



# Patient Handbook

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A publication of the **International Myeloma Foundation**



**Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.**

**RESEARCH** The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

**EDUCATION** The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT** The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

**Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.**

**Contact us at 818.487.7455 or 800.452.CURE,  
or visit [myeloma.org](http://myeloma.org).**

Improving Lives **Finding the Cure**®

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## The IMF is here to help

The International Myeloma Foundation (IMF) is committed to providing information and support for myeloma patients and caregivers, and their friends and family members. We achieve this through our website [myeloma.org](http://myeloma.org), our InfoLine, Patient & Family Seminars, Regional Community Workshops, teleconferences, and other programs and services. IMF publications can be accessed online at [publications.myeloma.org](http://publications.myeloma.org) and are available free-of-charge.

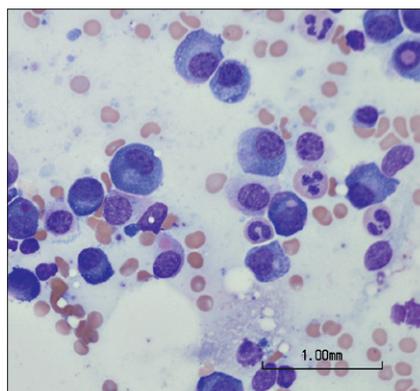
The IMF's *Patient Handbook* is designed to help you to understand **multiple myeloma** (which we refer to simply as "myeloma"). Myeloma is called "multiple" because it frequently involves multiple areas in the body. The *Patient Handbook* focuses on the questions and decisions that a newly diagnosed patient faces. It will help you learn medical terms and concepts you may not have encountered before. Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions*, located at [glossary.myeloma.org](http://glossary.myeloma.org).

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. In order to be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful that discussion will be.

## Myeloma is a highly treatable disease

In the past 15 years, many highly effective "novel agents" have been approved for the treatment of myeloma. Ongoing **clinical trials** are adding more promising therapies to the growing list of treatment options. Many myeloma patients lead full and productive lives for years, even decades, after diagnosis. Survival and quality of life of myeloma patients are improving steadily. Learning about myeloma and understanding how it is

**Figure 1. Myeloma cells as seen in a bone marrow aspirate**



treated can help patients and their loved ones reduce their anxiety, gain a sense of control, and make it easier to come to terms with the diagnosis.

## Why you should see a specialist

Myeloma is a highly individual disease. Often, it is slow-moving. Sometimes, it can be very aggressive. A skilled myeloma specialist (a hematologist-oncologist who specializes in myeloma and other diseases of the plasma cells) can tailor a treatment approach best suited to each patient's individual situation. Myeloma specialists at large "high-volume" treatment centers and large academic institutions see hundreds of patients, conduct clinical trials with new drugs, develop the experience and expertise needed to make appropriate decisions, and can anticipate and prevent treatment-related problems.

If there is no myeloma specialist near you, we encourage you to travel for a scheduled consultation with a specialist. If this is not possible, your local oncologist can schedule a telephone consultation with a myeloma specialist to discuss your case, then work collaboratively with the myeloma specialist in administering your care. A local oncologist may see only a few myeloma patients per year or none at all, which is why it is so important to consult with a myeloma specialist. A large study published in 2016 shows that **overall survival (OS)** rates are higher for patients who are cared for at "high-volume" centers than in smaller medical practices.

## The healthcare team

While hematologist-oncologists plan and administer treatments, your healthcare team will likely also include several of the following important members:

- Primary care physician or family doctor,
- Nurse or nurse practitioner,
- Orthopedic surgeon (bone specialist),
- Pharmacist,
- Nephrologist (kidney specialist),
- Dentist and/or oral surgeon.

Optimal care occurs when the members of your healthcare team and you or your designated caregiver all effectively communicate with each other.

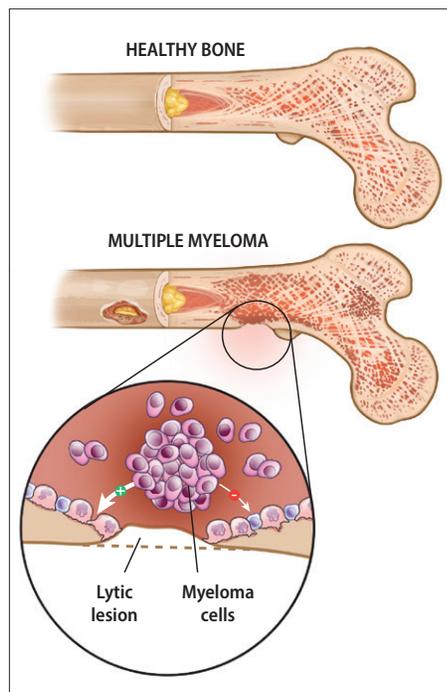
## What is myeloma and where does it grow?

Myeloma is a cancer of **plasma cells**, a type of **white blood cell (WBC)** in the **bone marrow** that is responsible for making **immunoglobulins**. In Greek, the language of most medical terms, "myelo" refers to the blood-producing cells in the bone marrow, and "oma" refers to a tumor or mass of cancer cells. A **malignant** plasma cell is called a myeloma cell.

Myeloma most often grows in the marrow within the bones of the spine, skull, pelvis, rib cage, shoulders, and hips. Usually, the bones of the hands, feet, and lower parts of the arms and legs are not affected, preserving the function of these critical areas.

Myeloma can appear as a **tumor** and/or as an area of bone loss. In either case, this is called a **lesion**. Areas of bone loss caused by myeloma are referred to as **lytic lesions**. The only time that myeloma is not “multiple” is in the rare case of a **solitary plasmacytoma of bone (SPB)**, a single myeloma tumor that may appear either inside or outside the bone marrow.

**Figure 2. Healthy bone compared to myeloma bone**



## Some myeloma statistics

Currently, there are approximately 750,000 people living with myeloma worldwide, with approximately 180,000 in the United States. The American Cancer Society estimates that 30,770 Americans will be diagnosed with myeloma in 2018.

Myeloma is most frequently diagnosed in individuals who are 65 to 74 years old, but it is now also being diagnosed in people younger than 50. Only 5%–10% of myeloma patients are under the age of 40. Myeloma in children has been reported, but it is extremely rare.

Men are more likely than women to develop myeloma. The disease is twice as common in people of African descent. It appears that the incidence of myeloma is increasing in several parts of the world, especially in Asia.

## What are the causes or triggers of myeloma?

Exposure to toxic chemicals, atomic radiation, anything that interferes with or suppresses the **immune system**, or infection with cancer-causing **viruses** have all been implicated as causes or triggers of myeloma.

Toxic chemicals that have been identified include:

- Benzene.
- Dioxins (such as those found in Agent Orange).
- Agricultural chemicals (such as defoliants and pesticides).
- Solvents.
- Fuels.
- Engine exhausts.
- Cleaning materials.
- Several viruses, including HIV (the AIDS virus), hepatitis, and several herpes viruses. Simian virus 40 (SV40), a contaminant in Sabin polio **vaccine** preparations that were used between 1955 and 1963, has also been implicated as a possible trigger for myeloma.

## Is myeloma hereditary?

Approximately 5%–7% of myeloma diagnoses occur in individuals who have a close relative previously diagnosed with myeloma or **monoclonal gammopathy of undetermined significance (MGUS)**. If you have a relative with myeloma or MGUS, tell your primary care physician to include this information in your medical record. If you are a patient with myeloma or MGUS, your relatives should inform their physicians to include your diagnosis in their medical history.

## MGUS, SMM, and active myeloma

The earliest stage of myeloma is not cancer at all, but is a benign condition called MGUS, the presence of a low level of **monoclonal protein (M-protein)** without any indicators of active myeloma. People with MGUS are monitored carefully to make sure the diagnosis is correct and there is no change in their status. As time goes by, if the level of M-protein remains stable and there are no other health changes, the time between visits to the hematologist can be extended. All myeloma patients have MGUS before they progress to active myeloma, but only 20% of people diagnosed with MGUS eventually get myeloma. The risk of progression from MGUS to myeloma is 1% per year.

The stage of myeloma between MGUS and active myeloma is called **smoldering multiple myeloma (SMM)**, which is characterized by a higher level of M-protein than MGUS but with no indicators of active myeloma. The risk of progression to active myeloma among patients with standard-risk SMM is 10% per year for the first five years, 3% per year for the next five years, and 1%–2% per year for the next 10 years. For more information about MGUS and SMM, please read the IMF publication *Understanding MGUS and Smoldering Multiple Myeloma*.

## Plasma cells and myeloma cells

Healthy plasma cells are an important part of the immune system. They produce immunoglobulins, which are complex proteins that we call **antibodies**. Myeloma cells do not make normal, functioning antibodies, but instead produce an abnormal M-protein. The production of M-protein rather than normal immunoglobulins results in reduced ability to fight infection. The presence of myeloma cells within the bone marrow can lead to many other medical problems within and outside the bone marrow microenvironment.

## What are the criteria for diagnosing myeloma?

The most common medical problems caused by myeloma are called the CRAB criteria, defined as:

- An elevated level of **Calcium** in the blood.
- Kidney damage (or in medical terms, **Renal** damage).
- Low blood counts (especially low red blood cell count, or **Anemia**).
- **Bone** damage.

