Information on Newly Diagnosed Myeloma
ABOUT THE MYELOMA INSTITUTE

The Myeloma Institute at the University of Arkansas for Medical Sciences (UAMS) is a leading center in the world for comprehensive clinical care and research related to multiple myeloma and related diseases.

The Myeloma Institute has treated more than 11,000 patients from every state in the United States and more than 50 countries around the globe.

The Myeloma Institute is committed to accelerating curative therapies for multiple myeloma and related diseases through an integrated program of innovative research and outstanding patient care. Under the leadership of Dr. Gareth Morgan, internationally recognized myeloma researcher and clinician, the Myeloma Institute is revolutionizing personalized approaches to myeloma therapy through the use of genomics and other novel diagnostics, with the goals of better outcomes and cure.

The Myeloma Institute supports patients and caregivers throughout the course of treatment. You can trust that the Myeloma Institute will provide you with all the information you need. To learn more about the Myeloma Institute visit www.myeloma.uams.edu or call 1-888-MYELOMA.
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INTRODUCTION

This Newly Diagnosed Myeloma Guide provides information about the management and treatment of multiple myeloma (myeloma). It is intended to help patients with newly diagnosed myeloma and their families and caregivers better understand the disease. Learning as much as possible about myeloma will help you make informed decisions about treatment with your health care team.

This guide is organized into sections to help you navigate the information as you need it. The glossary at the end will help you understand some of the terminology.

UNDERSTANDING MYELOMA

Myeloma is a cancer of plasma cells in the blood. It develops in the bone marrow, the soft, spongy tissue in the center of large bones where blood cells are produced.

Myeloma cells are abnormal plasma cells.

Plasma cells are white blood cells that are part of the immune system. They produce antibodies, also known as immunoglobulins, to help fight infection. In myeloma, plasma cells become abnormal and transform into cancerous myeloma cells. As they multiply, they crowd out and interfere with production of normal, healthy cells.

Low levels of red blood cells can result in anemia, characterized by weakness and fatigue; low levels of platelets can lead to increased bleeding and bruising; low levels of white blood cells can diminish the body’s ability to fight infections.

Myeloma cells tend to collect in groups scattered throughout the skeleton, typically in the bones of the spine, skull, pelvis, rib cage, shoulders and hips. Therefore, the disease is often referred to as multiple myeloma. An isolated mass of myeloma cells is called a plasmacytoma.

You can read and print patient education materials from our website, www.myeloma.uams.edu
Unlike normal plasma cells, myeloma cells release only one type of antibody, a monoclonal protein known as M protein or paraprotein. When this monoclonal protein is measured in blood and urine it is referred to as an M-spike; it is an indicator of disease activity and response to treatment. Some patients do not produce any monoclonal protein, in which case the presence of disease must be assessed by other methods.

Immunoglobulins, the antibodies produced by plasma cells, are made up of protein chains: 2 long (heavy) chains and 2 short (light) chains. There are 5 distinct types of heavy chains - IgG, IgA, IgM, IgD, and IgE - and 2 distinct types of light chains - kappa and lambda. Myeloma can be classified by the type of light and heavy chains produced, such as IgG kappa, IgG lambda, IgA kappa, or IgA lambda, etc. The most common type of heavy chain produced in myeloma is IgG, followed by IgA and then IgD.

Occasionally, myeloma cells produce only the light chain component of the antibody. This is called “light chain myeloma.” In such cases, the light chains are often excreted into the urine, where they are known as Bence-Jones protein.

Myeloma cells can prevent bone cells from forming new bone. They can also cause bone to break down, resulting in release of calcium into the blood stream. Prevention of new bone formation and breakdown of existing bone cause weak, thin bones characterized by holes known as lytic lesions. Lytic lesions resemble the holes in Swiss cheese. Lytic lesions can cause significant bone pain and increase the risk of fractures. Increased calcium in the blood stream, known as hypercalcemia, can cause nausea, fatigue and confusion.

The rounded “punched out” lesions of myeloma appear as lucent areas in this skull radiograph.
Myeloma is the second most common blood cancer, accounting for approximately 12% of all hematologic cancers and 1.4% of all cancers. About 114,000 new cases globally and 25,000 new cases in the United States are diagnosed each year.

In the United States, the lifetime risk of getting myeloma is 1 in 143, or 0.7%. The risk of myeloma increases as people age. Most people diagnosed are at least 65 years old. The disease is rare in people younger than 35. Men are more likely to develop myeloma than women. It is more common in African Americans than in white Americans.

The risk of developing myeloma is also higher among those with monoclonal gammopathy of undetermined significance (MGUS). MGUS occurs in about 1% of the general population and in about 3% of healthy individuals older than 70 years. MGUS is a benign condition that does not require treatment. However, MGUS progresses to multiple myeloma at a rate of 1% per year.

The causes of myeloma are not known, but the interaction of patients’ inherited genetic and environmental factors is thought to play a role. Researchers at the Myeloma Institute are exploring the biology of myeloma to better understand the impact of genetics and the environment.

Some patients have no obvious symptoms or complications at diagnosis, but blood tests indicate a potential problem.

**Bone pain.** Pain can be a symptom of bone disease that often occurs in myeloma. The pain can be in any bone, but the middle or lower back, rib cage, hips and skull are the most frequently affected areas. The pain is often persistent, dull and aching and is usually made worse by movement.

**Bone fractures.** The bones that most commonly fracture due to myeloma bone disease are the spine and ribs. Breaks can sometimes occur with only minor pressure or injury. Fractures of the bones of the spine (vertebrae) can lead to spinal collapse with associated height loss and, occasionally, spinal cord compression.

