Understanding Bisphosphonate Therapy
About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH** The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION** The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our 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** Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 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 Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or visit myeloma.org.

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The Understanding series and 10 Steps to Better Care

The IMF’s Understanding series of booklets is designed to acquaint you with treatments and supportive care measures for multiple myeloma (which will be referred to as myeloma for the sake of brevity).

For a general overview of myeloma, the IMF’s Patient Handbook should be your first step, while the IMF’s Concise Review of the Disease and Treatment Options is a more in-depth summary for healthcare professionals and knowledgeable readers outside the medical community. Both publications, as well as the many booklets in the IMF’s Understanding series, are available on the IMF website, myeloma.org, where you will find a wealth of information. You can also order copies of IMF booklets by calling 800-452-CURE (2873) toll-free in the United States and Canada, or 818-487-7455 worldwide, or by emailing theIMF@myeloma.org.

To help you navigate the IMF website, we have organized our information according to the 10 Steps to Better Care®, which takes you from diagnosis (Step 1) through clinical trials and how to find them (Step 10). Information relevant to each step along the way, including guidelines for testing, treating, transplanting, assessing response, managing side effects, monitoring, and treating relapsed disease, is available under the appropriate step on the path to better care.

Words in bold type are explained in the “Terms and definitions” section at the end of this booklet. A more complete compendium of myeloma-related vocabulary, the IMF’s Glossary of Myeloma Terms and Definitions, is located at glossary.myeloma.org.

What you will learn in this booklet

This booklet is devoted to therapy that is given to patients with myeloma bone involvement. Bisphosphonate therapy is not treatment for myeloma, but it does help to prevent skeletal complications of myeloma. Understanding Bisphosphonate Therapy fits into the IMF’s 10 Steps to Better Care schema in:

- Step 4 – Supportive Care

It is vital for you to learn as much as possible about the disease and its treatments so that you are empowered to make good decisions about your care with your doctor.

About myeloma bone disease

Approximately 80% of patients with myeloma develop bone disease. Bone disease can cause the bones to become thinner and weaker (osteoporosis), and it can make holes appear in the bone (lytic lesions). The weakened bone is more likely to break under minor pressure or injury (pathologic fracture). The bones most commonly affected are the axial skeleton (spine, pelvis, ribs, and skull) and the upper ends of the long bones of the arms and legs.

In the healthy skeleton, there is a balance between the breakdown of old bone tissue (performed by cells called osteoclasts) and the building of new bone tissue (formed by osteoblasts). Myeloma cells send signals to osteoclasts, causing them to break down much more bone than is required for normal skeletal health. Myeloma cells also inhibit the formation of osteoblasts, thus preventing the repair of bone loss. In addition to giving rise to bone disease, this process of accelerated bone breakdown releases calcium from the bones into the bloodstream. If this release happens too quickly, a condition called hypercalcemia can occur. Both myeloma bone disease and hypercalcemia can be treated with a group of drugs called bisphosphonates.

What are bisphosphonates?

Bisphosphonates are small inorganic molecules that bind to a substance called hydroxyapatite on the surface of damaged bones. At the sites of bone damage, bisphosphonates inhibit and destroy osteoclasts. Since bone damage is caused by the increased numbers and activity of these osteoclasts, treatment with bisphosphonates reduces bone damage and, when the myeloma is well controlled, allows bone healing to occur.

Bisphosphonates have several beneficial effects, including:
- Preventing further bone damage
- Reducing bone pain and the need for painkillers
- Correcting and preventing hypercalcemia
- Reducing the need for radiotherapy
- Reducing pathologic fractures due to myeloma (i.e., fracture at a site where myeloma has weakened the bone)
- Improving quality of life
- Improving the chances of healing and recovering bone strength.

Are bisphosphonates a type of chemotherapy?