**Table 1. Definitions of MGUS and myeloma**

NAME	DEFINITION
<b>Monoclonal Gammopathy of Undetermined Significance (MGUS)</b>	<ul style="list-style-type: none"> <li>• Monoclonal protein present but usually &lt; 3.0 g/dL</li> <li>• No CRAB features or other indicators of active myeloma</li> <li>• Bone marrow monoclonal plasma cells &lt; 10%</li> </ul>
<b>Smoldering Multiple Myeloma (SMM)</b>	<ul style="list-style-type: none"> <li>• Higher level of disease than MGUS: serum M-component can be &gt; 3.0 g/dL and/or bone marrow plasma cells between 10% and 60%, but</li> <li>• No CRAB features or other indicators of active myeloma</li> </ul>
<b>Myeloma based on MDE</b>	<ul style="list-style-type: none"> <li>• &gt; 60% bone marrow plasma cells</li> <li>• Free light chain ratio &gt; 100</li> <li>• &gt; 1 MRI focal lesion</li> </ul>
<b>Myeloma based on CRAB</b>	<ul style="list-style-type: none"> <li>• Monoclonal protein present, and</li> <li>• One or more CRAB features and/or indicators of organ damage*</li> </ul>

\*Organ damage classified as CRAB or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment

**C** – calcium elevation (> 10 mg/dL)

**R** – renal dysfunction (creatinine > 2 mg/dL or creatinine clearance < 40 ml/min)

**A** – anemia (hemoglobin < 10 g/dL or > 2g/dL decrease from patient’s normal)

**B** – bone disease (one or more osteolytic lesions detected on skeletal radiography, WBLC CT, or PET/CT)

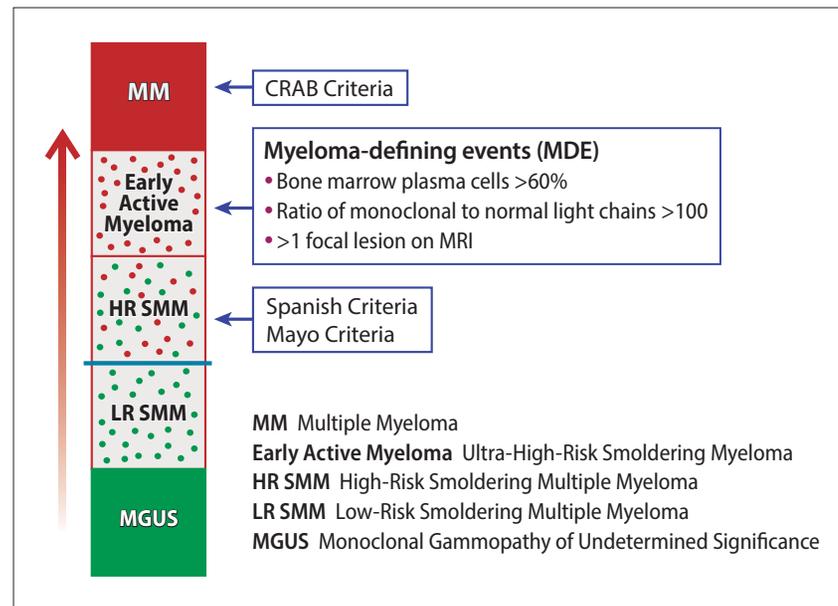
**One or more CRAB features** or other significant problem required for diagnosis of **Symptomatic Myeloma**

For many years, the CRAB criteria were the sole basis for a diagnosis of active myeloma. Without one of these signs that myeloma had already caused what is known as “end-organ damage,” patients were monitored at regular intervals by a physician but not treated. However, within the last few years, more effective treatments for myeloma and better methods of assessing early disease have led to changes in the treatment paradigm.

Members of the IMF’s research arm, the International Myeloma Working Group (IMWG), studied patients with **asymptomatic** SMM to find biological markers that could predict that end-organ damage would occur within 18 months to two years. After this research was completed and published, the IMWG wrote new guidelines for the diagnosis of myeloma to include three new **myeloma-defining events (MDE)** that precede the CRAB criteria. Each of these events independently indicates the need for treatment before the imminent appearance of CRAB criteria:

- Presence of 60% or more plasma cells in the bone marrow.
- A ratio of involved free light chains to uninvolved free light chains of at least 100 (uninvolved light chains are those that are not made by myeloma cells).
- The presence of more than one focal lesion of at least 5 mm in size seen on **magnetic resonance imaging (MRI)**.

**Figure 3. New definitions of myeloma and early myeloma**



These myeloma-defining events can be identified using the results of tests that would be a part of a newly diagnosed patient's myeloma work-up:

- Bone marrow **biopsy**.
- Freelite® test (**serum** free light chain assay).
- MRI scan.

**Table 2. Medical problems related to myeloma**

EFFECTS OF INCREASED MYELOMA CELLS IN BONE MARROW CRAB criteria	CAUSE	IMPACT ON PATIENT
<b>C</b> – Increase in blood <b>Calcium</b>	Release of calcium from damaged bone into bloodstream.	<ul style="list-style-type: none"> <li>• Mental confusion</li> <li>• Dehydration</li> <li>• Constipation</li> <li>• Fatigue</li> <li>• Weakness</li> <li>• Renal or kidney damage</li> </ul>
<b>R</b> – <b>Renal</b> problems – kidney damage	Abnormal monoclonal proteins produced by the myeloma cells are released into the bloodstream and can pass into the urine and produce kidney damage. High blood calcium, infections, and other factors can also cause or increase the severity of kidney damage.	<ul style="list-style-type: none"> <li>• Sluggish circulation</li> <li>• Fatigue</li> <li>• Mental confusion</li> </ul>
<b>A</b> – <b>Anemia</b>	Decrease in number and activity of red blood cell-producing cells in the bone marrow.	<ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Weakness</li> </ul>
<b>B</b> – <b>Bone</b> Damage • Thinning (osteoporosis) or • Areas of more severe damage (called lytic lesions), fracture, or collapse of a vertebra	The myeloma cells activate osteoclast cells, which destroy bone and block osteoblast cells, which normally repair damaged bone.	<ul style="list-style-type: none"> <li>• Bone pain</li> <li>• Fracture or collapse of a bone</li> <li>• Bone swelling</li> <li>• Nerve or spinal cord damage</li> </ul>
<b>Additional types of organ dysfunction</b>	Local or systemic effects of myeloma, other than CRAB features.	<ul style="list-style-type: none"> <li>• Neuropathy</li> <li>• Recurrent infections</li> <li>• Bleeding problems</li> <li>• Other individual problems</li> </ul>
<b>Abnormal immune function</b>	The myeloma cells reduce the number and activity of normal plasma cells capable of producing antibodies against infection.	<ul style="list-style-type: none"> <li>• Susceptibility to infection</li> <li>• Delayed recovery from infection</li> </ul>

## Possible urgent problems at diagnosis

Because the **vertebrae** are often affected by myeloma, and because the spinal cord runs through the vertebrae, painful vertebral fractures that in turn cause nerve compression are not uncommon. Loss of motor nerves can cause paralysis. Myeloma tumors (plasmacytomas) growing in the vertebrae can also press on spinal nerves. Breakdown of calcium from bones can result in **hypercalcemia**, a high level of calcium in the blood. Both hypercalcemia and high levels of M-protein in the blood can seriously affect the kidneys, causing kidney failure.

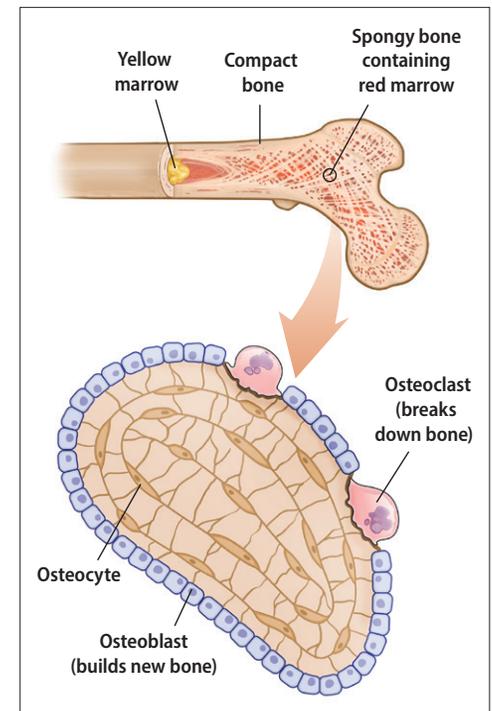
Vertebral compression fractures, damage to the nerves of the spinal cord, infections, and kidney failure are all emergency medical problems that require attention before beginning systemic therapy for myeloma. However, we encourage early consultation with a myeloma specialist to ensure that any treatment of urgent problems leaves all therapeutic options open for the future. For example, radiation therapy to shrink a plasmacytoma that is pressing on nerve tissue must be weighed carefully against a surgical option; radiation may permanently damage the bone marrow and limit choices for later treatment depending on where it is focused and how much is given.

## Myeloma's effects in the bone marrow

Myeloma cells release many proteins and other chemicals into the local bone marrow micro-environment and directly into the bloodstream. All the blood cells – white blood cells, **red blood cells**, and **platelets** – are made in the bone marrow. When myeloma grows in the bone marrow, the effects include a reduction in blood cell production. **Anemia**, a low level of red blood cells, is an early and common sign of myeloma.

Cells in healthy bone marrow maintain our skeletons in a

**Figure 4. Bone-building anatomy**



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dynamic, balanced process of bone breakdown and bone build-up. The presence of myeloma cells in the bone marrow stimulates the cells that break down bone (**osteoclasts**) and suppresses cells that build new bone (**osteoblasts**). This upsets their balance, resulting in bone pain, fractures, and the release of calcium into the blood.

## Myeloma's effects outside the bone marrow

Myeloma's effects outside the bone marrow are largely due to the M-protein produced by myeloma cells. As myeloma cells reproduce and build up in the bone marrow, M-protein that is specific to the type of myeloma is released into the circulating blood. M-protein can cause tissue damage at distant sites. For example, kidney damage is quite common. M-protein can also interfere with blood clotting and/or circulation, potentially causing other organ or tissue damage, such as damage to nerve tissue (**peripheral neuropathy, PN**). Treatment for myeloma controls bone breakdown and tumor growth, as well as the diverse effects caused by myeloma proteins and the **cytokines** they stimulate.

## Types of myeloma

There are different types and subtypes of myeloma, which are based on the type of immunoglobulin protein produced by the myeloma cells. There are five types of normal heavy chain immunoglobulin – G, A, D, E, and M – each of which performs different functions in the body. Each immunoglobulin is made up of two heavy chains bound to two light chains. The two types of light chains are kappa ( $\kappa$ ) and lambda ( $\lambda$ ).

The typing of myeloma is done with the **immunofixation electrophoresis (IFE)** test, which identifies both heavy and light chain protein types. Myeloma cells make protein **monoclonal**, a group of identical cells from a common ancestor cell. Therefore, myeloma cells make only a single type of immunoglobulin protein. Approximately 65% of myeloma patients have immunoglobulin G (**IgG**) myeloma with either kappa or lambda light chains. The next most common type is immunoglobulin A (**IgA**) myeloma, also with either kappa or lambda light chains. **IgD**, **IgE**, and **IgM** myelomas are quite rare.

Approximately one third of myeloma patients produce **free light chains** (separate from heavy chains) in addition to the complete molecule combination of light chains bound to heavy chains. In approximately 15%–20% of patients, the

**Table 3.**  
Subtypes of  
immunoglobulins

IgG kappa	IgG lambda
IgA kappa	IgA lambda
IgD kappa	IgD lambda
IgE kappa	IgE lambda
IgM kappa	IgM lambda

myeloma cells produce only light chains and no heavy chains. This is called light chain or **Bence-Jones myeloma**, named for the English doctor who first detected and identified light chains and published his findings in 1848. Light chain monoclonal proteins are smaller and weigh less than heavy chains, making it possible for them to fit through the tiny capillaries that send blood to the kidneys. The light chains that arrive by blood to the kidneys may build up to the point of blocking the kidney's tubules, causing reduced kidney function.

