
 - What sort of treatments, tests or procedures should I expect? How do they compare with what I would receive if I didn't participate?
 - What are the possible short- and long-term risks, side effects and benefits for me? How do these risks, side effects and benefits compare to those of the usual treatment?
 - If the study requires other medications – either as part of the treatment or for side effects – will they be supplied by the study? If not, will they be covered by my private or public drug plan?
 - How might being in the trial affect my daily life? Is there anything my family should know about the treatment?

To learn more about the trials underway in Canada, go to the following websites:

- Myeloma Canada (www.myeloma.ca)
- Cancer View Canada (www.canadiancancertrials.ca)
- International Myeloma Foundation (www.myeloma.org)
- US National Institutes of Health (www.clinicaltrials.gov)

The drug approval process in Canada

Just because a new therapy has been shown to be effective in a Phase III trial doesn't mean that it is automatically available in Canadian hospitals, clinics or pharmacies. Before a drug can be used in Canada, it must go through a rigorous approval process by Health Canada. Health Canada does not look solely at whether a new agent is safe, but at the balance between risks and benefits.

If the drug company's submission is approved, Health Canada will issue a Notice of Compliance (NOC) and give the drug a Drug Identification Number (DIN). This means the company is now allowed to market the new drug in Canada. In some cases, Health Canada may award a Notice of Compliance with Conditions (NOC/c). A drug awarded with a NOC/c is given a DIN but the sponsoring company must agree to special conditions or requirements, such as research or professional and patient education.

Once a new cancer drug is approved for use in Canada, the manufacturer must make a submission to the pan-Canadian Oncology Drug Review (pCODR) for evaluation. The pan-Canadian Oncology Drug Review was set up by the provincial and territorial Ministries of Health to make recommendations as to whether new drugs should be covered under provincial formularies – the list of medications they will pay for. The hope is that it will streamline the drug review process and help encourage greater consistency in cancer drug funding across the country. For more information, visit www.pcodr.ca.

The Pan-Canadian Pricing Alliance (PCPA) conducts joint provincial/territorial price negotiations with the drug manufacturer on behalf of all provinces and territories (except Québec) for new drugs in Canada. All new drugs coming forward for public funding through the pan-Canadian Oncology Drug Review (pCODR) are now considered for negotiation through the PCPA.

Despite the national review processes that are in place, most publically-funded drug plans continue to make their own decisions as to which medications they will or will not list. As a result, the coverage of new treatments often varies across the country. In some cases, even when a new drug is added to a formulary, the decision as to whether to pay for it is made on a case-by-case basis. This special authorization process requires your physician to write a letter to the drug plan, explaining why you require this particular medication.



Reimbursement of new therapies



There are basically four ways of paying for cancer drugs:

- The drug is on the list of approved medications of the government health insurance drug plan of which you are a member (either as a general benefit or through a special authorization process).
- You have a private drug plan that will pay for the drug in question (many private plans also have formularies or lists of drugs they will cover).
- You pay for the drug yourself.
- If you meet certain financial eligibility criteria, assistance may be provided by the drug manufacturer.

It may take some research to ensure you have optimal access to new prescription medications – and to minimize your own out-of-pocket costs. Here are some tips to help you.

- Know your health insurance coverage. Some provinces only provide drug coverage for people who are 65 and older or on social assistance. But others may have a variety of plans, such as special coverage for those facing substantive prescription drug costs. Drugs provided through cancer care centres can also vary from province to province. Talk with your cancer team social worker or pharmacist, or call your provincial Ministry of Health to learn about all your options.
- If you have private health insurance or a drug plan at work, sit down and carefully review your benefits. If you are employed, meet with your Human Resources department or union representative to help you better understand your benefits. Ask your doctor what drugs you may need in the future, and check to see if your plan covers them. Try to coordinate the benefits so any portion of a drug cost that is not paid for by one plan is applied to the next.
- Some private insurance plans require that you pay up-front and then apply for reimbursement. If this is a problem for you (e.g. you need a very expensive drug), ask your insurance company to allow your pharmacy to send the bill directly to them.

- Don't be afraid to advocate for yourself. For instance, if your employee health plan does not cover a certain drug, ask your employer or human resources manager if the company can make an exception in your case. Or ask your employer if they would waive the cap on your drug coverage.
- Find someone to work with you to advocate for the drug coverage you need. This someone can be a family member, for instance, or a friend. This person can help continue to advocate for you even when you cannot.
- If you are refused coverage of a medication you need, appeal. Sometimes the refusal may be the result of nothing more than faulty paperwork. And sometimes insurance companies will change their mind if you appeal.
- Some pharmaceutical companies have free services that will help you search for coverage of specific drugs or even supply you with the drug you require. Talk with your cancer care team or search online to see if you may be eligible for such a program.

For more information, check out www.DrugCoverage.ca, a free resource providing information about prescription drug reimbursement in Canada.