**Spinal cord compression.** Spinal cord compression is often recognized by sudden, severe pain in the back or neck. It can radiate through the lower back and into the buttocks or legs. It can spread down the arms and can also cause numbness in the legs, toes or fingers, muscle weakness or loss of bladder or bowel control.

**Fatigue.** Feeling tired all the time is common. Persistent fatigue may be related to the myeloma itself or to one or more of its complications.

**Low blood counts.** Reduced numbers of red blood cells, white blood cells and blood platelets are common.
Anemia results from a reduction in the number of red blood cells. It can cause fatigue, weakness, breathlessness and dizziness.

Leukopenia results from a reduction in the number of white blood cells. It can increase the risk of infection.

Thrombocytopenia results from a reduction in the number of platelets, which help the blood clot. It can cause patients to bruise more easily.

Nerve damage. The abnormal proteins produced by myeloma cells can cause damage to nerves, which can lead to weakness and numbness.

Hypercalcemia. When myeloma causes bone to break down, calcium is released into the bloodstream, causing high levels of calcium in the blood. Hypercalcemia can cause:

- Extreme thirst
- Increased urination
- Dehydration
- Kidney problems
- Severe constipation
- Abdominal pain
- Loss of appetite
- Weakness
- Drowsiness
- Confusion

Kidney problems. The abnormal proteins produced by myeloma cells and hypercalcemia can damage the kidneys. As kidneys begin to fail they lose the ability to dispose of excess salt, fluid, and waste products. This can lead to weakness, shortness of breath, itching and leg swelling.

Infection. Myeloma interferes with the immune system, making patients more susceptible to significant infection, including pneumonia.

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**DIAGNOSING MYELOMA**

Myeloma can be difficult to diagnose because many of the symptoms are not specific only to myeloma. Sometimes myeloma is first indicated by an abnormality found during routine blood work or results of an X-ray for a broken bone.

The Myeloma Institute utilizes a full array of standard diagnostic tools, such as blood profiling, Magnetic Resonance Imaging (MRI), skeletal survey, bone densitometry, Positron Emission Tomography-Computed Tomography (CT/PET), bone marrow biopsy and more.

In addition, we utilize genetic testing at the molecular level to reveal information about gene expression patterns and disease nuances. This helps us predict how myeloma cells are likely to respond to different therapeutic agents and strategies.

**DIAGNOSTIC TESTING UTILIZED AT THE MYELOMA INSTITUTE:**

**Complete Blood Profile** identifies counts of white cells, red cells and platelets and other indicators of blood composition. Blood profile results can indicate the quality of bone marrow, kidney function and liver function.
Protein Electrophoresis measures the amount of M protein in serum and urine. An abnormal amount of M protein is an indicator of the extent of the disease.

Bone Marrow Aspiration and Biopsy are used to estimate the number of myeloma cells, their activity in bone marrow and the degree of damage they have caused. The bone marrow sample is also used for cytogenetic testing and gene expression profiling.

Cytogenetic Testing identifies chromosomal abnormalities in myeloma cells from a patient’s bone marrow sample. Chromosomal abnormality information helps guide treatment choices.

Gene Expression Profiling, utilizing the bone marrow sample, indicates molecular classification of myeloma, which helps define the nuances of a patient’s myeloma and drive treatment decisions.

Gene Mutation Detection, via molecular genetics tests done on a tissue sample from the bone marrow, helps identify the specific myeloma subtype. This information is used to develop precision treatment designed for each individual patient.

Axial Skeletal Survey, including X-rays of the shoulders, backbone, pelvis and skull, is used to identify and evaluate the extent of bone disease caused by the myeloma.

Bone Densitometry indicates status of bone strength and the amount of bone loss, even when no overt symptoms exist. Bone densitometry results provide baseline information that is helpful for future treatment decisions.

Magnetic Resonance Imaging (MRI) is a scan of bone and bone marrow, conducted with computerized measurements of radio waves, that enables a close-up view of the bone marrow. It is more effective than standard X-rays for highlighting the presence of myeloma. MRI can identify the exact location(s) and approximate volume of myeloma cells, and it can indicate whether the myeloma has spread.

Diffusion Weighted Whole Body Imaging (DWIB) MRI is a functional MRI that detects water diffusion through cells. It is used to assess and follow the resolution of bone lesions. The Myeloma Institute is one of the only centers that utilizes DWIB MRI to guide treatment decisions.

Positron Emission Tomography-Computed Tomography (CT/PET) scanning is used to show the presence of active cancer and other abnormalities. The technique combines PET and CT; the images from both devices can be superimposed on each other. This enables alignment of functional imaging, which depicts metabolic activity that can detect cancer cells, with anatomic imaging.

Patients at the Myeloma Institute can view test results online.
# BLOOD AND URINE TESTS