In rare instances, only in about 1%–2% of patients, the myeloma cells produce very little or no monoclonal protein of any type. This is called **non-secretory myeloma**. However, the Freelite test can detect minute amounts of light chains in the blood of about 70% of these very low-secreting patients. A Mayo Clinic study of 124 patients with non-secretory myeloma published in 2015 found that the survival of patients with non-secretory myeloma appears superior to that of patients with secretory disease.

## Behavior of the different types of myeloma

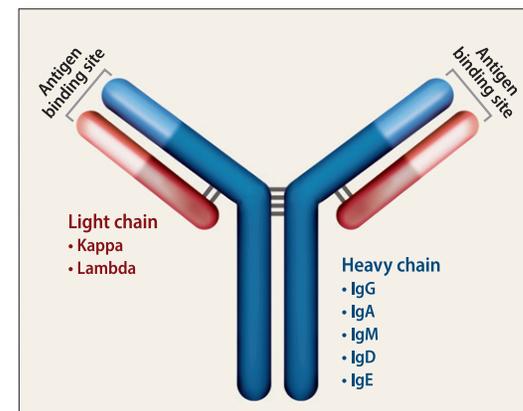
Because it is the most common type of myeloma, the behavior of IgG myeloma conforms to the usual CRAB features.

IgA myeloma can sometimes be characterized by tumors outside of the bone.

IgD myeloma can be accompanied by plasma cell leukemia, which is characterized by high levels of myeloma cells circulating in the blood. IgD myeloma is also known to cause kidney damage.

Light chain myeloma is most likely to cause kidney damage and/or lead to deposits of light chains in the kidneys and/or on nerves or other organs. Depending upon the characteristics of the light chain deposits, this condition is called either **amyloid light-chain amyloidosis (AL amyloidosis)** or light chain deposition disease (LCDD).

**Figure 5. Structure of an immunoglobulin (antibody)**



**Table 4. Types of myeloma and related diseases**

DISEASE TYPE	DESCRIPTION
<b>Myeloma:</b> IgG κ or λ IgA κ or λ <b>Rarer subtypes:</b> IgD, E, or M	<ul style="list-style-type: none"> <li>• <b>Typical myeloma:</b> majority of patients.</li> <li>• Monitored by tracking monoclonal protein in serum using SPEP (IgG) and/or quantitative immunoglobulin (QIG) measurement (IgA/D/E). For IgA myeloma, quantitative immunoglobulin measurement is often more reliable.</li> </ul>
<b>Light Chain only or Bence Jones (BJ) myeloma:</b> κ or λ types	<ul style="list-style-type: none"> <li>• <b>Bence Jones myeloma:</b> approximately 15%–20% of patients.</li> <li>• Monitored by tracking monoclonal light chains in the urine using UPEP and/or with serum free light chain measurements (Freelite®) in the serum.</li> </ul>
<b>Non-secretory myeloma:</b> κ or λ types	<ul style="list-style-type: none"> <li>• <b>Less common myeloma:</b> 1%–2% of patients.</li> <li>• Since both SPEP and UPEP are negative (no monoclonal spike in serum or urine), disease is monitored using Freelite® testing.</li> </ul>
<b>IgM myeloma:</b> κ or λ subtypes	<ul style="list-style-type: none"> <li>• <b>IgM myeloma</b> is a very rare subtype.</li> <li>• Typically, IgM production occurs in a disease called Waldenström’s macroglobulinemia, which is more like a lymphoma (lymph node cancer) versus myeloma, which is a bone marrow cancer.</li> </ul>
<b>Amyloidosis:</b> AL or immunoglobulin light chain type κ or λ subtypes	<ul style="list-style-type: none"> <li>• <b>In amyloidosis</b>, the light chains are deposited in a linear fashion (β-pleated) in tissues rather than being broken down and/or excreted in the urine.</li> <li>• There are many varieties of amyloidosis involving deposits of different types of protein. For example, Alzheimer’s disease involves deposits of proteins in the brain.</li> <li>• <b>In myeloma-related amyloid</b> light chains can be deposited in many tissues, including skin, tongue, heart, kidneys, nerves, lungs, liver, and intestines.</li> <li>• Tissues stain positive with a “congo red” dye test, which is diagnostic. More detailed testing with mass spectroscopy and/or electron microscopy may be appropriate and necessary.</li> </ul>
<b>Light Chain Deposition Disease (LCDD):</b> κ or λ subtypes	<ul style="list-style-type: none"> <li>• <b>In LCDD</b>, the light chains are deposited in a more disorganized fashion (random cross links).</li> <li>• Tissues stain positively with direct κ or λ immunostaining. Congo red staining is usually negative.</li> <li>• There are different patterns of tissue deposits often involving the kidneys, the lining of the lungs (pleura) or peritoneum (around intestines) or within the eyes.</li> </ul>
<b>POEMS syndrome:</b> Usually IgG or IgA λ (rarely κ subtype)	<ul style="list-style-type: none"> <li>• <b>POEMS syndrome</b> is a complex disorder involving polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Diagnosed and treated differently from myeloma. See text for discussion.</li> </ul>

Two other related diseases of the plasma cells are **Waldenström’s macroglobulinemia (WM)**, which is associated with IgM monoclonal protein, and POEMS syndrome, a rare disease associated with neuropathy, enlarged organs, endocrine disorders, monoclonal protein, and skin changes.

## It’s important to know your myeloma type

Knowing your type of myeloma will help you to understand and follow your test results over the course of your treatment. The Freelite assay mentioned above, along with serum protein electrophoresis (SPEP), are tests used to monitor the levels of light chain and heavy chain monoclonal protein produced by your myeloma cells. Measuring the output of myeloma cells is an indirect but effective way to assess the amount and activity of the cancer. The only way to observe myeloma cells directly is through bone marrow biopsy.

Tests to monitor your level of monoclonal protein, and many other tests as well, will be performed regularly to assess your response to treatment and keep track of your status during periods of remission. We strongly advise you to keep an ongoing record of your test results and to familiarize yourself with tests used in myeloma by reading the IMF’s publication *Understanding Your Test Results*.

## Staging of myeloma

When myeloma is diagnosed, the stage of the disease varies from patient to patient. The most commonly used clinical staging system, the Durie-Salmon Staging System, demonstrates the correlation between the amount of myeloma and the damage it has caused, such as bone disease or anemia.

The “measured myeloma cell mass” for the Durie-Salmon Staging System was calculated from studies in which the amount of myeloma protein per myeloma cell was measured. Studies of body metabolism of monoclonal protein were also conducted, which allowed calculation of the exact number of myeloma cells in the body. This led to the understanding that for some patients who produce a lot of protein, the number of myeloma cells can be quite low. Conversely, in patients with low protein production, the number of myeloma cells can be high.

Staging of myeloma can also be done according to prognosis or expected survival. The most commonly-used staging system for myeloma that is based on prognostic factors is the International Staging System (ISS).

The ISS is the result of the collaboration of more than 20 research institutions worldwide. Analysis of their joint data identified which of

**Table 5. The Durie-Salmon Staging System**

STAGE	CRITERIA	MEASURED MYELOMA CELL MASS (myeloma cells in whole body)
<b>STAGE I</b> (low cell mass)	All of the following: <ul style="list-style-type: none"> <li>• Hemoglobin value &gt; 10 g/dL</li> <li>• Serum calcium value normal or &lt; 10.5 mg/dL</li> <li>• Bone X-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only</li> <li>• Low M-component production rates IgG value &lt; 5 g/dL; IgA value &lt; 3 g/dL</li> <li>• Urine light chain M-component on electrophoresis &lt; 4 g/24h</li> </ul>	600 billion/m <sup>2</sup>
<b>STAGE II</b> (intermediate cell mass)	Fitting neither Stage I nor Stage III	600 to 1,200 billion/m <sup>2</sup>
<b>STAGE III</b> (high cell mass)	One or more of the following: <ul style="list-style-type: none"> <li>• Hemoglobin value &lt; 8.5 g/dL</li> <li>• Serum calcium value &gt; 12 mg/dL</li> <li>• Advanced lytic bone lesions (scale 3)</li> <li>• High M-component production rates IgG value &gt; 7 g/dL; IgA value &gt; 5 g/dL</li> <li>• Urine light chain M-component &gt; 12 g/24h</li> </ul>	> 1,200 billion/m <sup>2</sup>
<b>SUBCLASSIFICATION</b> (either A or B)	<ul style="list-style-type: none"> <li>• A: relatively normal renal function (serum creatinine value) &lt; 2.0 mg/dL</li> <li>• B: abnormal renal function (serum creatinine value) &gt; 2.0 mg/dL</li> </ul> <i>Examples:</i> <ul style="list-style-type: none"> <li>• Stage IA (low cell mass with normal renal function);</li> <li>• Stage IIIB (high cell mass with abnormal renal function)</li> </ul>	

**Table 6. Prognostic factors**

TEST	SIGNIFICANCE
Serum $\beta 2$ microglobulin (S $\beta 2M$ )	The <b>higher</b> the level, the more advanced the stage.
Serum Albumin (S ALB)	The <b>lower</b> the level, the more advanced the stage.
C-reactive protein (CRP)	Increased with active disease.
Serum lactate dehydrogenase (LDH)	Increased with active disease.
Abnormal chromosomes on bone marrow cytogenetics and Fluorescence In Situ Hybridization (FISH)	Several chromosome deletions or translocations are considered high-risk; can be associated with shorter duration of remission.

**Table 7. International Staging System (ISS) for myeloma**

STAGE	VALUES ( $\beta 2M$ = Serum $\beta 2$ microglobulin; ALB = Serum albumin)
<b>STAGE 1</b>	$\beta 2M < 3.5$ mg/L; ALB $\geq 3.5$ g/dL
<b>STAGE 2</b>	$\beta 2M < 3.5$ mg/L; ALB < 3.5 g/dL; or $\beta 2M 3.5 - 5.5$ mg/L
<b>STAGE 3</b>	$\beta 2M > 5.5$ mg/L

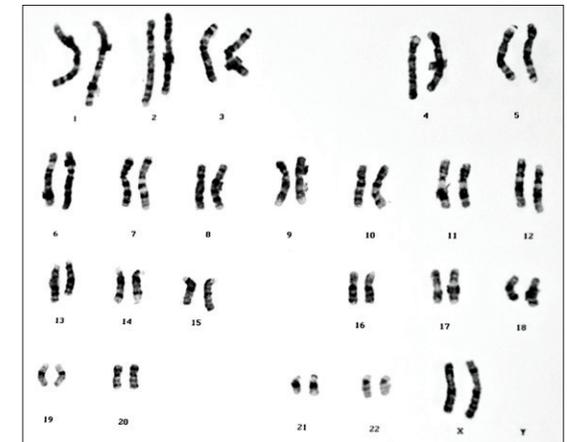
the many tests used to assess disease behavior were most predictive of aggressive myeloma. The ISS is based on four highly predictive markers of aggressive disease, all of which are blood-borne proteins: serum **beta 2 microglobulin (S  $\beta 2M$ )**, serum **albumin (S ALB)**, **C-reactive protein (CRP)**, and serum **lactate dehydrogenase (LDH)**.