Bisphosphonates are not a type of chemotherapy, nor are they a treatment for myeloma. Several clinical trials have demonstrated that bisphosphonates have no anti-myeloma effect and do not prevent progression of early myeloma.

Bisphosphonates are used to treat several types of bone disease, including osteoporosis and the bone-thinning effects of steroid treatment. Bisphosphonates were first introduced more than 20 years ago as an additive to toothpaste to reduce dental decay.

Bisphosphonates are generally safe and do not have the types of risks or side effects associated with chemotherapy, which is used to directly attack the myeloma.

Who benefits from bisphosphonates?

Bisphosphonates are recommended for all patients with myeloma-related bone disease. The American Society of Clinical Oncology (ASCO) guidelines recommend ongoing use of bisphosphonates for all myeloma patients with documented bone disease who start on systemic treatment for myeloma.
Bisphosphonate therapy was introduced for myeloma in 1995 with US Food and Drug Administration (FDA) approval of Aredia® (also known by the generic drug name pamidronate). Prior to that time, myeloma patients had few options at their disposal other than radiation therapy to control bone pain and reduce the risk of pathologic fractures. Bisphosphonates are particularly helpful for patients being treated with steroids such as prednisone or dexamethasone. Steroids reduce bone mass or density; bisphosphonate use improves this negative effect on bones.

What are the different types of bisphosphonates?

Several bisphosphonates are commercially available, and more potent products have been developed over the years in an effort to achieve better bone healing. Thus far, the various products approved and available have produced “equivalent” major benefits. However, these products are associated with several important differences in:

- Administration (e.g., intravenous versus oral delivery, and the length of intravenous infusion time)
- Potential side effects (e.g., fever, possible kidney toxicity, or bone disease in the jaw).

Pamidronate

Since the FDA approval in 1995, use of pamidronate by monthly intravenous (IV) infusion became the standard of care for myeloma patients. It has become established as a safe, helpful drug for the treatment of myeloma bone disease.

Zoledronic acid

Zometa® (also known by the generic drug names zoledronate or zoledronic acid) was approved by the FDA in 2001 based upon study results comparing it with pamidronate. Zoledronic acid produces more rapid and prolonged reduction in elevated blood calcium than pamidronate when elevated levels are present. However, results evaluating effects on bone disease, known as skeletal-related events (SREs), showed that zoledronic acid and pamidronate affect SREs equivalently. The major difference between zoledronic acid and pamidronate is the infusion time (see next section of this booklet).

Clodronate

Clodronate (Clasteon®, Bonefos*) is approved for use in Canada, Australia, Italy, and other countries. It is taken orally rather than administered intravenously, like pamidronate and zoledronic acid.

How are bisphosphonates given?

Both pamidronate and zoledronic acid are given intravenously on a monthly basis. A 90mg dose of pamidronate is given over 2 to 4 hours by IV infusion, and premedication with one or two 325-mg acetaminophen tablets can be helpful. A 4mg dose of zoledronic acid is given over 15 to 45 minutes by IV infusion, and premedication may also be beneficial.

Toxicities associated with both medications, especially potential renal (kidney) toxicities, are related to dose, duration of infusion, and frequency of infusion. If kidney toxicity is a concern, the infusion time of pamidronate can be increased to 4 hours, and the infusion time of zoledronic acid can be increased from 15 minutes to 30 or 45 minutes.

Occasionally, patients can benefit from oral bisphosphonates, especially patients who are intolerant of intravenous infusion, have nephrotoxicity (kidney disease), and/or are concomitantly using steroids, which can cause bone loss. If a patient experiences difficulty with intravenous bisphosphonates, oral bisphosphonates can be considered.

In the US, oral bisphosphonates Fosamax® (alendronate) and Actonel® (risedronate) are not approved specifically for myeloma by the FDA. Outside the US, myeloma patients can be treated with clodronate if there are problems with intravenous bisphosphonates, however a large randomized trial in the UK demonstrated that zoledronic acid is more effective than clodronate.