<table>
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<tr>
<th>TEST</th>
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<tr>
<td>Complete blood count (CBC)</td>
<td>Measures the levels of red cells, white cells and platelets in the blood. It is used to determine the extent to which myeloma is inhibiting the production of normal blood cells.</td>
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<tr>
<td>Quantifiable Immunoglobulins</td>
<td>There are several different types of heavy protein chains that make up antibodies in the blood: IgA, IgD, IgE, IgG, and IgM. Each can be quantified and followed to assess response to treatment.</td>
</tr>
<tr>
<td>Serum protein electrophoresis (SPEP)</td>
<td>Blood test that measures all of the proteins in plasma and also identifies an abnormal monoclonal spike. Finding a monoclonal protein in the blood is often the first step in diagnosing myeloma. The SPEP differentiates and quantifies abnormal from normal proteins and is helpful in following disease progression.</td>
</tr>
<tr>
<td>Immunofixation electrophoresis (IFE), or immunoelectrophoresis</td>
<td>Used to determine the exact type of abnormal antibody proteins in the blood, including heavy chain and light chain. IFE is especially helpful if proteins cannot be identified by SPEP.</td>
</tr>
<tr>
<td>Free Light Chain (FLC)</td>
<td>Measures antibody light chains known as kappa or lambda. FLC is most helpful in the rare cases of myeloma in which no monoclonal protein is found by SPEP.</td>
</tr>
<tr>
<td>Beta 2-microglobulin (β2-M) level</td>
<td>A protein produced by myeloma cells. Although this protein itself does not cause problems, high levels can indicate that the disease is advanced.</td>
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<tr>
<td>Chemistry profile</td>
<td>Helps to assess kidney and liver function, bone status and the extent of disease. For example, BUN and creatinine levels are measures of kidney function. Low levels of albumin, a protein found in blood, and high levels of calcium can be signs of more advanced myeloma.</td>
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<tr>
<td>Urinalysis</td>
<td>Used to evaluate kidney function.</td>
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<tr>
<td>Urine protein level (24 hour urine)</td>
<td>Determines the presence and level of light chains, known as Bence-Jones protein.</td>
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<tr>
<td>Urine protein electrophoresis</td>
<td>Determines the presence and levels of certain proteins in the urine, including monoclonal protein and Bence-Jones protein.</td>
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This table outlines some of the tests and procedures used at the Myeloma Institute to confirm a myeloma diagnosis.
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<td>Bone marrow aspirate and biopsy</td>
<td>A needle is inserted into the bone and fluid is removed (aspirated). This fluid is primarily blood, but mixed in are bone marrow particles, which are then put onto glass slides, stained and examined by pathologists to determine the number and percentage of normal and cancerous plasma cells in the bone marrow.</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>A part of the biopsy sample is treated with special antibodies that attach only to specific molecules on the cell surface. The antibodies cause color changes that can be seen under a microscope. This can be helpful in identifying myeloma cells.</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Test performed with a small portion of the bone marrow aspirate to help confirm the percentage of plasma cells in the bone marrow and to identify other abnormalities.</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Evaluates the chromosomes in normal bone marrow cells and myeloma cells. Some myeloma cells may have too many chromosomes, too few chromosomes or other chromosome abnormalities. The cells are evaluated to see if the chromosomes have any changes, such as translocations (part of one chromosome has broken off and attached to another chromosome) or deletions (part or all of a chromosome is missing).</td>
</tr>
<tr>
<td>Fluorescent in situ hybridization (FISH)</td>
<td>Similar to cytogenetic testing, it uses special dyes that attach only to specific parts of chromosomes. In addition to identifying most of the chromosome changes, such as translocations and deletions, FISH can also identify some changes too small to be seen with usual cytogenetic testing.</td>
</tr>
<tr>
<td>Molecular Diagnostics, including Risk Profiling, Molecular Subtyping, Mutational Subtyping</td>
<td>These are tests performed on DNA from the bone marrow sample. They characterize molecular features of myeloma that provide insight about predicted response to treatment and which patients will benefit the most from specific therapies.</td>
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This table outlines some of the tests and procedures used at the Myeloma Institute to confirm a myeloma diagnosis.
# IMAGING TESTS

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<tr>
<td>Axial skeletal survey</td>
<td>X-rays that can detect bone destruction caused by the myeloma cells.</td>
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<tr>
<td>Computed tomography (CT) Scans</td>
<td>Imaging modality that can detect myeloma effects on bone and that has a higher sensitivity than regular x-rays for detecting small lytic lesions. Can also be used to guide a biopsy needle into a tumor (called a CT-guided needle biopsy, a fine needle biopsy sample or a core needle biopsy). A sample is then examined under a microscope.</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI) scans</td>
<td>A very sensitive imaging technique that can identify areas of active myeloma and impending fractures. Whole-body MRI is used to detect focal myeloma in the spine and extra-axial skeleton.</td>
</tr>
<tr>
<td>Diffusion-weighted whole body imaging (DWIB)</td>
<td>A form of MRI imaging that allows the mapping of the diffusion process of molecules, mainly water, in biological tissues. It can quantify changes within tissues and provide information on lesions throughout the entire skeleton.</td>
</tr>
<tr>
<td>Positron emission tomography (PET) scans</td>
<td>A nuclear medical technique using tiny amounts of radioactively-labeled sugar, which identifies plasma cell tumors in bones. It quickly identifies responses and relapses and provides a view of the entire body.</td>
</tr>
<tr>
<td>PET/CT imaging</td>
<td>A reliable technique for assisting with (1) diagnosis of myeloma by identifying optimal sites for biopsy, (2) staging and restaging the cancer, (3) detecting extramedullary disease, and (4) monitoring response to treatment. It is effective for both secretory and non-secretory disease.</td>
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</table>

This table outlines some of the tests and procedures used at the Myeloma Institute to confirm a myeloma diagnosis.
A new patient visit at the Myeloma Institute typically includes multiple days of diagnostic testing followed by an appointment with the physician.

THE IMPORTANCE OF MYELOMA RISK-PROFILING TESTING

Our scientists are continually working to better understand the biology of multiple myeloma through the study of genetic abnormalities. Genomic studies reveal DNA alterations in myeloma cells. Patterns of activity within the cells provide information about why and how such activity causes myeloma.