Inexpensive laboratory tests can be used to assess these markers of aggressive myeloma. In general, abnormal test results indicate more active myeloma and possibly, less likelihood of having a long response to treatment.

## Genetic studies of disease risk

In addition to the four predictive markers used in ISS, standard bone marrow cytogenetics (karyotyping) and **fluorescence in situ hybridization (FISH)** are studies that also assess disease risk. These two chromosomal studies are performed on bone marrow aspirate samples. We strongly recommend that these chromosomal studies be done on bone marrow samples taken at the time of diagnosis.

**Figure 6. Karyotype analysis of human chromosomes**



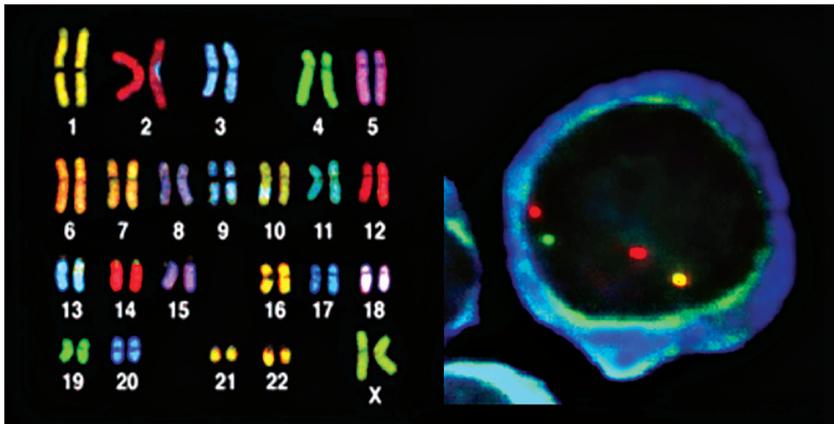
## Cytogenetics

Cytogenetics is the laboratory assessment of chromosomes in dividing myeloma cells. Since the active growth rate of myeloma cells is usually very low (fewer than 3%, and often fewer than 1%, of the cells are proliferating), this provides an incomplete assessment of any chromosomal changes present. Nonetheless, if abnormalities are noted, they are important because they appear on the few cells that are actually growing.

## Fluorescence in situ hybridization (FISH)

FISH is the assessment of the chromosomes of all myeloma cells in a bone marrow sample. FISH allows detection of changes whether myeloma cells are growing or not. Special gene probes that fluoresce (glow) are added to the bone marrow sample. These probes track genetic material after cell division and signal the presence or absence of chromosomal abnormalities that are known to occur in myeloma. Each chromosome

**Figure 7. Fluorescence in situ hybridization (FISH) of a myeloma cell**



is given probes of a different color. If, for example, genetic material from chromosome 4 is wrongly connected to chromosome 14, then the differently colored dots of genetic material from these chromosomes appear together, indicating the high-risk abnormality t(4;14), which is shorthand for “translocation of genetic material between chromosomes 4 and 14.” Other abnormalities that are considered high-risk are t(14;16), t(14;20), 17p-, which stands for “loss of the short arm (upper part) of chromosome 17,” and 1q+, which stands for “an additional long arm (lower part) of chromosome 1.” The presence of translocations, missing pieces, extra pieces, and loss of chromosomes can all be detected by FISH testing.

The presence of abnormal chromosomes generally suggests poor prognosis, but this is a trend and not a guaranteed outcome. For example, approximately one third of patients with any of the so-called high-risk abnormalities can do well and have normal outcomes with standard, current approaches to treatment, including **induction therapy** followed by autologous stem cell **transplant**. Prompt and effective treatment is essential for any myeloma patient, especially for those with features of high-risk disease.

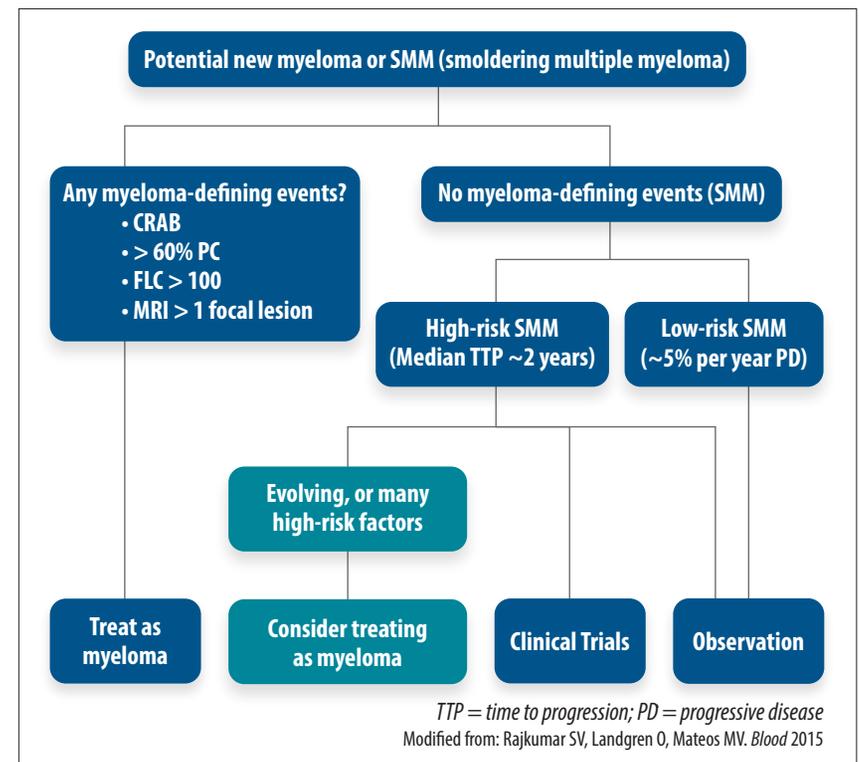
## Treatment for newly diagnosed myeloma

Whether or not treatment is necessary is the most important initial decision. Baseline testing, staging, and prognostic classification are essential. Treatment is recommended for active, symptomatic myeloma and for smoldering, asymptomatic myeloma with myeloma-defining events. The urgency of treatment depends upon the exact problems faced by an individual patient. This is why the experience and expertise of a myeloma specialist is of such importance.

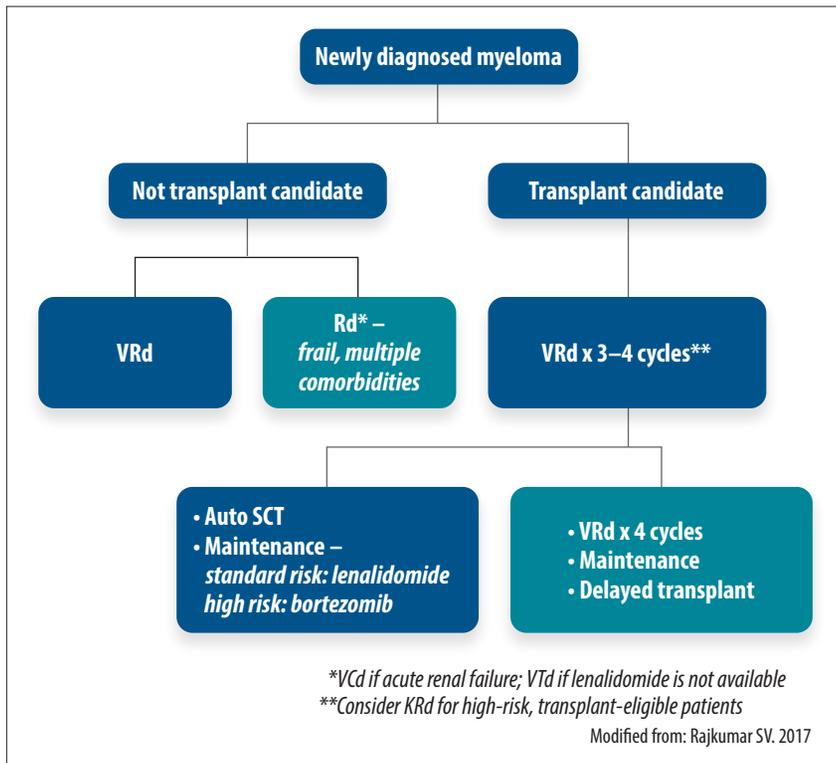
Many studies have demonstrated the superiority of three-drug combination therapies over two-drug combinations for fit, newly-diagnosed myeloma patients. In the United States, the most commonly-used induction therapy for fit, transplant-eligible patients is the combination of Velcade® (bortezomib) + Revlimid® (lenalidomide) + low-dose dexamethasone (VRd). The National Comprehensive Cancer Network (NCCN) designated preferred treatment regimens for myeloma in March 2018. These include VRd as the preferred treatment for first therapy regardless of whether the patient is eligible for autologous stem cell transplant (ASCT) or not. Other recommended therapies include:

- Velcade + cyclophosphamide + dexamethasone (VCD or CyBORd)
- Revlimid + dexamethasone (Rd)
- Velcade + doxorubicin + dexamethasone (PAD)
- Kyprolis (carfilzomib) + Revlimid + dexamethasone (KRd)
- Ninlaro (ixazomib) + Revlimid + dexamethasone (IRd).

**Figure 8. When should treatment be started?**



**Figure 9. Initial treatment of myeloma**



After maximum response to induction therapy has been achieved, your physician may recommend a maintenance regimen. The benefit of continuous therapy until disease progression has been amply demonstrated to improve survival, but it is not necessary or appropriate for every patient. The financial, physical, and emotional implications of continuous therapy must be taken into consideration along with the characteristics of each patient’s myeloma.

The IMF’s *Understanding* series of booklets includes information about the individual drugs used to treat myeloma. (<https://www.myeloma.org/imf-publications/understanding-series>)

In addition to baseline test results, one must consider several important issues when selecting a treatment regimen:

- **Day-to-day functioning:** Will treatment affect the ability to perform daily activities?
- **Work:** Will any changes or interruptions be required?
- **Age:** Is this a factor in treatment selection and expected outcomes?