What are the possible side effects of bisphosphonates?

Generally, bisphosphonates are tolerated well. The most common side effects are:

Fever

Fever associated with bisphosphonates is typically mild (i.e., 100°F to 101°F), occurring a few hours after the intravenous infusion and lasting for a few hours at most. It typically occurs with the first or second infusion, and less frequently – if at all – thereafter. Fever is usually easily treated or prevented by pretreating with one or two 325-mg acetaminophen tablets. Occasionally patients have severe recurrent fever and cannot tolerate intravenous bisphosphonates. Oral bisphosphonates are an option for such patients (see above).

Vein irritation

Vein irritation (mild phlebitis) can occur at the site of the infusion. It is usually mild, and patients typically recover within 1 to 2 days. Careful infusion is recommended to avoid any leakage of medication around the vein. Also, a short infusion of saline at the end of the bisphosphonate infusion is recommended to clear the pamidronate or zoledronic acid from the area and reduce the chance of phlebitis.

General aches and pains

These effects sometimes occur briefly, along with fever.

Kidney dysfunction

A main concern with bisphosphonate therapy relates to kidney side effects. All bisphosphonates are potential toxins for the kidneys. Since myeloma itself can impact kidney function (through damage caused by myeloma light chain protein and/or by elevated blood calcium), the possibility of kidney-related side effects is of particular concern.

- Aredia has been used widely for over two decades, including the initial trials...
period. The type of kidney toxicity that has emerged is an excess of a serum protein, called albumin, in the urine (known as albuminuria or nephrotic syndrome). This toxicity has occurred predominantly with uses of higher than recommended doses (e.g., 180 mg versus 90 mg) and/or more frequent than recommended dosing schedules (e.g., every 2 weeks versus once per month). This side effect is usually reversible with dose and/or schedule adjustments or, in occasional severe cases, by discontinuing pamidronate. Very rare irreversible damage has occurred. Periodic monitoring (e.g., every 3 to 6 months) of urine protein levels with 24-hour urine collection is recommended to prevent any significant kidney damage.

**Dosing of pamidronate**

In 2010, the Nordic Myeloma Study Group published a randomized, double-blind, phase III clinical trial in Lancet Oncology that compared 30 mg versus the standard dose of 90 mg of pamidronate in patients with newly diagnosed myeloma. Their concern was to find the lowest effective dose of pamidronate, given the toxicities associated with long-term bisphosphonate treatment. The study concluded that “monthly infusion of pamidronate 30 mg should be the recommended dose for prevention of bone disease in patients with multiple myeloma.” If you do require a dose adjustment of pamidronate, you can discuss this option with your oncologist knowing that a large study validated the efficacy of one third of the standard dose.

- Zometa has been used for more than 10 years, including the clinical trial period. The major kidney toxicity-related concern that has emerged with zoledronic acid is an increase in serum creatinine, which is an indication of kidney dysfunction. Reports of both increased creatinine and occasionally more severe kidney damage (acute tubular necrosis) have raised concerns that this much more potent bisphosphonate must be used more cautiously with respect to kidney function. To minimize the potential for kidney-related problems, your doctor should follow several recommendations:
  - Your doctor should be especially cautious with the use of zoledronic acid if there is concern from the outset for kidney dysfunction (i.e., with Bence Jones myeloma, diabetes, long-standing high blood pressure, or in elderly or frail patients). Zoledronic acid should not be used in patients with known kidney deterioration as determined by creatinine level over 3 mg/dL.
  - Your doctor should check your serum creatinine level before each dose of zoledronic acid.
  - If the serum creatinine value has increased by 0.5 mg/dL in a patient with normal renal function at the outset, the doctor should hold the next dose of zoledronic acid until the creatinine value returns to within 10% of baseline.
  - If the serum creatinine value has increased by 1.0 mg/dL in a patient with abnormal renal function at the outset, the doctor should hold the next dose until the value returns to within 10% of baseline.
  - In a patient who has experienced a mild elevation in serum creatinine value that has returned to 10% of baseline, the doctor may consider adjustments to the treatment schedule. Adjustments may include increasing the time of infusion from 15 to 30 minutes or more, using a larger volume of diluting fluids, or delaying the administration of the next dose. The doctor should use his or her judgment to determine which option is the most appropriate for an individual patient.