The Myeloma Institute has developed risk-based tests to characterize molecular features of myeloma. This helps physicians predict response to treatment and which patients will benefit the most from specific therapies. These tests are conducted by analyzing the RNA or DNA from myeloma cells obtained via bone marrow biopsy. Tests are conducted as part of initial diagnosis and are repeated periodically throughout the treatment regimen.

Myeloma can be categorized based on cellular and molecular characteristics. The goal is to design personalized treatments based on the molecular characteristics of each patient’s myeloma cells for optimal outcomes.

CLASSIFICATIONS AND STAGES OF MYELOMA

Myeloma is classified and staged according to the results of diagnostic testing.

Myeloma is classified into three distinct groups:

- Monoclonal gammopathy of undetermined significance (MGUS), a “precursor” condition
- Smoldering myeloma, which is asymptomatic disease
- Active myeloma, which is symptomatic disease

Patients with MGUS do not actually have myeloma, but should be monitored for signs of progression to active disease. Patients with smoldering myeloma are typically monitored and might receive therapy, especially those patients who are at risk for progression to symptomatic myeloma. Active myeloma requires immediate treatment.

Staging myeloma is important for developing an appropriate treatment plan. The International Staging System (ISS) divides myeloma into 3 stages based on the serum beta-2 microglobulin (ß2-M) and serum albumin levels.

- STAGE I: Beta-2 microglobulin is less than 3.5 mg/L and the albumin level is 3.5 g/dL or greater
- STAGE II: Beta-2 microglobulin level is between 3.5 and 5.5 mg/L (with any albumin level) OR Beta-2 microglobulin is less than 3.5 mg/L and albumin is below 3.5 g/dL
- STAGE III: Beta-2 microglobulin is 5.5 mg/L or greater
IDENTIFYING MOLECULAR SUBGROUPS VIA GENE EXPRESSION PROFILING

Gene Expression Profiling (GEP) is used to identify Low-Risk myeloma, which accounts for approximately 85% of patients, and High-Risk myeloma, which accounts for approximately 15% of patients. Cure rates are much higher for Low-Risk than for High-Risk myeloma. Different molecular subgroups of myeloma tend to have different clinical outcomes.

MUTATIONAL CLASSIFICATIONS OF MYELOMA

Understanding the genetic landscape of myeloma is key to treating the disease most effectively. Each patient’s myeloma contains populations of cancer cells with different mutations. Frequent mutations in several key genes, including NRAS, KRAS, BRAF, are known to play an important role in myeloma. Research has shown that many of these telltale mutations are not present in all cancer cells within a tumor; rather, they are often found in only a smaller fraction of the tumor cells, known as a subclonal population.

Many promising therapies target specific genetic mutations. As additional mutations are identified, new targeted treatments can be developed.

Through gene expression profiling (GEP), researchers at the Myeloma Institute have discovered that myeloma is not one disease, but seven different disease subtypes. While being morphologically indistinguishable from case to case, myeloma can be caused by different molecular defects. This discovery helps explain why some patients respond well to current therapies and others do not. The figure above is known as a heatmap. The heatmap represents the expression level of 700 genes in myeloma cells from 351 newly diagnosed myeloma patients. Red means the gene is expressed at high levels and green means the gene is low. Of more than 54,000 gene probes tested, we have identified 700 genes (100 for each subtype) with differential expression. Each disease subtype is characterized by a unique over-expression (red) or under-expression (green) of 100 genes, resulting in the “staircase” appearance of the figure. Genes that are over-expressed in one subtype (for example in CD-1 subtype) are not over-expressed in the other six subtypes. A computer algorithm developed by our researchers uses these gene expression levels to provide a molecular diagnosis of each person’s disease, enabling us to develop individual, disease subtype-specific treatments.
TREATMENT OF MYELOMA – THE ARKANSAS APPROACH

Treatment is aimed at controlling the disease, relieving symptoms and complications, extending and improving the quality of life, and, ultimately, cure.

Each patient’s treatment plan is based on a number of factors, including age, overall health, clinical laboratory and imaging results and prior treatment. The Myeloma Institute also utilizes specialized genetic diagnostic testing to help determine the best treatment regimen for each patient. This individualized approach holds the greatest promise of cure.

Treatment may or may not include stem cell transplantation, combinations of chemotherapy, bone-strengthening drugs and immunotherapy. The Myeloma Institute’s team of specialists is constantly developing new, innovative treatments with maximum effectiveness and minimal side effects that target malignant cells but spare healthy cells. Our goal is to harness the power of biological understanding for the best possible outcome.

By personalizing treatment based on each patient’s genetics and other health and risk factors, we are accelerating targeted treatment strategies tailored for each individual. We work in partnership with each patient to determine an optimal treatment plan.

With a multi-disciplinary team that includes myeloma physicians, pathologists, radiologists and other specialists, the Myeloma Institute ensures that all aspects of a patient’s disease and care needs are fully addressed in a complete, comprehensive fashion.

Initial therapy at the Myeloma Institute is often based on prognostic features that identify low-risk disease or high-risk disease. Therapy using certain drugs and avoiding others is chosen accordingly.

The overarching goal of treatment is to cure myeloma, and in order to do this it is important to bring the myeloma under control using various combinations of anti-myeloma agents to destroy the myeloma cells in the bone marrow. Treatment combinations usually include different types of drugs that work well together, such as chemotherapy drugs, steroids, immunomodulatory drugs and proteasome inhibitors. Additional drugs might be prescribed to help prevent or manage side effects of treatment.

Chemotherapy drugs interfere with the way rapidly dividing cells, such as myeloma cells, work and stop or slow down their growth. Chemotherapy drugs are given over set periods of time known as cycles. Cycles may last from weeks to months. Common chemotherapy drugs used for myeloma include Doxil® (doxorubicin), melphalan, and Cytoxan (cyclophosphamide).