- **Treatment side effects:** How significant will these be?
- **Other medical issues:** Will they affect treatment choices and tolerance of treatment?
- **Transplant:** Is high-dose chemotherapy with transplant of blood-making stem cells recommended?
- **Speed of response:** How rapidly will the treatment work? How will that be assessed?
- **Initial and later decisions:** How much needs to be decided right away?
- **Financial considerations:** Which part of my treatment will be covered by my insurer, and what will my financial responsibility be? Are there resources to help me pay for my treatment?

**Key point:** *If one treatment does not work, this does not mean that another treatment cannot work extremely well and provide an excellent remission.*

If a particular induction therapy is not working, there are numerous treatment options available beyond the scope of this introductory handbook. **However, it is not advisable to rapidly skip from one treatment regimen to another without exhausting available options.**

## Stem cell transplant

It’s best to keep the door open for stem cell transplantation if you and your doctor feel it can be an option for you. The current consensus of the IMWG is that all transplant-eligible patients should store stem cells for possible future need. In general, patients who are younger than 65 years (and have no other medical conditions that would put them at risk) and older patients whose doctors believe they are physiologically fit are considered candidates for stem cell transplant. Although definitive clinical trial results with overall survival data are not yet available, studies indicate that deeper responses and longer duration of remission – known as **progression-free survival (PFS)** – occur among patients who have autologous stem cell transplant as a planned part of their initial therapy for myeloma.

In the United States, Medicare insurance will cover a single autologous stem cell transplant for eligible patients of any age if they have Durie-Salmon stage II or III myeloma. Their myeloma must be either newly diagnosed or must still be responsive to treatment, and they must have adequate heart, liver, lung, and kidney function. Medicare will not cover “tandem” (two back-to-back) autologous transplants.

If a patient has a transplant that is covered by Medicare and then relapses after a remission of two years or longer, Medicare may cover another transplant at that time. Eligibility for stem cell transplant must

be evaluated on an individual basis, taking into account health status, other illnesses, and treatment history. Many older patients are in excellent physical health and would be considered fit and transplant-eligible.

## Clinical trials

Clinical trials for induction therapy are available. A clinical trial can be an excellent way to receive a new combination therapy or new treatment that would not otherwise be available. Even in a randomized trial, where patients have an equal chance of receiving the standard of care or a

**Table 8. Baseline testing**

TEST	PURPOSE
<b>Bone Marrow Biopsy</b> Testing to assess prognosis (e.g., chromosomes, immune typing, staining for amyloid)	This is the single most critical test to determine both the presence and the percentage of myeloma cells in the bone marrow. In Stage I disease or for a solitary plasmacytoma, direct biopsy of the tumor mass may be necessary. Chromosome analysis (cytogenetic testing) can reveal good or poor chromosomal features using direct (Giemsa stained for banding) and/or FISH analysis. A fresh sample is needed for this type of testing.
<b>Blood Testing</b> Complete blood count (CBC)	To assess presence/severity of anemia (low hemoglobin), to assess for low white cell count, and to assess for low blood platelet count.
Chemistry panel	Used to assess kidney function (creatinine and BUN), liver functions, albumin, calcium level, and LDH.
Special protein testing	This shows the presence of the monoclonal myeloma protein “spike.”
Serum protein electrophoresis (SPEP)	The amount of the abnormal myeloma heavy chain protein.
Immunofixation electrophoresis (IFE)	Shows the heavy chain (G, A, D, E, and M) and light chain (kappa [κ], lambda [λ]) types of the myeloma protein.
Freelite® assay	Can be used to measure the amount of free kappa or lambda light chains if no SPEP or UPEP abnormality discovered.
Hevlyte® assay	Can be used to measure normal and abnormal levels of intact immunoglobulins.
<b>Urine Testing</b> Special protein testing similar to serum above: • Urine Protein Electrophoresis (UPEP) • Immunofixation	Shows the presence, amount, and type of abnormal myeloma protein in urine.

(Table 8 continues on next page)

**Table 8. Baseline testing** (continued from previous page)

TEST	PURPOSE
<b>Bone Testing</b>	To assess the presence, severity, and location of any areas of bone damage:
<b>X-Rays</b>	X-rays are still used in searching for myeloma bone damage. In a majority of patients, X-rays show characteristic myeloma bone disease (lytic lesions or “holes” in the bones). However, X-rays can be negative in approximately 25% of patients with active myeloma and further imaging with whole-body MRI, whole-body low-dose CT, or PET/CT is needed to rule out possible bone involvement. A full skeletal survey for myeloma using a series of X-rays is needed to show loss or thinning of bone (osteoporosis or osteopenia caused by myeloma bone destruction), lytic lesions, and/or any fracture or collapse of bone.
<b>MRI</b> (Magnetic Resonance Imaging)	Used when X-rays are negative and/or for more detailed testing of particular areas such as spine and/or brain. Can reveal the presence and distribution of disease in the bone marrow when X-rays show no bone damage. Can also reveal disease outside of bone, which may be pressing on nerves and/or the spinal cord.
<b>CT Scan</b> (Computed Tomography)	Used when X-rays are negative and/or for more detailed testing of particular areas. Especially useful for detailed evaluation of small areas of possible bone damage or nerve pressure.
<b>Nuclear Medicine Scans</b>	Routine bone scans used for other cancers. Not useful in myeloma and should not be performed <i>unless ruling out other diagnoses</i> .
<b>FDG/PET Scan or PET/CT Scanning</b>	A much more sensitive whole body scanning technique. Useful for disease monitoring, especially for non-secretory disease. CT used to assess sites of PET-positive disease.
<b>Bone Density Testing</b>	Helpful to assess the severity of diffuse bone loss in myeloma and to measure the serial improvement with bisphosphonate therapy.

new therapy, a trial provides rigorously documented treatment and monitoring. If you choose to participate in a clinical trial, it is vital for you to understand the full scope of the treatment trial protocol. For a comprehensive discussion of clinical trials, read the IMF publication *Understanding Clinical Trials*.

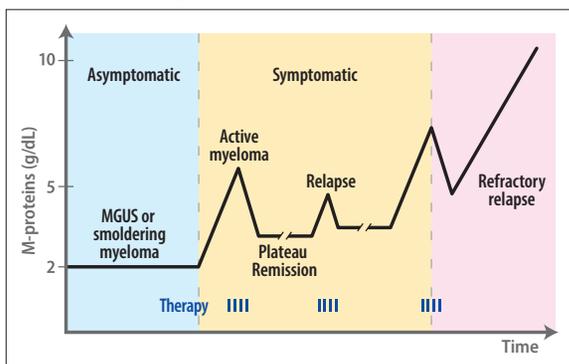
## Supportive care

Treatments are available to alleviate the physical and emotional impact of myeloma. Early use of supportive care measures is just as important as initiating induction therapy. Beyond the management of specific

symptoms, such as bone disease (see the IMF publication *Understanding Treatment of Myeloma Bone Disease*), a range of other supportive measures is critically important:

- **Physical activity:** Check with your physicians to clarify if full physical activity is feasible or if adjustments must be made due to bone disease or particular areas of bone damage. Usually, some physical activity can be planned, such as walking or swimming, flexibility and strengthening exercises, and/or a personalized yoga program.
- **Diet:** No specific diet has been developed for myeloma patients, although research has clearly demonstrated the link between obesity and myeloma. We recommend a healthy, Mediterranean diet emphasizing fruits, vegetables, fish, other lean animal proteins, whole grains, and unprocessed “real” foods. Avoid foods that include processed sugars and artificial trans fats. Caution should be used in two areas:
  - **Herbal and vitamin supplements:** Talk to your physician or pharmacist *BEFORE* taking supplements while receiving treatment for myeloma. Some drug-supplement interactions can prevent myeloma treatments from working effectively and some interactions can create serious medical problems. Pharmacies often have reference resources to help identify potential interactions.
  - **Vitamin C:** Doses greater than 1000 mg per day may be counter-productive in myeloma and can increase the risk of kidney damage.
- **Mental health:** Your mental health is critical as you move forward with planned treatment. Make sure you’re comfortable with the treatment plan. Schedule an appointment with a mental health professional if you believe that you might be depressed, or if others are concerned that you might be depressed. This is a normal response to a cancer diagnosis, and most cancer patients will need some help at one time or another. A myeloma support group can be helpful in this context. Gathering information and support

**Figure 10. Disease phases**



among peers is vital at this time. For a referral to a myeloma support group in your area, call the IMF InfoLine or visit [support.myeloma.org](http://support.myeloma.org) to search for a group near you.

- **Regular sleep:** This is very important for your immune system.
- **Make adjustments:** Reduce or eliminate stress in job, family, or social situations. Avoid close contact with school-age children. Avoid crowds as much as possible. Wash hands frequently. Your immune system is compromised both by the disease and the treatments. Management of the myeloma is the top priority until remission or a stable situation has been reached.

## In closing

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

**Table 9. Goals of myeloma treatment**

TYPE OF TREATMENT	Stabilizing	Palliative
OBJECTIVE	Countering the life-threatening disruptions to body chemistry and the immune system	Relieving discomfort and increasing the patient’s ability to function
EXAMPLES	<ul style="list-style-type: none"> <li>• Plasmapheresis to thin the blood and avoid stroke</li> <li>• Hemodialysis when kidney function is impaired</li> <li>• Drugs to reduce hypercalcemia (may include chemotherapy)</li> </ul>	<ul style="list-style-type: none"> <li>• Radiation to stop bone destruction</li> <li>• Red cell transfusion to relieve anemia</li> <li>• Orthopedic surgery to repair and/or strengthen bone</li> </ul>
TIME TO DECIDE	Hours to Days	Days to Months
TYPE OF TREATMENT	Remission-Inducing	Curative
OBJECTIVE	Improving symptoms, slowing or arresting the course of the disease	Permanent remission*
EXAMPLES	<ul style="list-style-type: none"> <li>• Therapy to kill malignant cells throughout the body</li> <li>• Radiation to kill malignant cells at a tumor site</li> </ul>	<ul style="list-style-type: none"> <li>• Bone marrow transplants as a means of delivering high-dose chemotherapy</li> </ul>
TIME TO DECIDE	Weeks to Months	Weeks to Months

\*Cure means permanent eradication of myeloma, which is rarely documented. The term “functional cure” has been used to describe complete remissions which last for over four years. Complete response (including at the molecular level) can be followed by relapse, so long-term follow-up is required.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit [myeloma.org](http://myeloma.org) for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at [InfoLine@myeloma.org](mailto:InfoLine@myeloma.org) or 818.487.7455 or 800.452.CURE.