Your doctor should be aware that certain medications with the potential to affect kidney function may be more likely to do so if they are given at the same time as bisphosphonates. Some examples of these medications are certain antibiotics, thalidomide, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and Celebrex® (celecoxib).

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw (ONJ) is a problem that occurs in 3%-4% of patients with myeloma or other cancers who have been treated with pamidronate or zoledronic acid. This condition is often preceded by inflammation or an infection in the mouth, and produces pain, swelling, and bone damage around the tooth sockets in the jaws. There is bone necrosis or loss of bone which can lead to loose teeth, sharp edges of exposed bone, bone spurs, and the breaking loose of small bone spicules or dead bone. Symptoms may not be obvious at first, or may include pain, swelling, numbness, a “heavy jaw” feeling, or loosening of a tooth.

- Consultation with an oral surgeon or dental oncologist familiar with osteonecrosis is strongly recommended for patients who suspect that they may have ONJ. Management without surgery is recommended as a first step. Minor dental work to reduce sharp edges or remove injured tissue may be required. A protective mouth guard may also be helpful.
- Antibiotic treatment is recommended if there is infection. The type of therapy selected depends upon the type of infection that is documented. Oral rinses can also be used.
- If problems persist and/or if healing is slow, consideration can be given to stopping bisphosphonate therapy for two to four months to facilitate recovery. Although study results are lacking, there are anecdotal reports of benefit with brief interruption of pamidronate or zoledronic acid treatment.
If dental surgery is absolutely required, interruption of bisphosphonate therapy is strongly recommended. Current data indicate very poor healing with continued bisphosphonates in this setting.

Dentures can be worn, but many need adjustment. Placement of dental implants appears to be contraindicated. Use of hyperbaric oxygen does not appear to be helpful.

Careful monitoring and follow-up are required.

Prevention can help patients avoid or reduce the scope of the problem. Inform your dentist about this potential risk for patients who take bisphosphonates; maintain excellent oral hygiene, and make sure that you have regular visits to the dentist. Avoid tooth extraction and/or any elective jaw surgery if at all possible. If there is an opportunity, proceed with careful dental evaluation and any required preventive dental care before starting bisphosphonate therapy.

The incidence of ONJ appears to have decreased dramatically, probably due to increased awareness and proactive dental practice.

**Other side effects**

Other side effects are generally rare. However, reactions occasionally occur and may include rash, upset stomach, blurred vision, headache, and shortness of breath. Severe allergic reactions are very rare, although possible. Two additional concerns have emerged with long-term use of bisphosphonates that bear noting. Rare atypical fractures of the femur (thigh bone) known as subtrochanteric and diaphyseal femur fractures have been seen after five or more years of bisphosphonate treatment. The FDA reviewed the data on the occurrence of these atypical femur fractures and issued a safety announcement in October 2010, which was then added to the Warnings and Precautions section of the labels of all approved bisphosphonate drugs.

**Who should not take bisphosphonates?**

- Patients without documented myeloma-related bone disease should not take bisphosphonates. This means that, in general, patients with monoclonal gammopathy of undetermined significance (MGUS) and asymptomatic myeloma without bone disease do not need or benefit from bisphosphonates. However, this remains an area of ongoing research.

- As noted, bisphosphonates must be used with caution in patients with pre-existing kidney disease or known elevation in serum creatinine, especially >3.0 mg/dL, but also any value above the normal range.