Steroids mimic a naturally occurring hormone produced in the body. They curb myeloma cell growth and help prevent inflammation and associated pain in areas affected by myeloma. The most commonly prescribed steroid for myeloma is dexamethasone.

Immunomodulatory drugs (IMiDs) modify the immune system through mechanisms of action that affect myeloma cell survival. IMiDs used for myeloma include thalidomide, Revlimid® (lenalidomide), and Pomalyst® (pomalidomide).

Many effective drugs introduced over the last several years have changed the face of myeloma therapy.
Proteasome inhibitors block the action of proteasomes in human cells. Proteasomes are involved in the removal, breakdown and recycling of damaged or unwanted proteins. Proteasome inhibitors allow proteins to build up in cancer cells, causing the cells to become toxic and die. Proteasome inhibitors used for myeloma include Velcade® (bortezomib) and Kyprolis® (carfilzomib).

Anti-myeloma antibodies include elotuzumab, which is used in combination with Revlimid® and dexamethasone for relapsed patients, daratumumab, which has shown promise in heavily pretreated patients, and Sylvant ® (siltuximab), which is FDA-approved for Castleman Disease and is being investigated for myeloma.

STEM CELL TRANSPLANTATION

Autologous stem cell transplantation is a process by which a patient’s own blood stem cells are collected and stored prior to treatment with high-dose, intensive chemotherapy, and are then infused back into the patient. High-dose chemotherapy damages the bone marrow, such that it cannot produce blood cells. Infusion of the patient’s blood stem cells promotes recovery of the bone marrow. High-dose chemotherapy followed by stem cell transplantation to “rescue” the bone marrow has been used as a treatment for myeloma for many years. Patients receive induction (also called frontline) therapy with a combination of drugs aimed at bringing the myeloma under control in order to kill as many myeloma cells as possible before collecting stem cells and administering high-dose chemotherapy.

Studies confirm that autologous transplantation effectively increases the number of patients achieving a complete remission. It is often regarded as the most potent therapy against myeloma and improves the odds of achieving complete remission and cure.

Sometimes a second transplant may be appropriate, especially if the first transplant was effective, resulting in many years of disease control. Two transplants administered within a few months of each other are referred to as tandem transplants.

Not all patients are eligible for an autologous stem cell transplant. In such cases, combinations of effective drugs and other treatments are employed.

MAINTENANCE THERAPY

Maintenance therapy, typically with a drug or combination of drugs, is started after successful response to transplantation or other treatment. It is intended to prolong the response and improve survival.

Throughout all phases of pre-transplantation treatment, the transplantation process and post-transplantation therapy, patients are monitored via blood and urine tests, imaging tests and bone marrow biopsies. Results of these tests indicate how well a patient has responded to treatment and can help detect detrimental side effects and disease relapse.

TREATMENT OF HIGH-RISK MYELOMA

The goal in treating high-risk myeloma is to keep chemotherapy actively working on the cancer cells in order to prevent relapse and to control the disease long-term. Current research is focused on better understanding the biology of high-risk

We are accelerating the development of targeted treatment strategies tailored for each patient’s disease.
myeloma in order to determine optimal timing and sequence of therapy that integrates novel agents and transplantation in a patient-tailored-treatment approach for improved outcomes.

**TREATMENT OF LOW RISK MYELOMA**

The goal in treating low-risk myeloma is to maximize response and cure rates. Low-risk myeloma patients typically receive chemotherapy. When appropriate, high-dose chemotherapy with bone marrow rescue via autologous stem cell transplantation is employed. Our ability to identify each patient’s genetic characteristics and other risk factors supports a personalized medicine approach to ensure that each patient receives the most optimal treatment for disease-free survival.

**MANAGEMENT OF OLDER OR FRAIL PATIENTS**

While there is no strict age cut-off for receiving intensive versus less intensive treatment, patients over the age of 70 are more likely to be candidates for non-intensive treatment. Those between the ages 65 and 70 years are carefully assessed for overall health status. In all cases, a complete physical and history and diagnostic test results help determine the most appropriate course of treatment.

**MANAGEMENT OF SIDE EFFECTS**

The drugs used to treat myeloma can cause side-effects. Some patients experience minimal side effects, while others experience more. Most side effects are short-term, can be managed, and usually resolve once treatment is finished.

Common side effects of chemotherapy include nausea, infection, diarrhea, anemia, fatigue, sore mouth and hair loss or thinning.

Common side effects of steroids include insomnia, stomach pain, elevated blood sugar level, increased risk of infection, increased appetite, trembling fingers, mood swings and muscle weakness.

**Common side effects of IMIDs:**

- Thalidomide - birth defects if taken during pregnancy, drowsiness, constipation, peripheral neuropathy, blood clots
- Revlimid® (lenalidomide) - birth defects if taken during pregnancy, anemia, fatigue, decreased blood counts, increased risk of infection, blood clots, peripheral neuropathy
- Pomalyst ® (pomalidomide) – fatigue, weakness, constipation, shortness of breath, diarrhea, fever, back pain, nausea

**Common side effects of proteasome inhibitors:**

- Velcade® (bortezomib) - peripheral neuropathy, nausea, constipation, anemia, fatigue, loss of appetite
- Kyprolis® (carfilzomib) - upper respiratory infection, headache, cough, swelling, compromised kidney function, nausea, constipation, back pain

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Common side effects of anti-myeloma antibodies:

- **Elotuzumab** - low white and red blood cell and platelet counts, nausea, dizziness, headache, fever
- **Daratatumab** - low white and red blood cell and platelet counts, low platelet counts, fever, chills, cough, nausea, changes in blood pressure, flushing, rash, fatigue
- **Sylvant®** (siltuxumab) - itching, rash, edema, upper respiratory tract infections, weight gain, abdominal pain/distension, hyperuricemia (higher than normal uric acid in the blood)

Side effects can be managed or even prevented with a range of supportive treatments or with dosing adjustments. For example:

- Anti-sickness (antiemetic) drugs can help prevent nausea and vomiting. Anti-diarrhea, laxative, and antacid drugs can help with gastrointestinal problems.
- Anti-clotting drugs or low-dose aspirin can prevent formation of blood clots.
- Blood transfusions can increase red blood cell counts. Erythropoietin is a drug that promotes production of red blood cells.
- Antibiotics and antivirals can prevent or treat infection.
- Peripheral neuropathy can be managed by reducing the dose and frequency of administration of the drug that is causing the neuropathy.
- Bisphosphonates minimize and prevent myeloma bone disease, hypercalcemia, bone pain and fractures.

**CLINICAL TRIALS**

Clinical trials, also known as protocols, are research studies designed to test new drugs or combinations of drugs or other therapies in order to develop more effective treatments, reduce side effects and improve quality of life.

Clinical trials are essential for moving new treatments from the laboratory (“the bench”) to the clinical setting (“the bedside”). The primary objective of clinical trials is improved patient care outcomes and survival.

Clinical trials are conducted only after laboratory studies confirm the safety and the potential of the drug(s) or procedure(s) to work better than existing drugs or procedures.

Clinical trials are conducted in a series of steps, called phases. Each phase is designed to answer a separate research question.

*The Myeloma Institute’s unique “bench to bedside” approach applies basic science discovery to the clinical setting through cutting-edge clinical trials.*
PHASE I CLINICAL TRIAL

A phase I trial is designed to test a new drug or combination of drugs and/or new procedure(s) in a small group of patients to assess safety, appropriate dose range (often called the maximum tolerated dose) and side effects. Phase I trials are usually the first testing in humans of the new treatment, although individual drugs used in combination drug trials may already have been tested.

PHASE II CLINICAL TRIAL

A phase II trial is designed to further assess in a larger group of patients the response rate of the new treatment that has been tested in phase I trials. Phase II trials also further evaluate the safety of the treatment.

If results from a phase II trial show sufficient promise, the treatment may then be tested in a phase III trial. If the results from a phase II are unquestionably much better than results from standard treatment, it might not be necessary to continue to a phase III trial, and the treatment might become standard practice based on the phase II trial results alone.

PHASE III CLINICAL TRIAL

The goal of a phase III trial is usually overall survival or progression-free survival.

Phase III trials are often designed so that patients are randomly separated into groups called “arms” in order to compare a new, experimental treatment to a standard treatment. Patients who receive the experimental therapy are in the “experimental arm” and patients who receive the standard treatment are in the “control arm.” This process of separating patients into two groups is called randomization.

Some phase III trials compare a new treatment that has had good results in phase II trials with a well-known, standard treatment.

Informed Consent

Every patient who participates in a clinical trial must give his/her informed consent. Clinical investigators and members of the healthcare team educate eligible participants about the clinical trial, so that patients can make an informed decision about whether or not to participate. The informed consent document explains all aspects of the trial, including treatment details and potential risks.

Participating in a Clinical Trial

Taking part in a clinical trial is completely voluntary. For each clinical trial there are certain conditions and requirements that patients must meet in order to be deemed eligible. All patients who participate are referred to as “subjects” and must meet the same eligibility criteria, so that researchers have consistent data with which to address the scientific questions of the study.

Eligibility requirements may include age, overall health, disease specifics, results of medical tests and/or other conditions or complications.
History of Clinical Trials at the Myeloma Institute

Thanks to pioneering research and clinical trials at the Myeloma Institute, begun in 1989, treatment for myeloma and related diseases has evolved to new heights with greatly improved survivals and cures. Treatments developed at the Myeloma Institute have set standards for treatments used across the U.S. and the world.

A program of clinical trials that challenge the traditional body of thought on disease treatment in order to improve outcomes has always been a hallmark of the Myeloma Institute. Our physicians work in tandem with myeloma scientists to optimize diagnosis and treatments.

The Myeloma Institute’s “Total Therapy” approach to the treatment of newly diagnosed myeloma, with a focus on attacking myeloma from all fronts, has been at the core of our successful outcomes. Starting with the first Total Therapy clinical trial in 1989, outcomes have continued to improve through the incorporation of new drugs and adjustments in the transplant and maintenance phases of care.

Myeloma Institute researchers are continuing the success of the Total Therapy trials by adding novel agents aimed at targeting each patient’s specific disease based on genetic risk profiling and diagnostic testing results. Customized care based on each individual’s genetic profile and risk factors is the way of the future and is the driving force of the Myeloma Institute research.

LIVING WITH MYELOMA

A diagnosis of myeloma can be overwhelming. While you most likely will have to make adjustments to your daily routine, it is important to remain involved in the activities that are important to you as best you can.

Here are some pointers about daily activities:

- You will want to review your options related to your work. You will need support from your employer at different times during the treatment process. Your caregiver(s) might have to adjust their work schedules, too.

- Eating a healthy, well balanced diet will help maximize your body’s healing ability and maintain your energy level.

- There are certain times when you may have difficulty eating. For example, you may experience treatment-induced loss of appetite and/or nausea.