**Table 10. May 2018: Drugs in current use for myeloma frontline and relapse treatment**

Alkylating agent	
<b>GENERIC NAME</b>	<b>melphalan</b>   <b>BRAND NAME</b> Alkeran®
<b>INDICATION</b>	<ul style="list-style-type: none"> <li>• For use in palliative treatment of myeloma.</li> <li>• Approved for use throughout disease course.</li> </ul>
<b>ADMINISTRATION: DOSE</b>	<ul style="list-style-type: none"> <li>• IV (intravenous injection): 200 mg/m<sup>2</sup></li> <li>• Oral: 6 mg (3 tablets) daily.</li> </ul>
<b>SIDE EFFECTS</b>	Suppression of blood cell counts, hypersensitivity reactions, gastrointestinal toxicity, pulmonary toxicity, infertility, secondary malignancies (leukemia).
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Used as high-dose therapy in autologous transplant.</li> <li>• Used in combination with prednisone ± third drug for non-transplant patients (MPV, MPR).</li> </ul>
Cyclophosphamide	
<b>GENERIC NAME</b>	<b>cyclophosphamide</b>   <b>BRAND NAME</b> Cytoxan®
<b>INDICATION</b>	For the treatment of myeloma alone or in combination with other agents.
<b>ADMINISTRATION: DOSE</b>	<ul style="list-style-type: none"> <li>• IV: 40–50 mg/kg divided over 2–5 days.</li> <li>• Oral: 300 mg/m<sup>2</sup> once weekly.</li> </ul>
<b>SIDE EFFECTS</b>	Suppression of blood cell counts, infections, urinary tract and renal toxicity, cardiotoxicity, pulmonary toxicity, secondary malignancies, fever, alopecia (IV), nausea, vomiting, diarrhea.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Sometimes used to mobilize stem cells from the marrow to the peripheral blood for harvest prior to ASCT.</li> <li>• Used orally in combination therapies such as CyBorD.</li> <li>• Used IV in combination therapies such as DCEP and DVSPACE.</li> </ul>

(Table 10 continues on next page)

**Table 10. May 2018: Drugs in current use for myeloma frontline and relapse treatment** (continued from previous page)

Anthracycline	
<b>GENERIC NAME</b>	<b>doxorubicin; doxorubicin hydrochloride liposome injection</b> (plus Velcade + dexamethasone)
<b>INDICATION</b>	In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.
<b>ADMINISTRATION: DOSE</b>	<ul style="list-style-type: none"> <li>• IV regular doxorubicin: 9 mg/m<sup>2</sup> days 1–4 of a 28-day cycle; 20 mg/m<sup>2</sup>.</li> <li>• IV doxorubicin liposome injection: 30 mg/m<sup>2</sup> day 1 of a 28-day cycle.</li> </ul>
<b>SIDE EFFECTS</b>	Cardiotoxicity, secondary cancers, decreased blood cell counts, infusion site reactions, change in the color of urine, infection, lower sperm count, early menopause, hair loss, nausea, vomiting, mouth sores, eye problems, allergic reactions, hand-foot syndrome.
<b>REMARKS</b>	Liposomal doxorubicin (Doxil) went off patent. Now there is an FDA-approved generic for Doxil as well as generic doxorubicin.
Corticosteroid	
<b>GENERIC NAME</b>	<b>dexamethasone</b>   <b>BRAND NAME</b> Decadron®
<b>INDICATION</b>	<ul style="list-style-type: none"> <li>• No specific FDA approval for myeloma.</li> <li>• Approved for “palliative management of leukemias and lymphomas.”</li> <li>• Used in almost every regimen for frontline and relapsed myeloma.</li> <li>• Not used in maintenance because of side effects from long-term use.</li> </ul>
<b>ADMINISTRATION: DOSE</b>	<ul style="list-style-type: none"> <li>• Can be given IV</li> <li>• Usually given weekly at 40 mg orally (10 pills) (“low-dose” dexamethasone).</li> <li>• As monotherapy, given orally at 40 mg 4 days on, 4 days off.</li> </ul>
<b>SIDE EFFECTS</b>	Infections, cardiac conditions/fluid retention, acne, rash, elevated blood glucose, GI disorders, weight gain, coughing, hoarseness, osteoporosis, muscle pain, ophthalmologic disorders, psychiatric effects, sleeplessness.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Caution about drug interactions. For details, read IMF publication <i>Understanding Dexamethasone and Other Steroids</i>. Several studies have demonstrated that reducing dexamethasone dose in combination therapy improves tolerance, extending treatment duration and overall survival.</li> <li>• ASH 2015 Karolinska Institute study demonstrated that on achieving at least a partial remission with Revlimid + dexamethasone second-line therapy, continuing with dexamethasone in addition to Revlimid does not add benefit.</li> </ul>

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**Table 10. May 2018: Drugs in current use for myeloma frontline and relapse treatment** (continued from previous page)

Immunomodulatory drug (IMiD)	
<b>GENERIC NAME</b>	<b>thalidomide</b>   BRAND NAME Thalomid (plus dexamethasone) (Celgene)
<b>INDICATION</b>	Approved in combination with dexamethasone for the treatment of newly diagnosed myeloma, but is used throughout the disease course, including for maintenance therapy (without dexamethasone).
<b>ADMIN: DOSE</b>	Oral: approved at 200 mg daily, but is rarely given above 100 mg daily because it is effective at lower doses and higher doses are generally not well tolerated.
<b>SIDE EFFECTS</b>	Embryo-fetal toxicity, venous and arterial thromboembolism, peripheral neuropathy, constipation, drowsiness, dizziness, low white blood cell counts, rash.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients must participate in a risk evaluation and mitigation strategies (REMS) program.</li> <li>• Both partners must use contraception.</li> <li>• Causes irreversible peripheral neuropathy.</li> </ul>
<b>GENERIC NAME</b>	<b>lenalidomide</b>   BRAND NAME Revlimid® (plus dexamethasone) (Celgene)
<b>INDICATION</b>	Approved throughout the disease course, including as maintenance therapy (without dexamethasone).
<b>ADMIN: DOSE</b>	Oral: 25 mg days 1–21 of a 28-day cycle.
<b>SIDE EFFECTS</b>	Embryo-fetal toxicity, low white blood cell counts, low platelet counts, venous and arterial thromboembolism, diarrhea, fatigue, anemia, constipation, rash.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients must participate in a risk evaluation and mitigation strategies (REMS) program.</li> <li>• Both partners must use contraception.</li> <li>• Given in combination with dexamethasone, anti-thrombotic prophylaxis (type determined by risk factors) is recommended.</li> <li>• FIRST trial demonstrated the benefit of continuous Revlimid in newly diagnosed myeloma patients who are not candidates for transplant.</li> </ul>
<b>GENERIC NAME</b>	<b>pomalidomide</b>   BRAND NAME Pomalyst® (plus dexamethasone) (Celgene)
<b>INDICATION</b>	In combination with dexamethasone for the treatment of patients with myeloma who have relapsed after at least 2 prior therapies including Revlimid and a proteasome inhibitor.
<b>ADMIN: DOSE</b>	Oral: 4 mg days 1–21 of a 28-day cycle.
<b>SIDE EFFECTS</b>	Embryo-fetal toxicity, low white blood cell counts, low red blood cell counts, low platelet counts, venous and arterial thromboembolism, fatigue, weakness, dizziness and confusion, constipation, nausea, diarrhea, neuropathy.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients must participate in a risk evaluation and mitigation strategies (REMS) program.</li> <li>• Both partners must use contraception.</li> <li>• Anti-thrombotic prophylaxis (type determined by risk factors) is recommended.</li> </ul>

(Table 10 continues on next page)

**Table 10. May 2018: Drugs in current use for myeloma frontline and relapse treatment** (continued from previous page)

Proteasome inhibitor	
<b>GENERIC NAME</b>	<b>bortezomib</b>   BRAND NAME Velcade® (Takeda)
<b>INDICATION</b>	Approved as treatment for myeloma and as retreatment for patients who had previously responded to treatment and who have relapsed at least 6 months after completing prior Velcade treatment.
<b>ADMIN: DOSE</b>	IV or SQ (subcutaneous) injection at 1.3 mg/m <sup>2</sup> days 1, 4, 8, 11 of every 21-day cycle.
<b>SIDE EFFECTS</b>	Peripheral neuropathy (SQ administration preferred), fatigue, nausea, diarrhea, thrombocytopenia, low blood pressure; more rarely headache, insomnia, fever, back pain, muscle cramps.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• May be given weekly for patients with PN or other ongoing side effect(s) and for frailer patients; dose may also be reduced to 1.0 mg/m<sup>2</sup>.</li> <li>• Anti-viral therapy for prevention of herpes zoster virus (shingles) is recommended.</li> </ul>
<b>GENERIC NAME</b>	<b>carfilzomib</b>   BRAND NAME Kyprolis® (alone or plus Revlimid + dexamethasone) (Amgen)
<b>INDICATION</b>	<ul style="list-style-type: none"> <li>• As a single agent for patients with myeloma who have received at least 2 prior lines of therapy including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days after last therapy</li> <li>• In combination with lenalidomide and dexamethasone for patients with relapsed myeloma who have received 1–3 prior lines of therapy.</li> </ul>
<b>ADMIN: DOSE</b>	IV: 10-minute infusion twice-weekly on 2 consecutive days for 3 weeks out of every 4-week cycle. 20 mg/m <sup>2</sup> cycle 1, days 1 + 2; 27 mg/m <sup>2</sup> cycle 1, days 8, 9, 15, 16 and all future cycles.
<b>SIDE EFFECTS</b>	Fatigue, anemia, thrombocytopenia, shortness of breath, diarrhea, fever, low blood pressure, cardiac failure and other cardiac events, infusion reactions, embryo-fetal toxicity.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients with pre-existing heart conditions may be at greater risk for cardiac complications.</li> <li>• Outperformed Velcade + dexamethasone in relapsed myeloma for PFS, OS (regardless of age, cytogenetics, prior treatment).</li> <li>• Anti-viral therapy for prevention of herpes zoster virus (shingles) is recommended.</li> </ul>
<b>GENERIC NAME</b>	<b>ixazomib</b>   BRAND NAME Ninlaro® (plus Revlimid + dexamethasone) (Takeda)
<b>INDICATION</b>	In combination with Revlimid + dexamethasone for treatment of patients with myeloma who have received at least 1 prior therapy.
<b>ADMIN: DOSE</b>	Oral: 4 mg on days 1, 8, 15 of a 28-day cycle.
<b>SIDE EFFECTS</b>	Thrombocytopenia, neutropenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema (swelling of the feet) rash, liver toxicity, back pain, upper respiratory tract infection.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Dose should be 3 mg for patients with moderate to severe liver or kidney impairment.</li> <li>• Causes embryo-fetal toxicity.</li> <li>• Anti-viral therapy for prevention of herpes zoster virus (shingles) is recommended.</li> </ul>

(Table 10 continues on next page)