Chapter 9

How To Be Your Own Advocate



Being diagnosed with cancer can be overwhelming. You are facing a number of major life changes. One of the most important things you can do to help yourself is to become your own advocate.

1. Document your experience

It is important that people with myeloma keep a binder or log with detailed information on their treatments, test results and consultations. Such a log can help you to better understand your condition and support your efforts to act as your own advocate.

The sort of information you may want to collect includes:

- Names and contact information for all professionals involved in your care.
- Dates of all appointments, reasons for the appointments and any outcomes or decisions that were made.
- Copies of all test results (blood and urine tests and X-rays).
- Dates and details of all treatments you undergo.
- Details of all medications you are prescribed (dose, how and when you are supposed to take them, side effects you are supposed to report).
- Daily reports of any side effects or symptoms you experience during treatments or while taking medications.



- If you are experiencing fatigue, try keeping a log of your energy level on a scale of 0 (absolutely exhausted) to 10 (full of energy) at different points of the day. Keeping a log may help to identify when you have the most and the least energy, so you can plan your activities accordingly.
- A pain log can also be extremely helpful in identifying the type of pain you are experiencing and how it should be treated. At different points of the day, write down how severe your pain is on a scale ranging from 0 (pain-free) to 10 (the most excruciating pain possible). You might also want to describe the type of pain, where it is and whether it moves or changes throughout the day.

2. Sort out the type of information or services you need and identify the appropriate person to address each need

During your treatment for myeloma, you will have a number of different needs. Sorting out what these needs are will help you identify the most appropriate person or organization to address them. For example, your medical needs are addressed, best, by your healthcare team; emotional or spiritual needs by a social worker, counsellor, clergy or spiritual advisor; personal issues such as housekeeping and transportation by your family; or job-related and/or financial issues by your employer, accountant or lawyer.





3. Prepare for each appointment

We prepare for all the important events of our life, such as job interviews, presentations, weddings and celebrations. Your medical appointments are equally important, so be sure to prepare for them too.

Keeping your myeloma record will be a big help in preparing for your medical appointments. A quick review of your record may help to clarify in your mind what sorts of questions you should ask.

During most medical appointments, things happen so quickly that it can be difficult to remember what you meant to ask. Don't take chances – come with your list of questions and give it to the healthcare professional at the beginning of your appointment. If there isn't enough time to cover all of the questions on your list, ask if you can book another appointment so you can address them or if there is someone else on your cancer care team who can talk with you.



4. Take, review and store notes of your visits

During appointments and treatments you will probably be given a lot of information. Don't expect that you will be able to accurately remember everything. Bring a notepad with you and take notes during your appointment and as you talk with different members of your healthcare team. Or bring a tape recorder and record the appointment. Don't be afraid to ask questions, especially if someone uses unfamiliar terms. If you want, bring someone with you to take notes for you or to help you make a record of your visit. Review these notes when you get home and call your healthcare team contact if anything is unclear to you. Add these notes to your permanent record or binder.

5. Educate yourself

While it may be overwhelming at the beginning, it is important to educate yourself about myeloma and about your own condition. Ask your healthcare team for literature and brochures to read. Consult reputable web sites, such as those we describe below. Ask at your cancer care treatment centre about support groups in your area, or consult the listing on the Myeloma Canada website.

6. Involve others

Support is essential when you are living with myeloma. There are various ways in which different people can help. Some may be able to offer emotional support. Others may give practical support, such as running errands or driving you when you are not feeling well.

When you feel too tired or ill to act as your advocate, it can be very helpful to have someone who can step in and take over this role for you. Whether going with you to your appointment, taking notes, or asking questions, having someone to advocate for you can be extremely helpful.

Finally, don't forget to look for patient support groups in your area. Patient support groups can be valuable sources of information and support. Many arrange for talks by healthcare providers, or can give you access to resources such as brochures or booklets. Ask at your hospital or cancer centre if there is a myeloma patient support group in your area, or check the Myeloma Canada website. If there is no group in your area, consider forming one. Myeloma Canada will give you information and support on how to start a patient group in your area.





Resources

Myeloma Canada

(www.myeloma.ca)

Let's begin with a resource that is unique to Canada, and therefore most pertinent to Canadians. On the internet, your first stop should be Myeloma Canada. This bilingual website gives you:

- Information about myeloma and living with myeloma
- Publications you can download
- Links to listings of clinical trials currently underway in Canada, as well as the U.S. and elsewhere
- Events and meetings
- Information on support groups in communities across Canada, so you can meet with others facing the same challenges and experiences
- Links to other Canadian and international resources

Joining an existing support group is an excellent way of learning more about myeloma. When you meet with other myeloma patients, you not only benefit from their support and experiences – but you help others. If there is no support group in your area, contact Myeloma Canada for information on how to start one.