- Eat more frequent, smaller meals rather than three large meals and drink 80-100 ounces of fluids each day.

We use our understanding of the genetic basis of myeloma to design clinical trials that incorporate targeted treatments aimed at each patient’s unique disease characteristics.
- Be sure to talk to your doctor to ensure that any vitamins and supplements you want to take are safe and will not interact with your medications.

- Being physically active can improve your physical and emotional well-being. Talk with your doctor before starting any exercise regimen.

- Your ability to drive will depend on how well you are feeling. Your doctor may recommend that you avoid driving if you are taking medications that can cause drowsiness.

- Myeloma and its treatments can reduce the white blood cell count, which affects the body's ability to fight infection. Wash hands frequently. Watch for signs of infection such as elevated temperature, chills, sore throat, painful rashes, diarrhea, nausea or vomiting.

**HELPFUL HINTS**

**TIPS TO HELP YOU AND YOUR LOVED ONES WITH A DIAGNOSIS OF MYELOMA**

A diagnosis of multiple myeloma can be difficult for both patients and their loved ones. The Myeloma Institute has numerous resources and services that can help make the journey a bit easier. We are here to help guide you every step of the way.

**INFORMATION**

Being well-informed can help you better understand your diagnosis and make sound decisions about treatment and care. The internet is often the first source of information for many patients. It is important to seek information from trusted websites, as incorrect information can be misleading. In all cases, information found on the internet should not replace the advice you get from your medical team.

*The Myeloma Institute has a wide range of printed and online information.*

[www.myeloma.uams.edu](http://www.myeloma.uams.edu)
TALKING

Emotional support plays an important role in coping with a diagnosis. It is normal for patients and family members to feel scared, confused, anxious, or even angry, and these emotions may make it difficult to discuss worries or fears. Talking to someone who understands what you are going through can reduce anxiety and can ease many of your fears.

It can be extremely beneficial to talk to another patient who has gone through what you are experiencing now.

The Myeloma Institute has enlisted a group of experienced patients who serve as advisors and sounding boards for new patients. Experienced patients know what new patients are going through. They can be good listeners, offer advice and alleviate concerns. New patients who would like to be contacted by an experienced patient can call us at 1-888-MYELOMA (693-5662) or 501-686-7105.

The Myeloma Institute Social Work Department provides a variety of services to meet the psychosocial needs of patients and their families. Social workers are available to provide advocacy services; resource navigation; emotional support; individual, family, and group therapy; financial aid counseling; information about local housing and transportation; information about national support organizations and programs; and referrals for healthcare services and discharge planning following hospitalization.

Myeloma Support Groups provide an opportunity in an informal setting for sharing stories and information. Patients, family members and caregivers often find it helpful to talk with others who are dealing with the same issues. More information about Support Groups can be found online at www.myeloma.uams.edu or by talking with one of the Myeloma Institute social workers.

Online forums, social networks and blogs provide additional opportunities for connecting with others.

TELLING PEOPLE

You may find it difficult to talk about your diagnosis and how you feel, or you might be worried about how your family and friends will react.

These tips may be helpful:

- Tell people in the way that feels best for you. Sometimes it is easier to share the news over the telephone, through a letter or by email rather than face-to-face.

- Give the information in small pieces. Start with a few sentences and check every now and then to be sure the other person understands what you are saying.

- There may be moments of silence. If this makes you feel uncomfortable, you can ask, ‘What are you thinking about?’
Be honest. The truth may be painful for your loved ones, but it is best to be up-front with them, so they can understand the seriousness of the diagnosis and provide appropriate support.

Do not be afraid to ask for help with telling others. You may want to ask someone with whom you have already spoken to let others know. This will save you from having to repeat difficult and emotionally upsetting news.

Be prepared for unexpected reactions. Loved ones may not always react the way you think they will. Cancer provokes different emotions in different people.

TIPS WHILE UNDERGOING TREATMENT

Appointments

Writing down questions and concerns before your appointment can be very helpful. Be sure all your questions are answered by your healthcare team and take notes. It is a good idea to bring someone with you to your appointments. Another pair of ears can be very helpful.

Sometimes healthcare professionals forget that most patients do not understand medical language. If you do not understand something, say so and ask for information in layman’s terms.

Be sure to tell your doctor if you are taking any over-the-counter medicines or any supplements, such as vitamins or herbal therapies. Some medications can interact with other medications.

Medications

Your doctor will write a prescription for medications to be taken orally.

You may be on multiple drugs that have to be taken at different times of the day or on different days. Drugs can sometimes have more than one name (for example, lenalidomide is also called Revlimid), which can make things confusing.

Ask your nurse to go over all of your different drugs with you, so you know what to take on each day.

You might find it helpful to have a pill box marked with the days of the week to help you keep track of the drugs you have to take. It is a good idea to have at least one family member aware of your medication schedule.
The packaging and/or color and size of medications can look different from time to time. Try to set up a routine process that helps you keep track of what to take when.

- It is very important to take your medication at the right times. If you miss a dose at the time you normally take a medication, check with your doctor or nurse about what to do.

- If your local doctor has also prescribed medications, be sure to let your doctor or nurse know.

- If you have any questions or notice any new symptoms between appointments, contact your doctor or nurse. Do not wait until your next appointment.

Dealing with side-effects

- You may find that side-effects of medications and treatments are difficult and that you feel worse than you did before you started treatment. If you have any side-effects that you think are due to your treatment, let your doctor or nurse know.

- You should be honest about any side-effects with your healthcare team. There are many ways of dealing with side effects without needing to stop treatment. For example, a temporary dose reduction or an anti-nausea medication can help.