**Table 10. May 2018: Drugs in current use for myeloma frontline and relapse treatment** (continued from previous page)

Monoclonal antibody (mAb)	
<b>GENERIC NAME</b>	<b>daratumumab</b>   BRAND NAME Darzalex® (Janssen)
<b>INDICATION</b>	<ul style="list-style-type: none"> <li>• In combination with Rd or Vd for myeloma patients who have had at least 1 prior therapy.</li> <li>• In combination with Pd for patients who have had at least 2 prior therapies including Revlimid and a proteasome inhibitor.</li> <li>• In combination with VMP for newly diagnosed, non-transplant-eligible patients.</li> <li>• As monotherapy for patients have had at least 3 prior therapies including a PI and an IMiD or who are double-refractory to a PI and an IMiD.</li> </ul>
<b>ADMIN: DOSE</b>	IV: 16 mg/kg weekly cycles 1–8, every 2 weeks cycles 9–24, every 4 weeks cycle 25 onward.
<b>SIDE EFFECTS</b>	Infusion reactions, fatigue, nausea, back pain, fever, cough, low blood cell counts.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients must be premedicated prior to infusion to reduce/prevent infusion reactions.</li> <li>• Clinical trial in progress to test new SQ administration.</li> <li>• Anti-viral therapy for prevention of herpes zoster virus (shingles) is recommended.</li> </ul>
<b>GENERIC NAME</b>	<b>elotuzumab</b>   BRAND NAME Empliciti® (plus Revlimid + dexamethasone) (BMS)
<b>INDICATION</b>	In combination with Revlimid + dexamethasone for myeloma patients who have received 1–3 prior therapies.
<b>ADMIN: DOSE</b>	IV: 10 mg/kg cycles 1 + 2 once weekly of a 28-day cycle; thereafter every other week, days 1 and 15, every 28 days.
<b>SIDE EFFECTS</b>	Infusion reactions, low blood counts, infections, fatigue, diarrhea, fever, constipation, muscle spasms, decreased appetite.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Anticoagulation is advised for the combination with Revlimid due to high incidence of deep vein thrombosis and pulmonary embolism.</li> <li>• Patients must be pre-medicated prior to each dose to prevent infusion reactions.</li> </ul>
HDAC Inhibitor (histone deacetylase inhibitor)	
<b>GENERIC NAME</b>	<b>panobinostat</b>   BRAND NAME Farydak® (plus Velcade + dexamethasone) (Novartis)
<b>INDICATION</b>	In combination with bortezomib + dexamethasone for myeloma patients who have received at least 2 prior regimens, including bortezomib and an IMiD.
<b>ADMIN: DOSE</b>	Oral: 20 mg every other day for 3 doses per week (days 1, 3, 5, 8, 10, 12) of weeks 1 + 2 of each 21-day cycle, for 8 cycles.
<b>SIDE EFFECTS</b>	Low blood counts, diarrhea, nausea or vomiting, cardiac toxicity, hemorrhage (due to low platelets), infections, liver toxicity, embryo-fetal toxicity, fatigue.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Patients with a history of recent myocardial infarction or unstable angina should not receive Farydak.</li> <li>• Patients with severe hepatic impairment should not receive Farydak; dose should be lowered for those with mild or moderate impairment.</li> <li>• Reduce dose to 10 mg if given with strong CYP3A inhibitors, including clarithromycin (Biaxin®).</li> </ul>

**Table 11. May 2018: Drugs in current use for supportive care**

Bisphosphonate	
<b>GENERIC NAME</b>	<b>pamidronate</b>   BRAND NAME Aredia®
<b>INDICATION</b>	For the treatment of osteolytic bone metastases in conjunction with standard antineoplastic therapy.
<b>ADMIN: DOSE</b>	IV: 90 mg infused over 2–4 hours once monthly.
<b>SIDE EFFECTS</b>	Renal toxicity, fever, vein irritation, general aches and pains, osteonecrosis of the jaw.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Long-term use (5+ years) can lead to atypical fractures of the femur.</li> <li>• Patients without documented myeloma-related bone disease should not take bisphosphonates.</li> </ul>
<b>GENERIC NAME</b>	<b>zoledronate, zoledronic acid</b>   BRAND NAME Zometa® (Novartis)
<b>INDICATION</b>	For the treatment of myeloma bone disease.
<b>ADMIN: DOSE</b>	IV: 4 mg over no less than 15 min every 3–4 weeks; usually 30–45 min once monthly.
<b>SIDE EFFECTS</b>	Renal toxicity, fever, vein irritation, general aches and pains, osteonecrosis of the jaw.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• Long-term use (5+ years) can lead to atypical fractures of the femur.</li> <li>• Patients without documented myeloma-related bone disease should not take bisphosphonates.</li> <li>• Dose should be reduced for patients with renal impairment.</li> <li>• 500 mg calcium and 400 IU vitamin D should be taken daily.</li> </ul>
Bone-modifying agent	
<b>GENERIC NAME</b>	<b>denosumab</b>   BRAND NAME Xgeva® (Amgen)
<b>INDICATION</b>	For prevention of skeletal-related events.
<b>ADMIN: DOSE</b>	SQ: 120 mg every 4 weeks.
<b>SIDE EFFECTS</b>	Hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, embryo-fetal toxicity, diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, upper respiratory tract infection, rash, headache.
<b>REMARKS</b>	<ul style="list-style-type: none"> <li>• All patients should receive calcium and vitamin D.</li> <li>• Oral exam should be done prior to starting treatment.</li> </ul>
Stem cell mobilizer	
<b>GENERIC NAME</b>	<b>plerixafor</b>   BRAND NAME Mozobil® (Genzyme)
<b>INDICATION</b>	For use in combination with GCSF to mobilize hematopoietic stem cells prior to ASCT
<b>ADMIN: DOSE</b>	IV: at 0.24 mg/kg body weight.
<b>SIDE EFFECTS</b>	Nausea, vomiting, diarrhea, tiredness, headache, dizziness, joint or muscle pain, injection site reaction, low platelets.
<b>REMARKS</b>	May cause embryo-fetal harm.

**Table 12. Supportive care**

SYMPTOM	TREATMENT	COMMENTS
<b>Fatigue and weakness due to anemia</b>	<ul style="list-style-type: none"> <li>Blood transfusion (packed red blood cells: leukoreduced, virus screened) if anemia severe</li> <li>Erythropoietin if anemia mild to moderate and induced by therapy</li> </ul>	The treatments are simple, usually highly beneficial, and improve feelings of well-being.
<b>Bone pain</b>	<ul style="list-style-type: none"> <li>Bisphosphonate (e.g., Aredia® 90 mg IV over 2–4 hrs monthly; Zometa® 4 mg IV over 15–45 min monthly)</li> <li>Pain medication as needed (e.g., acetaminophen, oral morphine derivatives, fentanyl)</li> </ul>	<ul style="list-style-type: none"> <li>Relief of bone pain is important in itself and improves physical activity, which in turn promotes bone strength and healing and improves emotional well-being.</li> <li>Potential damage to kidneys and jaws, though rare, can result from chronic bisphosphonate therapy.</li> <li>Awareness is the key to prevention.</li> </ul>
<b>Fever and/or evidence of infection</b>	<ul style="list-style-type: none"> <li>Appropriate antibiotics</li> <li>Neupogen® if necessary to boost low white blood cell count</li> <li>Intravenous gamma globulin for severe infections</li> <li>Tests as needed to diagnose the exact type of infection should be performed (except for dangerous biopsies/cultures)</li> </ul>	<ul style="list-style-type: none"> <li>Although antibiotics should be selected and used with care, it is extremely important that infections be brought under control promptly.</li> <li>Having an antibiotic on hand for emergency use (especially if traveling) is recommended.</li> </ul>
<b>Gastrointestinal side effects</b>	<ul style="list-style-type: none"> <li>Appropriate medications to treat nausea, vomiting, constipation, or diarrhea</li> <li>Maintain adequate fluid intake and nutrition</li> </ul>	Discuss symptoms with healthcare providers; severe symptoms may require hospitalization.
<b>Blood clots and thromboembolic events</b>	<ul style="list-style-type: none"> <li>Clotting events are medical emergencies; treatment based on event and patient risk factors</li> <li>Aspirin or anti-clotting medications may be prescribed</li> </ul>	Risk may be reduced by exercise, weight loss, and not smoking.
<b>Peripheral neuropathy</b>	<ul style="list-style-type: none"> <li>Pain medications</li> <li>Adjustment of dose, schedule, and/or route of administration</li> <li>Physical therapy, vitamin and other supplements</li> </ul>	<ul style="list-style-type: none"> <li>Discuss symptoms with healthcare providers.</li> <li>Early intervention can prevent permanent damage and allow continued treatment.</li> <li>Do not adjust doses on your own.</li> <li>Do not take supplements without discussing with doctor.</li> </ul>
<b>Steroid side effects</b>	<ul style="list-style-type: none"> <li>Take with food early in the morning</li> <li>Be aware of signs and symptoms of infection, changes in blood sugar</li> <li>Medications to prevent shingles and yeast infections</li> </ul>	<ul style="list-style-type: none"> <li>Report side effects and symptoms to healthcare providers.</li> <li>Do not stop or adjust doses on your own.</li> </ul>

Please visit [myeloma.org](http://myeloma.org) or contact the IMF for patient education sheets on preventing blood clots and thromboembolic events, managing steroid-associated side effects, managing myelosuppression, preventing peripheral neuropathy, and managing gastrointestinal side effects.

## Terms and definitions

**Albumin (ALB):** Simple water-soluble protein found in blood serum. Production of albumin is inhibited by interleukin-6 when myeloma is very active.

**Amyloid light-chain amyloidosis (AL amyloidosis):** A condition in which myeloma light chains cross-link with each other in a beta-pleated fashion and then are deposited in tissues and organs throughout the body, such as the heart, nerves, and kidneys, rather than being excreted by the kidneys. This condition is also known as primary amyloidosis.

**Amyloidosis:** A group of systemic diseases characterized by the deposition of amyloid protein in various organs and/or tissues. One type (AL amyloidosis) is related to multiple myeloma; other types include hereditary amyloidosis, AA amyloidosis, wild-type ATTR amyloidosis, ALECT2 amyloidosis, and AB2M amyloidosis.

**Anemia:** A decrease in hemoglobin, a protein which is contained in red blood cells and carries oxygen to the body’s tissues and organs. Anemia is usually defined as hemoglobin below 10 g/dL, and/or as a decrease of  $\geq 2$  g/dL from the normal level for an individual. Over 13–14 g/dL is considered normal.

**Antibody:** A protein produced by white blood cells called plasma cells in response to an antigen that enters the body. The medical term for antibody is “immunoglobulin.”