International Myeloma Foundation

(www.myeloma.org)

The International Myeloma Foundation is a U.S.-based organization that provides information for patients and healthcare professionals, and funds myeloma research. Its website will give you access to a wealth of information, including a world-wide listing of support groups. When using this site remember that units of measurement and some drug names may vary from those used in Canada.

Myeloma UK

(www.myeloma.org.uk)

Established in 1997, Myeloma UK is the only organization in the United Kingdom dealing exclusively with myeloma.



Your Journey Has Begun



In this handbook, we have covered a lot of material. Don't expect to be able to understand or remember all of it. Focus your attention on those parts that are most relevant to your situation at this time. Come back whenever you have questions, are unclear about something or want to learn more.

Hundreds of years ago, explorers set sail, uncertain of where they would end up or what they would encounter. Being diagnosed with a disease such as myeloma is similar in many ways. The life and world you have known has changed, and you are embarking on a journey in a new and often unfamiliar world. Sometimes it may seem overwhelming and frightening. But there are people to help and support you. Some of them are in your home and community; others are at your hospital, cancer clinic or place of worship.

The journey you are facing is challenging. The outcome is uncertain. But remember that you are never alone. Around the world, patient groups, healthcare professionals and researchers are working hard to improve the outlook for myeloma patients everywhere.



Glossary

Accrual: The process of enrolling patients in a clinical research study (trial), or the number of patients already enrolled in a trial or anticipated to enroll in a trial.

Acute: A sudden onset of symptoms or disease.

Albumin: Simple water-soluble proteins that are found in blood serum.

Alkylating agent: A chemotherapeutic agent such as melphalan or cyclophosphamide. Alkylating refers to the way in which these agents cross-link the DNA of myeloma cells and block cell division.

Allogeneic: See “Transplantation”

Amyloidosis: A condition in which myeloma light chains (Bence-Jones proteins) are deposited in tissues and organs throughout the body. This occurs more commonly with lambda versus kappa Bence-Jones proteins. In patients with amyloidosis, the light chain proteins bind to certain tissues such as heart, nerves and kidney rather than being excreted out of the body through the kidneys.

Analgesic: Any drug that relieves pain. Aspirin and acetaminophen are mild analgesics.

Analogue: A chemical compound that is structurally similar to another but differs slightly in composition.

Anemia: A decrease in the normal number of red blood cells. Myeloma in the bone marrow blocks red blood cell production, causing shortness of breath, weakness, and tiredness.

Angiogenesis: Blood vessel formation, which usually accompanies the growth of malignant tissue, including myeloma.

Angiogenesis inhibitors: Compounds that attempt to cut off the blood supply to tumours.

Antibody: A protein produced by certain white blood cells (plasma cells) to fight infection and disease in the form of antigens such as bacteria, viruses, toxins or tumours. Each antibody can bind only to a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies disable antigens directly. Others make the antigen more vulnerable to destruction by other white blood cells.

Anti-emetic agent: A drug that prevents or controls nausea and vomiting.

Antigen: Any foreign substance (such as a bacteria, virus, toxin or tumour) that, when introduced into or arising in the body, causes the immune system to produce natural antibodies.

Antineoplastic agent: A drug that prevents, kills, or blocks the growth and spread of cancer cells.

Apoptosis: A normal cellular process involving a genetically programmed series of events leading to the death of a cell.

Aspiration: The process of removing fluid or tissue, or both, from a specific area.

Asymptomatic myeloma: Myeloma that presents no signs or symptoms of disease. Also called indolent, smoldering, or early myeloma.

B cells: White blood cells that develop into plasma cells in the bone marrow and are the source of antibodies. Also known as B lymphocytes.

Basophil: A type of white blood cell. Basophils are granulocytes.

Bence-Jones: A myeloma protein present in urine. The amount of Bence-Jones protein is expressed in terms of grams per 24 hours. Normally a very small amount of protein (< 0.1 g/24 h) can be present in the urine, but this is albumin rather than Bence-Jones protein. The presence of any Bence-Jones protein is abnormal.

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. MGUS is a benign condition.

Beta 2 microglobulin (β 2M): A small protein found in the blood. High levels occur in patients with active myeloma. Low or normal levels occur in patients with early myeloma and/or inactive disease. Approximately 10% of patients have myeloma that does not produce β 2M. For these patients, β 2M testing cannot be used to monitor the disease. At the time of relapse, β 2M can increase before there is any change in the myeloma protein level. Therefore, 90% of the time, β 2M is very useful for determining disease activity.

Biopsy: The removal of a sample of tissue for microscopic examination to aid in diagnosis.

Bisphosphonate: A type of drug that binds to the surface of bone where it is being resorbed (or destroyed) and protects against osteoclast activity.

Blood cells: Minute structures produced in the bone marrow; they include red blood cells, white blood cells and platelets.

Blood count: The number of red blood cells, white blood cells and platelets in a sample of blood.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells and platelets.