- Patients who have allergic reactions or are intolerant to bisphosphonate treatment should not take bisphosphonates.

- Oral bisphosphonates can cause esophagitis (irritation of the upper digestive tract) and/or other gastrointestinal complaints, which may make them inappropriate for patients with pre-existing esophageal or intestinal problems.

**Can bisphosphonates be combined with other therapies?**

In general, bisphosphonates can be safely combined with most other therapies. Your doctor may decide not to give pamidronate or zoledronic acid on or close to the same day as administration of intravenous chemotherapy. Caution about potential nephrotoxicity has been noted above.

**Will insurance cover the costs of bisphosphonates?**

Since Aredia and Zometa are FDA-approved medications, Medicare and most insurance programs in the US reimburse for their use. Any problems with reimbursement should be brought to the attention of your doctor and/or Novartis, the manufacturer of both brand-name medications. It is important to note that Aredia is off patent and is available as a generic drug in the US and abroad, and Zometa is off patent in several countries and will soon be available as a generic drug in the US.

Since hospitals and clinics set up contracts for one product versus another, it’s important to double-check which agent, from which source, is being administered to you. Some patients may experience a new side effect or be intolerant of the vehicle – the solution into which the active ingredients are added – in a generic medicine they haven’t had before. If this happens to you, be sure to find out what drug you received and which company manufactured it, and report your side effects to your doctor.

**What other approaches to bone care are available?**

**Kyphoplasty** provides a tool that may have an impact on bone care for myeloma patients. This procedure involves the injection of liquid cement using the balloon technique in an attempt to provide acute pain relief and improvement in the structural integrity of collapsed vertebrae or other damaged bones. The results of the CAFE study, a randomized clinical trial of kyphoplasty versus non-surgical intervention concluded that patients randomized to have kyphoplasty had improved pain relief, back function, and quality of life. For more information on this topic, read the IMF’s Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures booklet.

General measures to improve bone health are recommended, including:

- Adequate pain control to allow for movement and exercise.
- Radiation therapy and/or orthopedic surgery to restore structural integrity of bones and recovery of full mobility. Radiation therapy should be used sparingly for acute problems such as spinal cord compression, severe refractory pain, and treatment or prevention of pathologic fracture. Since radiation therapy can impair local bone healing, many doctors prefer to use systemic steroids and/or other anti-myeloma therapies. Orthopedic surgery should be used as necessary.
- Exercise, especially walking and/or swimming, to enhance bone strength, flexibility, and endurance.
Avoidance of risky activities (e.g., bicycling, skiing, skating, climbing ladders), which can increase the likelihood of falls and/or fractures.

Regular re-evaluation and follow-up testing of bones by x-ray/scan/bone density testing to rule out new bone disease and assess the impact of treatment.

Looking forward
Considerable new research is ongoing to investigate myeloma bone disease. Of particular interest is treatment that can improve bone cell function with activation of osteoblasts to promote bone healing. The future looks promising for useful new drug treatments.

Clinical trials are now under way for the following new agents:
- denosumab, a monoclonal antibody to RANK ligand;
- BHQ880, an anti-DKK1 antibody;
- sotatercept, a human fusion protein.

Results of a phase III clinical trial comparing denosumab and zoledronic acid were presented at the 2016 annual meeting of the American Society of Hematology (ASH), demonstrating comparable efficacy (neither inferior nor superior) and similar side effect profiles (including ONJ). Denosumab is not yet FDA-approved for prevention of SREs in patients with myeloma, but it is commercially available for treatment of osteoporosis in postmenopausal women as Prolia®, and for the treatment of patients with solid tumors that have metastasized to bone as Xgeva®.