**Asymptomatic myeloma:** Myeloma that presents no signs or symptoms of disease; early-stage myeloma. Also called “**Smoldering multiple myeloma (SMM)**.”

**Bence-Jones myeloma:** Myeloma characterized by the presence of Bence-Jones protein, an abnormal protein in urine made up of free kappa or lambda light chains.

**Bence-Jones protein:** A myeloma monoclonal protein. The protein is composed of either free kappa or free lambda light chains. Because of their small size, Bence-Jones light chains can be filtered through the kidneys and pass into the urine. The amount of Bence-Jones protein in the urine 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 in the urine is abnormal. Myeloma protein heavy chains are too large to be filtered through the kidneys.

**Beta-2 microglobulin (also called  $\beta$ 2-microglobulin,  $\beta_2$ M, or  $\beta$ 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  $\beta$ 2M. At the time of relapse,  $\beta$ 2M can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum  $\beta$ 2M levels.

**Bone marrow:** The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up when myeloma is growing.

**C-reactive protein (CRP):** A protein made in the liver that increases in amount when there is inflammation throughout the body.

**Calcium:** A mineral found mainly in the hard part of bone matrix (hydroxyapatite). If produced or released in excess, it can build up in the bloodstream. See “**Hypercalcemia.**”

**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 receives the standard treatment or placebo (no treatment).
- **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 or not.
- **Arm** – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.
- **End point** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.
- **Double blind** – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.
- **Phase I trial** – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I

trial, successive groups (“cohorts”) of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.

- **Phase II trial** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment. In addition, patients must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may be approved based on phase II trial results.
- **Phase III trial** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.
- **Phase IV trial** – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I–III clinical trials.

**Cytokine:** Cytokines are proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (for myeloma, in the bone marrow) and circulate in the bloodstream. Cytokines are normally released in response to infection.

**Extramedullary plasmacytoma:** A tumor made up of monoclonal plasma cells that is found in soft tissue outside of the bone marrow and separate from bone.

**Fluorescence in situ hybridization (FISH):** A procedure that allows researchers to locate the positions of specific DNA sequences on chromosomes.

**Free light chain:** An immunoglobulin (antibody) light chain is the smaller of two units that make up an antibody. There are two types of light chain: kappa and lambda. A light chain may be bound to a heavy chain or it may be unbound, or free. Free light chains circulate in the blood and are small enough to pass into the kidneys, where they may be filtered out into the urine or may stick together and block up the kidney's tubules.

**Frontline therapy:** A general term for the initial treatment used in an effort to achieve response in a newly diagnosed myeloma patient. Also see "**Induction therapy**" and "**Response**."

**Hypercalcemia:** A higher than normal level of calcium in the blood. In myeloma patients, it usually results from bone breakdown with release of calcium from the bone into the bloodstream. This condition can cause a number of symptoms, including loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness, and confusion. See "**Calcium**."

**IgG, IgA:** The two most common types of myeloma. The G and the A refer to the type of heavy chain 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. 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.

**IgD, IgE:** Two types of myeloma that occur less frequently. See "**IgG, IgA**."

**IgM:** Usually associated with Waldenström's macroglobulinemia. In rare cases, IgM can be a type of myeloma.

**Immune system:** The body's defense system from pathogens and foreign substances destroys infected and malignant cells, and removes cellular debris. The immune system includes white blood cells and organs and tissues of the lymphatic system.

**Immunofixation electrophoresis (IFE):** An immunologic test of the serum or urine used to identify proteins. 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 (also

called isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. The non-medical word for immunoglobulin is "antibody."

**Induction therapy:** A specific term used for the initial treatment given to a patient in preparation for an autologous stem cell transplant (ASCT). Also see "**Frontline therapy**" and "**Line of therapy**."

**Lactate dehydrogenase (LDH):** An energy-producing enzyme that is present in almost all of the tissues in the body. LDH levels in the blood-stream rise in response to cell damage. LDH may be used to monitor myeloma activity.

**Lesion:** An area of abnormal tissue; 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.

**Light chain:** An immunoglobulin light chain is the smaller of two units of an antibody (immunoglobulin). The light chains are bound by chemical bonds to the ends of the heavy chains, but we make extra light chains that enter the bloodstream. These are called "free light chains." There are two types of light chains: kappa and lambda.

**Line of therapy:** A term used to calculate the number of therapies a patient has received. Induction therapy + an autologous stem cell transplant (ASCT) is considered a single line of therapy. See "**Induction therapy**."

**Lytic (lysis):** Dissolution or destruction of cells or tissues.

**Lytic lesions:** The damaged area of a bone that shows up as a dark spot on an X-ray when at least 30% 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.

**Malignant:** Cancerous; capable of invading nearby tissue and spreading to other parts of the body.

**Monoclonal:** A clone or duplicate of a single cell. Myeloma cells are derived from a "monoclonal," a single malignant plasma cell in the bone marrow. 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) on the protein electrophoresis test.

**Monoclonal gammopathy of undetermined significance (MGUS):** A category of plasma cell disorder characterized by comparatively low levels of monoclonal protein in the blood and/or urine. Bone marrow plasma cell levels are low (< 10%). Myeloma-related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

**Monoclonal protein (myeloma protein, M-protein, M-spike):**

An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of myeloma patients. A monoclonal spike (M-Spike), the sharp pattern that occurs on protein electrophoresis, is the telltale indicator of M-protein in the blood, a marker for the activity of myeloma cells. See “**Monoclonal.**”

**Myeloma-defining event (MDE):** One of three biologic markers that indicate progression to symptomatic myeloma within 18 months to 2 years. One or more of these markers indicates the need for treatment of asymptomatic (smoldering) myeloma. The MDEs are (1) the presence of 60% or more clonal plasma cells in the bone marrow, (2) more than one focal lesion at least 5 millimeters in size, and (3) a Freelite ratio greater than or equal to 100.

**Non-secretory myeloma:** Approximately 1% of myeloma patients do not have detectable M-protein in the blood (serum) and urine. Some of these patients can be successfully monitored using the serum free light chain assay; others may be monitored with bone marrow biopsy and/or PET/CT scan. Patients with non-secretory myeloma are treated in the same fashion as those with M-protein-secreting disease.

**Osteoblast:** A bone cell associated with production of bone tissue. Osteoblasts produce osteoid, which then becomes mineralized with calcium to form new hard bone.

**Osteoclast:** A cell found at the junction between the bone marrow and the bone. It is responsible for breaking down or remodeling old bone tissue. In myeloma, the osteoclasts are overstimulated, while osteoblast activity is blocked. The combination of accelerated bone resorption and blocked new bone formation results in lytic lesions.

**Overall survival (OS):** The median number of individuals in a group who are alive after a particular duration of time. OS is often used as a measure of treatment efficacy in clinical trials. The lengthening duration of OS in myeloma trials makes it a difficult endpoint to use, leading to the effort to validate minimal residual disease status as a new endpoint.

**Peripheral neuropathy (PN):** Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

**Plasma cells:** Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein,

that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

**Plasmacytoma:** See “**Extramedullary plasmacytoma**” and “**Solitary plasmacytoma of the bone (SPB).**”

**Platelets:** One of the three major types of blood cells, the others being red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.

**Progression-free survival (PFS):** The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to determine how well a new treatment works. Also called PFS. See “**Progressive disease.**”

**Progressive disease:** Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of  $\geq 25\%$  from lowest confirmed response value in the myeloma protein level and/or new evidence of disease.

**Red blood cells (RBC, erythrocytes):** Cells in the blood that contain hemoglobin, deliver oxygen to all parts of the body, and take away carbon dioxide. 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. Myeloma patients can also become anemic because of myeloma cells' effect on the ability of bone marrow to make new red blood cells.

**Response or remission:** Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are interchangeable terms.

- **Stringent complete response (sCR)** – sCR is CR (as defined below) plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- **Complete response (CR)** – For myeloma, CR is negative immunofixation on serum (blood) and urine, and disappearance of any soft tissue plasmacytomas, and  $\leq 5\%$  plasma cells in bone marrow. CR is not the same as a cure.
- **Very good partial response (VGPR)** – VGPR is less than CR. VGPR is serum M-protein 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.

- **Partial response (PR)** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24-hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

**Smoldering multiple myeloma (SMM):** SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

**Solitary plasmacytoma of bone (SPB):** A discreet, single mass of monoclonal plasma cells in a bone. The diagnosis of SPB requires a solitary bone lesion, a biopsy of which shows infiltration by plasma cells; negative imaging results for other bone lesions; absence of clonal plasma cells in a random sample of bone marrow; and no evidence of anemia, hypercalcemia, or renal involvement suggesting systemic myeloma.

**Transplant (transplantation):** here are several different types of transplantation.

- **Peripheral blood stem cell (PBSC) transplant** – Doctors remove healthy blood-making stem cells from a patient’s circulating blood (not from the bone marrow), which are then frozen and stored. The patient receives high-dose chemotherapy to destroy the cancer cells, but healthy blood cells are also destroyed. The frozen stem cells are then defrosted and returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment.
- **Autologous transplant** – A procedure in which stem cells are removed from a patient’s blood and then are given back to the patient following intensive treatment.
- **Bone marrow transplant** – 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 (circulating) blood.
- **Allogeneic (allograft) transplant** – 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. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank. The donor’s immune system cells recognize the recipient’s myeloma cells as foreign, and attack them. Unfortunately, the donated cells also attack other tissues in the recipient’s body, causing graft-versus-host disease (GVHD), which may be fatal.

- **Reduced-intensity conditioning (RIC) allo transplant** – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity “mini-allo” transplant performed within 180 days after a standard autologous transplant.
- **Tandem transplant** – A term used to indicate two autologous transplants done in succession. Tandem transplants are usually planned with 3-month to 6-month intervals between transplants. Tandem transplantation has become less common in the US in the era of effective novel therapies.
- **Matched unrelated donor (MUD) transplant** – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an unacceptably high mortality rate from graft-versus-host disease (GVHD).
- **Syngeneic transplant** – The infusion of bone marrow or stem cells from one identical twin into another.
- **Umbilical cord blood transplant** – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks. Because multiple cords are needed to provide enough stem cells for an adult transplant, the risk of graft-versus-host disease is increased with this type of transplant, making it even riskier for myeloma patients.

**Tumor:** An abnormal mass of tissue that results from excessive cell division. In myeloma, a tumor is referred to as a plasmacytoma.

**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.

**Vertebra:** Any one of the 33 bony segments of the spinal column.

**Virus:** A small living particle that can infect cells and change how the cells function. The disease and the symptoms caused by a viral infection vary based on the type of virus and the type of cells that are infected.

**Waldenström’s macroglobulinemia (WM):** 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 bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, basophils, eosinophils, lymphocytes, and monocytes.