Bone marrow aspiration: The removal, by a needle, of a sample of fluid and cells from the bone marrow for examination under a microscope.

Bone marrow biopsy: The removal, by a needle, of a sample of tissue from the bone. The cells are checked to see whether they are cancerous. If cancerous plasma cells are found, the pathologist estimates how much of the bone marrow is affected. Bone marrow biopsy is usually done at the same time as bone marrow aspiration.

Bone remodelling: The normal coordination (coupling) between osteoclast cells (which resorb or destroy bone) and osteoblast cells (which create new bone matrix) to maintain a balanced state of bone production and destruction.

Calcium: A mineral found mainly in the hard part of bone matrix.

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Carcinogen: Any substance or agent that produces or stimulates cancer growth.

CAT or CT [Computerized (Axial) Tomography scan]: A test using computerized X-rays to create three-dimensional images of organs and structures inside the body, used to detect small areas of bone damage or soft tissue involvement.

Catheter: A tube that is placed in a blood vessel to provide a pathway for drugs or nutrients. The catheter allows medications, fluids, or blood products to be given and blood samples to be taken.

Cell differentiation: The process during which young, immature (unspecialized) cells take on individual characteristics and reach their mature (specialized) form and function.

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division.

Chemotherapy: The treatment of cancer with drugs that kill all rapidly-dividing cells.

- **Combination chemotherapy** – The use of more than one drug given in a chemotherapy regimen during cancer treatment.

Chromosome: A strand of DNA and proteins in the nucleus of a cell. Chromosomes carry genes and function in the transmission of genetic information. Normally, human cells contain 46 chromosomes.

Chronic: Persisting over a long period of time.

Clinical: Involving direct observation of a patient.

Clinical trial: A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose or treat cancer and to answer scientific questions.

- **Control group** – The arm of a randomized clinical trial that gets the standard treatment.
- **End point** – What a clinical trial is trying to measure or find out; the goal of the trial. Typical end points include measurements of toxicity, response rate and survival.
- **Experimental group** – The arm of a randomized trial that gets the new treatment.
- **Randomized clinical trial** – A research study in which subjects are randomly assigned to receive a particular treatment.

Creatinine: A small chemical compound normally excreted by the kidneys. If the kidneys are damaged, the serum level of creatinine builds up, resulting in an elevated serum creatinine. The serum creatinine test is used to measure kidney function.

Cytokine: A substance secreted by cells of the immune system that stimulates growth/activity in a particular type of cell. Cytokines are produced locally (i.e., in the bone marrow) and circulate in the bloodstream.

Dexamethasone: A powerful corticosteroid given alone or with other drugs.

Diagnosis: The process of identifying a disease by its signs and symptoms.

Dialysis: When a patient's kidneys are unable to filter blood, the blood is cleaned by passing it through a dialysis machine.

DNA: The substance of heredity; a large molecule that carries the genetic information that cells need to replicate and to produce proteins.

Drug resistance: The result of cells' ability to resist the effects of a specific drug.

Edema: Swelling; an abnormal accumulation of fluid in part of the body.

Electrophoresis: A laboratory test in which a patient's serum (blood) or urine molecules are subjected to separation according to their size and electrical charge. For myeloma patients, electrophoresis of the blood or urine allows both the calculation of the amount of myeloma protein (M-protein) as well as the identification of the specific M-spike characteristic for each patient. Electrophoresis is used as a tool both for diagnosis and for monitoring.

Enzyme: A substance that affects the rate at which chemical changes take place in the body.

Erythrocytes: Red blood cells (RBCs). RBCs carry oxygen to body cells and carbon dioxide away from body cells.

Erythropoietin: A hormone produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anemic. Injections with synthetic erythropoietin can be helpful. Blood transfusion is another alternative, especially in an emergency.

Free light chains: A portion of the monoclonal protein of light molecular weight that can be measured in a sensitive assay, the Freelite® test.

Gene: A specific sequence of DNA or RNA; the biological unit of heredity located in a specific place on a chromosome and found in all cells in the body. When genes are missing or damaged, cancer may occur.

Gene therapy: Treatment that alters genes; using genes to stimulate the immune system. In studies of gene therapy for cancer, researchers are trying to improve the body's natural ability to fight the disease and to make the tumour more sensitive to other kinds of therapy. Treatment focuses on replacing damaged or missing genes with healthy copies.

Genetic: Inherited; having to do with information that is passed from parents to children through DNA in the genes.

Graft-versus-host disease (GVHD): A reaction of donated stem cells against the recipient's own tissue.

Granulocyte: A type of white blood cell that kills bacteria. Neutrophils, eosinophils, and basophils are granulocytes.

Hematocrit (Hct): The percentage of red blood cells in the blood. A low hematocrit measurement indicates anemia.

Hematologic: Originating in the blood, or disseminated by the circulation or through the bloodstream.

Hematologist: A doctor who specializes in the problems of blood and bone marrow.