- Use a Patient Diary to record and track your side-effects. This will help you keep your health care team informed.

- If you are concerned about any new side-effects between appointments, be sure to let your doctor or nurse know.

- Some treatments may affect fertility and your ability to have children in the future. Infertility can be temporary, but some chemotherapy drugs can cause permanent infertility. The drugs used for myeloma treatment that are most likely to affect fertility include cyclophosphamide and melphalan. Be sure to talk to your doctor if you have questions about infertility.

- Hair loss is rare with oral anti-myeloma drugs, although hair thinning is possible. Hair loss is more common with the higher doses of chemotherapy used with stem cell transplantation. You can wear a wig, hat or scarf, or you might prefer not to wear anything on your head. It is always important to do what feels right for you.
Albumin: Major protein found in the blood. A person’s albumin level can provide some indication of overall health and nutritional status.

Anemia: Decreased number of red blood cells or hemoglobin level in the blood cells.

Antibody: Protein produced by plasma cells that helps protect the body from infection and foreign substances. Also called immunoglobulin (Ig).

Autologous transplant: A procedure in which a patient’s own stem cells are collected, stored and then given back following high-dose chemotherapy.

Bence-Jones protein: A light chain protein that is produced by myeloma cells and found in the urine.

Beta2-microglobulin (β2-microglobulin or β2-M): A protein normally found on the surface of various cells in the body. Increased levels of Beta2-microglobulin in the blood occur in inflammatory conditions and certain blood cell disorders, such as myeloma.

Bisphosphonate: A type of drug that binds to calcium and helps interrupt the process of bone breakdown that is common in myeloma.

Blood urea nitrogen (BUN): A byproduct of protein metabolism that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

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

Bone marrow biopsy: A procedure that involves placing a needle into bone (usually the hip bone) in order to extract a small sample of the bone marrow.

Calcium: Mineral important in bone formation. Elevated levels of calcium in the blood occur when there is bone destruction.

Chemotherapy: Treatment with potent drugs designed to kill cancer cells. Chemotherapy can be intravenous (into a vein) or oral (by mouth).

Chromosome: A thread-like structure in a living cell that contains genetic information.

Complete blood count (CBC): Blood test that measures the number of red blood cells, white blood cells and platelets in the blood and the relative proportions of the various types of white blood cells.

Computerized tomography (CT): Imaging technique that uses a computer to generate three-dimensional x-ray pictures.

Creatinine: A product of energy metabolism of muscle that is normally filtered out of the blood and found in the urine. Elevated levels in the blood can indicate decreased kidney function.

DNA: Genetic material of the cell located in the chromosomes.
Fluorescence in situ hybridization (FISH): A laboratory technique used to determine how many copies of a specific segment of DNA are present or absent in a cell.

Growth factor: Substance that stimulates cells to multiply.

Hemoglobin: Oxygen-carrying substance in red blood cells.

Hypercalcemia: A higher than normal level of calcium in the blood resulting from bone destruction that is common in myeloma.

Immunofixation electrophoresis (IFE): Type of electrophoresis that uses a special technique to identify specific types of antibodies (immunoglobulins); also called immunoelectrophoresis.

Immunoglobulin (Ig): Protein produced by plasma cells that helps protect the body from infection and disease (also called antibody).

Lactate dehydrogenase (LDH): An enzyme found in body tissues. Elevated blood levels occur when there is tissue damage; in the case of myeloma, elevated levels reflect tumor-cell burden.

Light chains: Short protein chains on antibodies.

Magnetic resonance imaging (MRI): Imaging technique that uses magnetic energy to provide detailed images of bones and soft tissues.

Maintenance therapy: Treatment that is given to help keep cancer from coming back after it has been wiped out by initial therapy.

Monoclonal gammopathy of undetermined significance (MGUS): A precancerous and asymptomatic condition noted by the presence of M protein in the serum or urine. MGUS may eventually progress to myeloma.

Monoclonal (M) protein: See Paraprotein

Neuropathy: Disorder of the nerves that can result in abnormal or decreased sensation or burning/tingling.

Osteolytic (or lytic) Lesion: Soft spot in the bone where bone tissue has been destroyed. The lesion appears as a hole on imaging tests.

Paraprotein: An abnormal antibody produced by myeloma cells and measured in the blood or urine of myeloma patients. Paraprotein is sometimes called M protein, monoclonal protein or M-spike. Measurements of paraprotein are used to monitor the activity of myeloma and its response to treatment.

Plasma cell: Specialized white blood cell that produces antibodies. Normal plasma cells produce antibodies to fight infection. In myeloma, cancerous plasma cells (myeloma cells) produce large amounts of abnormal antibodies that lack the ability to fight infection.
Plasmacytoma: Single tumor comprised of cancerous plasma cells that occurs in bone or soft tissue.

Platelets: Small blood cells which are involved in blood clotting.

Positron emission tomography (PET): Imaging technique in which radioactive glucose (sugar) is used to highlight cancer cells.

Proteasome inhibitor: A type of drug that slows myeloma cell growth and kills myeloma cells by interfering with processes that play a role in cell function.

Red blood cell: Blood cells which transport oxygen, in the form of hemoglobin, throughout the body.

Smoldering Myeloma: Asymptomatic and inactive form of myeloma.

Spinal cord compression: Pressure on the spine that can be caused by collapsing vertebrae or by the growth of a plasmacytoma within the spinal canal.

Steroids: Hormonal substances naturally produced by the body that suppress inflammation of the immune system. Dexamethasone and prednisone are examples of steroids used in the treatment of myeloma.

White blood cells: Blood cells that are part of the body’s immune system, which fights infection.