Questions to ask your doctor
Some questions you may want to ask your doctor about your medication are:
- For how long will I be taking bisphosphonates? The length of treatment depends, in part, on whether you continue to have bone disease and how well you respond to therapy for myeloma. There is no universally accepted standard of care on the duration of bisphosphonate therapy. Some doctors prefer to stop bisphosphonate therapy after one year if the patient is in complete remission with no active bone disease, and others prefer to continue it for two years, and still others continue it indefinitely at a reduced frequency. You must discuss this issue with your doctor and come to a decision that is tailored for you.
- How do I get repeat prescriptions?
- Of which side effects should I be aware?
- Is there anything I need to avoid while taking bisphosphonates?
- May I see a patient information leaflet about my medicine?

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.

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 for up-to-date information about myeloma, and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the best information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org, or 800-452-CURE (2873) or 818-487-7455.

Terms and definitions
**Acute tubular necrosis (ATN)**: The death of tubular epithelial cells that form the renal tubules of the kidneys. ATN is a form of acute renal failure. Kidney function can be recovered when not all tubular cells are affected.

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

**Albuminuria**: The presence of an excess of serum albumin in the urine.

**Asymptomatic myeloma**: Myeloma that presents no signs or symptoms of disease (i.e., anemia, renal failure, hypercalcemia, and lytic lesions). Also called smoldering multiple myeloma (SMM) or early-stage myeloma.

**Axial skeleton**: Spine, pelvis, ribs, and skull. In myeloma, the axial skeleton along with the upper ends of the long bones of the arms and legs are most commonly affected by myeloma.

**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 pass freely 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/24h) 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.

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

**Chemotherapy**: Any drugs used to kill cancer cells. “Combination chemotherapy” uses more than one drug in a cancer treatment regimen.

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

**Esophagitis**: Inflammation of the esophagus, which is the tube that transports food from the mouth to the stomach.

**Generic drug name**: A generic drug name refers to the chemical makeup of a drug rather than to its brand name. A generic name is given to a drug before it is approved and given a brand name. After a drug goes off patent, other manufacturers may make generic versions of the drug. For example: ibuprofen is the generic name for drugs brand-named Advil® and Motrin®.

**Hydroxyapatite**: A compound that helps form bones and gives them rigidity and strength.

**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."

**Kyphoplasty:** The injection of liquid cement into damaged bone using a balloon technique. This procedure may provide acute pain relief and improvement in structural integrity of collapsed vertebrae or other damaged bones.

**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.

**Monoclonal gammopathy of undetermined significance (MGUS):** A category of plasma cell disorder characterized by comparably 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 (M-protein):** An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M-protein indicates that myeloma cells are present in large numbers.

**Multiple myeloma:** A cancer arising from the plasma cells in the bone marrow. The cancerous plasma cells are called myeloma cells.

**Nephrotic syndrome:** A group of diseases characterized by excretion of large amounts of protein (mostly albumin) into the urine. Because of this, patients frequently develop edema.

**Nephrotoxicity:** The quality of being toxic or destructive to kidney cells.

**Nonsteroidal anti-inflammatory drug (NSAID):** A drug used to reduce fever, swelling, pain, and redness.

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

**Osteoclast:** A cell found in bone and bone marrow 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.

**Osteoid:** The protein produced by osteoblasts which becomes mineralized with calcium to form hard bone.

**Osteoporosis:** A progressive bone disease that is characterized by a decrease in bone mass and density, leading to an increased risk of fracture. Diffuse involvement of bones with myeloma produces what looks like osteoporosis on x-ray and bone density measurement.

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

**Phlebitis:** Inflammation of a vein.

**Skeletal-related event (SRE):** Bone damage or fracture.

**Steroid:** A type of hormone. Steroids are A type of hormone. Steroids are related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

**Transplant:** Do you need one?

**Response Assessment:** Is treatment working?

**Consolidation and/or maintenance.**

**Keeping Track of the Myeloma: Monitoring without mystery.**

**Relapse: Do you need a change in treatment?**

**New Trials: How to find them.**

Visit [10steps.myeloma.org](http://10steps.myeloma.org) to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.