Herpes simplex: A common virus, it causes sores often seen around the mouth, commonly called cold sores.

Herpes zoster: A virus that settles around certain nerves in patients who have previously had a chicken pox (varicella) infection, causing blisters, swelling, and pain. This condition is also called shingles.

Hormones: Chemicals produced by various glands of the body that regulate the actions of certain cells or organs.

Human leukocyte antigen (HLA) test: A blood test used to match a blood or bone marrow donor to a recipient for transfusion or transplant.

Hypercalcemia: A higher-than-normal level of calcium in the blood. This condition can cause a number of symptoms, including loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness and confusion. Common in myeloma patients and usually resulting from bone destruction with release of calcium into the blood stream. Often associated with reduced kidney function since calcium can be toxic to the kidneys. For this reason, hypercalcemia is usually treated on an emergency basis using IV fluids combined with drugs to reduce bone destruction along with direct treatment for the myeloma.

IgG, IgA: The two most common types of myeloma. The G and the A refer to the type of protein produced by the myeloma cells. The myeloma protein, which is an immunoglobulin, consists of two heavy chains, (for example of a G type) combined with two light chains, which are either kappa or lambda. Therefore, the two most common subtypes of myeloma have identical heavy chains (i.e. IgG kappa and IgG lambda). The terms heavy and light refer to the size or molecular weight of the protein, with the heavy chains being larger than the light chains. Since the light chains are smaller, they are more likely to leak out into the urine, resulting in Bence-Jones protein.

IgD, IgE: Two types of myeloma that occur less frequently.

IgM: Usually associated with Waldenstrom's macroglobulemia. In rare cases can be a type of myeloma.

Immune system: The complex group of organs and cells that produces antibodies to defend the body against foreign substances such as bacteria, viruses, toxins and cancers.

Immunodeficiency: A lowering of the body's ability to fight off infection and disease.

Immunofixation: An immunologic test of the serum or urine used to identify proteins in the blood. For myeloma patients, it enables the doctor to identify the M-protein type (IgG, IgA, kappa, or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy and light chain type of M-protein.

Immunoglobulin (Ig): A protein produced by plasma cells, an essential part of the body's immune system. Immunoglobulins attach to foreign substances (antigens) and assist in destroying them. The classes of immunoglobulins are IgA, IgG, IgM, IgD and IgE.

Immunosuppression: Weakening of the immune system that causes a lowered ability to fight infection and disease. Immunosuppression may be deliberate, such as in preparation for bone marrow transplantation to prevent rejection by the host of the donor tissue, or incidental, such as often results from chemotherapy for the treatment of cancer.

Immunotherapy: Treatment that stimulates the body's natural defenses to fight cancer. Also called biological therapy.

Incidence: The number of new cases of a disease diagnosed each year.

Induction therapy: The initial treatment used in an effort to achieve remission in a newly diagnosed myeloma patient. Also referred to as "front-line" or "first-line" therapy.

Informed consent: The process requiring a doctor to give a patient enough information about a proposed procedure for the patient to make an informed decision about whether or not to undergo it. The doctor must, in addition to explaining all procedures, address the issues of risks, benefits, alternatives and potential costs.

Infusion: Delivering fluids or medications into the bloodstream over a period of time.

Injection: Pushing a medication into the body with the use of a syringe and needle.

Interferon: A naturally produced hormone (cytokine) released by the body in response to infection or disease which stimulates the growth of certain disease-fighting blood cells in the immune system.

Interleukin: A naturally produced chemical released by the body or a substance used in biological therapy. Interleukins stimulate the growth and activities of certain kinds of white blood cells. Interleukin-2 (IL-2) is a type of biological response modifier that stimulates the growth of certain blood cells in the immune system that can fight some types of cancer. Interleukin-6 (IL-6) is a cytokine which is a potent stimulus to osteoclast and plasma cell activities.

LDH: Lactate dehydrogenase, an enzyme that may be used to monitor myeloma activity.

Lesion: An area of abnormal tissue change. A lump or abscess that may be caused by injury or disease, such as cancer. In myeloma, "lesion" can refer to a plasmacytoma or a hole in the bone.

Leukocytes: Cells that help the body fight infections and other diseases. Also called white blood cells (WBCs).

Leukopenia: A low number of white blood cells.

Lymphocytes: White blood cells that fight infection and disease.

Lytic lesions: The damaged area of a bone that shows up as a dark spot on an X-ray when enough of the healthy bone in any one area is eaten away. Lytic lesions look like holes in the bone and are evidence that the bone is being weakened.

M proteins (M spike): Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of multiple myeloma patients. M spike refers to the sharp pattern that occurs on protein electrophoresis when an M protein is present. Synonymous with monoclonal protein, paraprotein and myeloma protein. (See "monoclonal" below)

Maintenance therapy: Drugs given to patients in remission to delay or prevent a relapse.

Melanoma: A cancer of the pigment-forming cells of the skin or the retina of the eye. Not associated with myeloma despite the similar-sounding name.

Metastasis: To spread from one part of the body to another. When cancer cells metastasize and form secondary tumours, the cells in the metastatic tumour are like those in the original (primary) tumour. This term is commonly used to describe a disease process in solid tumours (e.g., breast, prostate) and not in myeloma, which is a blood-related cancer.

MGUS (Monoclonal Gammopathy of Undetermined Significance): A benign condition in which the M protein is present but there is no underlying disease.

Monoclonal: A clone or duplicate of a single cell. Myeloma develops from a single malignant plasma cell (monoclonal). The type of myeloma protein produced is also monoclonal; a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M spike) in the serum electrophoresis test.

Monoclonal antibodies: Artificially manufactured antibodies specifically designed to find and bind to cancer cells for diagnostic or treatment purposes. They can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to tumor cells.

Monocyte: A type of white blood cell.

MRI (Magnetic Resonance Imaging): A diagnostic test that uses magnetic energy, rather than X-ray energy, to produce detailed two- or three-dimensional images of organs and structures inside the body. Gives very fine resolution of soft tissues, especially encroachments on the spinal cord, but is less accurate for bone lesions.

Myelosuppression: A decrease in the production of red blood cells platelets and some white blood cells by the bone marrow.

Neutropenia: A reduced level of neutrophils. Cytotoxic chemotherapy has a tendency to induce neutropenia. In contrast, lymphocytes which are more important in viral infections, tend not to be affected by cytotoxic treatment. Neutropenia can be prevented or reduced using a synthetic hormone called G-CSF (e.g. Neupogen®).

Neutrophil: A type of white blood cell necessary to combat bacterial infection.

Oncogene: A gene that has the potential to cause a normal cell to become cancerous.

Oncologist: A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment.

Osteoblast: The cell that produces osteoid, which becomes mineralized with calcium to form new hard bone.

Osteoclast: A cell found in the bone marrow at the junction between the bone marrow and the bone that resorbs or breaks down old bone. In myeloma, the osteoclasts are over-stimulated while osteoblast activity is blocked. The combination of accelerated bone resorption and blocked new bone formation results in lytic lesions.

Osteonecrosis of the jaw: A previously rare jaw problem now being observed in a small percentage of patients taking bisphosphonates. The condition produces pain, swelling, and bone damage around the tooth sockets in the jaws. There is bone necrosis or loss of bone which can lead to loose teeth, sharp edges of exposed bone, bone spurs and the breaking loose of small bone spicules or dead bone. A case definition is ≥ 3 months with non-healing exposed bone. Symptoms may not be obvious at first, or may include pain, swelling, numbness or a “heavy jaw” feeling, or loosening of a tooth.

Osteoporosis: Reduction in bone density typically associated with old age. Diffuse involvement of bones with myeloma produces what looks like osteoporosis on X-ray and bone density measurement.

Palliative treatment: Aimed to improve the quality of life by relieving pain and symptoms of disease but not intended to alter its course.

Pathological fracture: A break in a bone usually caused by cancer or some disease condition. Occurs in myeloma-weakened bones, which can't bear normal weight or stress.

PET (Positron Emission Tomography) scan: A diagnostic test that uses a sophisticated camera and computer to produce images of the body. PET scans show the difference between healthy and abnormally functioning tissues.

Placebo: An inert (inactive) substance often used in clinical trials for comparison with an experimental drug.

Plasma: The liquid part of the blood in which red blood cells, white blood cells and platelets are suspended.

Plasma cells: Special white blood cells that produce antibodies. The malignant cell in myeloma. Normal plasma cells produce antibodies to fight infection. In myeloma, malignant plasma cells produce large amounts of abnormal antibodies that lack the capability to fight infection. The abnormal antibodies are the monoclonal protein, or M protein. Plasma cells also produce other chemicals that can cause organ and tissue damage (i.e. anemia, kidney damage and nerve damage).

Plasmacytoma: A collection of plasma cells found in a single location rather than diffusely throughout the bone marrow, soft tissue, or bone.

Plasmapheresis: The process of removing certain proteins from the blood. Plasmapheresis can be used to remove excess antibodies from the blood of multiple myeloma patients.

Platelet: One of the three major blood elements, others being the red blood cells and white blood cells. Platelets are the major defense against bleeding. Also called thrombocytes.

Port - Implanted: A catheter connected to a quarter-sized disc that is surgically placed just below the skin in the chest or abdomen. The catheter is inserted into a large vein or artery directly into the bloodstream. Fluids, drugs, or blood products can be infused, and blood can be drawn through a needle that is stuck into the disc.

Prognosis: The projected outcome or course of a disease; the chance of recovery; the life expectancy.

Progression-free survival: The time period during which the patient survives and the cancer does not become worse. The improved survival of a patient that can be directly attributed to the treatment given for the myeloma. This term identifies myeloma patients who are in complete remission versus those who have had an episode of relapse or progression.

Progressive disease: Disease that is becoming worse, as documented by tests.

Protocol: A detailed plan of treatment including the dose and schedule of any drugs used.

Precancerous: A term used to describe a condition that may, or is likely to become, cancer.

Radiation therapy: Treatment with X-rays, gamma rays, or electrons to damage or kill malignant cells. The radiation may come from outside the body (external radiation) or from radioactive materials placed directly in the tumour (implant radiation).

Radiologist: A doctor who specializes in creating and interpreting images of areas inside the body. The images are produced with X-rays, sound waves, magnetic fields, or other types of energy.

Recurrence: The reappearance of a disease after a period of remission.

Red blood cells (erythrocytes): Cells in the blood that contain hemoglobin and deliver oxygen to and take carbon dioxide from all parts of the body. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anemic. Injections with synthetic erythropoietin can be helpful. Blood transfusion is another alternative, especially in an emergency.

Refractory: Disease that is unresponsive to standard treatments.

Regression: The shrinkage of cancer growth.

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement.

Remission or response: Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are used interchangeably.

Shingles: See "Herpes zoster"

Side effects: Problems that occur due to drugs used for disease treatment. Common side effects of cancer chemotherapy are fatigue, nausea, vomiting, decreased blood cell counts, hair loss and mouth sores.

Skeletal survey (metastatic survey): A series of plain X-rays of the skull, spine, ribs, pelvis and long bones to look for lytic lesions and/or osteoporosis.

Stable disease: This describes patients who have some response to treatment but < 50 % reduction in myeloma protein levels. Stable disease is not necessarily bad or sub-optimal provided the myeloma has stabilized and is not progressing. With slow-moving myeloma, stabilization can last for many years.

Stage: The extent of a cancer in the body.

Staging: Doing exams and tests to learn the extent of the cancer in the body.

Stem cells: The immature cells from which all blood cells develop. Normal stem cells give rise to normal blood components, including red cells, white cells and platelets. Stem cells are normally located in the bone marrow and can be harvested for transplant.

Steroid: A type of hormone. Steroids are often given to patients along with one or more anticancer drugs and appear to help to control the effects of the disease on the body.

Supportive care: Treatment given to prevent, control, or relieve complications and side effects and to improve the patient's comfort and quality of life.

Thrombocyte: See "Platelet"

Thrombocytopenia: A low number of platelets in the blood. The normal level is 150,000-450,000. If the platelet count is less than 50,000, bleeding problems could occur. Major bleeding is usually associated with a reduction to less than 10,000.

TNF (Tumor Necrosis Factor): A type of biological response modifier that can improve the body's natural response to disease.

Transfusion: The transfer of blood or blood products.

Transplantation: The use of stem cells are to rescue a patient's blood-forming potential following high-dose chemotherapy and/or radiation treatment. Transplant is not a treatment, but a method of support to make high-dose treatment possible.

- **Bone marrow transplantation** – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral or circulating blood.
- **Peripheral blood stem cell transplantation** – Doctors remove healthy stem cells from a patient's circulating blood system (not from the bone marrow) and store them before the patient receives high-dose chemotherapy to destroy the cancer cells. The stem cells are then returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.
- **Allogeneic** – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor.
- **Autologous** – A procedure in which stem cells are removed from a patient's blood and then are given back to the patient following intensive treatment.
- **Matched unrelated donor transplants (MUDs)** – Refers to stem cell transplantation procedures in which the patient and the stem cells are genetically matched but are not from family members.
- **Syngeneic** – The infusion of bone marrow or stem cells from one identical twin into another.

Tumour: An abnormal mass of tissue that results from excessive cell division. Tumours perform no useful body function. They may either be benign or malignant.

Tumour marker: A substance in blood or other body fluids that may suggest that a person has cancer.

Vaccine: A preparation of killed microorganisms, living attenuated organisms, or living fully virulent organisms that is administered to produce or artificially increase immunity to a particular disease.

Waldenstrom's macroglobulemia: A rare type of indolent lymphoma that affects plasma cells. Excessive amounts of IgM protein are produced. Not a type of myeloma.

White blood cells (WBC): General term for a variety of cells responsible for fighting invading germs, infection and allergy-causing agents. These cells begin their development in the bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, granulocytes, lymphocytes, and monocytes.

X-ray: High-energy electromagnetic radiation used in low doses to diagnose diseases and in high doses to treat cancer.



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Myeloma Canada Scientific Advisory Board

Nizar J Bahlis, MD

Tom Baker Cancer Centre
Assistant Professor
University of Calgary
Foothills Medical Centre
Calgary, AB

Andrew R Belch, MD

Division of Medical Oncology
Department of Oncology
Cross Cancer Institute
University of Alberta
Edmonton, AB

Christine Chen, MD

Assistant Professor
Department of Medical
Oncology and Hematology
Princess Margaret Hospital
University Health Network
Toronto, ON

Jonathan Keats, PhD

Assistant Professor
Integrated Cancer Genomics Division
Translational Genomics
Research Institute
Phoenix, AZ

Richard LeBlanc, MD

Maisonneuve-Rosemont Hospital
Clinical Assistant Professor
of Medicine
University of Montreal
Montreal, QC

Paola Neri, MD, PhD

Clinical Assistant Professor
University of Calgary
Calgary, AB

Linda Pilarski, PhD

Division of Experimental Oncology
Department of Oncology
Cross Cancer Institute
University of Alberta
Edmonton, AB
Member, IMF Scientific Advisory Board

Donna E Reece, MD

Professor of Medicine
Director, Program for Multiple
Myeloma and Related Diseases
Department of Medical
Oncology and Hematology
Princess Margaret Hospital
University Health Network
Toronto, ON
Member, IMF Scientific Advisory Board

Tony Reiman, MD

Medical Oncologist
Saint John Regional Hospital
Assistant Dean of Research
Dalhousie Medicine
New Brunswick
Saint John, NB

Jean Roy, MD

Maisonneuve-Rosemont Hospital
University of Montreal
Montreal, QC

Michael Sebag, MD, PhD

Assistant Professor
McGill University Faculty of
Medicine
McGill University Health Centre
Montreal, QC

Chaim Shustik, MD

Associate Professor of Medicine
& Oncology
McGill University Faculty
of Medicine
Royal Victoria Hospital
Montreal, QC
Member, IMF Scientific Advisory Board

Kevin J Song, MD

BC Cancer Research Centre
Vancouver General Hospital
Vancouver, BC

**Rodger Tiedemann, PhD,
ChB, MB**

Scientist, Ontario Cancer Institute
Staff Hematologist
Division of Medical Oncology &
Hematology
Princess Margaret Hospital
Assistant Professor of Medicine
University of Toronto
Toronto, ON

Suzanne Trudel, MD

Assistant Professor
Clinician/Research Scientist
Department of Medical Oncology
and Hematology
Princess Margaret Hospital
University Health Network
Toronto, ON

Darrell White, MD

Nova Scotia Cancer Centre
Queen Elizabeth II Health
Services Centre
Dalhousie University
Halifax, NS



**MYELOMA CANADA
RESEARCH NETWORK**

MAKING MYELOMA MATTER

The mission of the Myeloma Canada Research Network is to conduct clinical and translational research in a collaborative manner to improve patient outcomes in multiple myeloma, and to provide scientifically valid and peer-reviewed consensus opinions on the diagnosis and treatment of multiple myeloma.

Make Myeloma Matter

Every year, Myeloma Canada provides information to thousands of people with myeloma, their families and caregivers, and helps many more by providing services such as the annual Myeloma Canada National Conference, Patient and Family InfoSessions, webinars and the Myeloma Matters newsletter.

Through the Myeloma Canada Research Network, we support Canadian myeloma research with funding of research grants and investigator-initiated clinical trials.

That is why we need your help. We depend on support and generous donations from people like you to provide support to myeloma patients, their families and their caregivers, advocate for access to new treatments, as well as to drive patient-focused research efforts. All donations are greatly appreciated and allow us to continue our vital work.

Ways you can help

Donate

You can make your donation online at www.myeloma.ca, over the phone by calling (514) 426-5885 or toll-free at 1-888-798-5771, or by mailing a cheque payable to Myeloma Canada to:

Myeloma Canada
PO Box 326
Kirkland, QC
H9H 0A4

Fundraise

There are other ways you can support Myeloma Canada, such as taking part in the annual Multiple Myeloma March held in cities across Canada, or by fundraising for Myeloma Canada in your local community. When so much about myeloma is beyond the control of the people that it affects and those who care for them, fundraising can be a rewarding and fun way of doing something positive for yourself and for others affected by myeloma.

Contact us at (514) 426-5885 or toll-free at 1-888-798-5771 for more information, or visit www.myeloma.ca.

Myeloma Canada

Mailing Address:

Myeloma Canada
PO Box 326
Kirkland, QC
H9H 0A4

Telephone:

(514) 426-5885
Toll-Free: 1-888-798-5771

E-mail:

info@myeloma.ca

Website:

www.myeloma.ca

International Myeloma Foundation

Mailing Address:

International Myeloma Foundation
12650 Riverside Drive, Suite 206
North Hollywood, CA
91607-3421
USA

InfoLine:

1-800-452-CURE (2873)

Telephone:

(818) 487-7455

E-mail:

TheIMF@myeloma.org

Website:

www.myeloma.org



**MYELOMA
CANADA**
MAKING MYELOMA MATTER

Please note that the information contained in this handbook is not intended to replace the advice of a qualified healthcare professional. Myeloma Canada is not engaged in rendering medical or other professional services.

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