MM101 Articles
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North Texas Myeloma Support Group

Myeloma 101

These articles are written by Peter Tischler and are based on information gathered from a variety of medical and experiential sources over the past eight years.

Myeloma 101 will try to explain the basics of our disease, diagnostic tests that are used, and treatments for the disease.

Because there are differing levels of education, understanding of things medical, and interest in details, I have attempted to address all levels by explaining things in three layers:

- Simple Explanation (written in the color green)

- More Details (written in the color blue)

- More Technical Stuff (written in the color orange)

For up-to-date copies of these articles, you may choose to go directly to the articles at http://northtexas.myeloma.org/mm101.html or you may choose to go to the North Texas Myeloma Support Group's website, http://northtexas.myeloma.org/newsletters.html and choose "Myeloma 101".

What is Multiple Myeloma?

Simple Explanation:

Multiple myeloma is a blood cancer. Other better-known blood cancers are leukemia and lymphoma. It is called "multiple" because this cancer typically causes problems in more than one place in the body.

The occurrence of myeloma is on the rise in the United States. It currently has no known cure, but it is usually slow-growing and can be treated. Myeloma has long been known as a disease of the elderly, but in recent years more and more younger people are being diagnosed with this cancer.

The cause of myeloma is not known, but it is thought that certain industrial products, farm fertilizers and pesticides, and radiation might all be contributing factors.

There is no known hereditary factor associated with myeloma, although the occurrence of myeloma within families is being studied.

Multiple myeloma is slightly more likely in men than in women, and it is more common in African-Americans than in Caucasians.

Common problems seen at and prior to diagnosis are tiredness, weakness, infections, bone pain, and fractures.

More Details:

Multiple myeloma is called a hematological cancer and affects the plasma cell, one of the blood cells that comprise the immune system. The plasma cell is an immunoglobulin-secreting cell. In other words, it is a "factory" that the immune system creates in order to generate massive amounts of antibodies, or immunoglobulins, in order to fight "invaders." Immunoglobulin is a protein that, when produced by a malignant plasma cell, is called myeloma protein or m-protein.

Normal bone marrow contains less than 5% plasma cells. In multiple myeloma there are usually more than 30% plasma cells and that number can increase to over 90%.

There are over 15, 000 new cases of myeloma in the U.S. each year, representing 15% of all blood cancers and 1% of all types of cancer.

According to the International Myeloma Foundation (IMF), "There is only a weak family tendency to develop myeloma. Approximately 3-5% of patients with myeloma give a history of myeloma or a related blood/bone marrow condition within the extended family. Thus far, no specific gene has been linked to this myeloma tendency."

More Technical Stuff:

Multiple myeloma is an incurable malignancy of immature, isotype-switched, immunoglobulin-secreting plasma cells that accumulate in the bone marrow, leading to marrow failure and bone destruction.

The Myeloma Cell

Simple Explanation:

In multiple myeloma, as with any cancer, there has been a mutation of a certain cell. From that single mutated cell a great many identical cells have grown. In the case of myeloma, the particular cell that had the mutation is known as a "plasma cell." In every human body there are many health plasma cells. In the body of someone with myeloma there are both healthy plasma cells and the mutated plasma cells.

The mutated (malignant) plasma cells, or myeloma cells, continuously multiply. Large numbers of myeloma cells form tumors. Tumors of myeloma cells can grow inside bones or on the outside of bones. Good blood cells are crowded out and the bones themselves are often damaged, leading to fractures.

All of the myeloma cells are identical and they are all deformed. They serve no useful purpose because they are defective. Normal plasma cells automatically die after a period of time, but the myeloma cells have lost the ability to die. Your immune system tries to kill them but is not able to get the job done.

More Details:

The malignant plasma cells, or myeloma cells, have an affinity for the bone marrow environment where they establish a destructive relationship with other stromal (bone matrix) cells. The myeloma cells secrete substances that cause bone destruction and lead to a further proliferation of the myeloma cells.

All of the myeloma cells are identical and are, therefore, called monoclonal. Depending on when the mutation took place, for a given individual, the myeloma cells will produce certain "fragments" of immunoglobulin (antibodies) that can be used to identify the type of myeloma.

From a single mutated plasma cell, trillions of identical myeloma cells (clones) are eventually created. Those myeloma cells may form one or more soft tumors (called plasmacytomas) and/or may infiltrate the marrow inside certain bones, usually the femur, humeris, pelvis, vertebrae, ribs, and skull.

Aggregations of myeloma cells are usually associated with bones, whether from the inside, the outside or both. The damage to the bone is known as a lesion. Lesions show up on imaging studies (x-ray, MRI, scans).

When the aggregations of myeloma cells occur inside the marrow-producing bones, the healthy cells of the immune system (e.g. red blood cells, white blood cells, platelets) are crowded out. In such cases, the immune system is compromised, causing increased risk of infections, tiredness, and weakness.

More Technical Stuff:

The myeloma cells establish a destructive relationship with bone remodeling cells called osteoclasts. Myeloma cells produce soluble signals called cytokines that activate the bone resorbing osteoclasts. Other cytokines that are osteoclast activating factors (OAFs) are lymphotoxin, interleukin-1b (IL-1b) and interleukin-6 (IL-6). In response, the osteoclasts and other stromal cells secrete even more IL-6, which stimulates the production of more myeloma cells.

With myeloma, there are two malignant cell populations: a slowly proliferative plasmablast (a plasma stem cell) and a slightly more differentiated plasma cell that cannot proliferate. That fact will be important when we get to treatment options.

Myeloma Protein

Simple Explanation:

Myeloma cells are malignant plasma cells, and the purpose of plasma cells is to pump out vast quantities of a protein called immunoglobulin. In the case of the myeloma cells, the protein that is created is defective, just as the myeloma cell itself is defective. Almost all cases of myeloma (99%) have the additional problem of an excess of this defective protein, which is also called myeloma protein, or m-protein.

Besides the problems that the myeloma cells can cause, the myeloma protein may cause further problems that have to be addressed. But first we need to understand a few things about the myeloma protein.

Good plasma cells create a variety of these proteins, depending on the reason why the plasma cell was created. In other words, the bodily invader caused a particular type of plasma cell to be created. Therefore, medical people refer to your type of myeloma according to the kind of protein it creates.

One way to measure the extent of your disease is to measure the amount of myeloma in your bone marrow. Another, and simpler, test is to measure the amount of myeloma protein that you have in your blood and urine.

Now, about the problems that the myeloma protein may cause. In order to get rid of the excessive protein that is being created by the myeloma cells, the kidneys must work very hard to do the job. In fact, the kidneys may become overwhelmed and the myeloma patient may develop kidney problems or even kidney failure. Great care must be taken by your oncologist and you to prevent this from happening. Your job is to drink plenty of water every day.

Another problem that may result from the excess protein is, in rare cases, thickening of the blood, leading to stress on the heart and other organs.

More Details:

Your type of myeloma relates to the kind of protein, or immunoglobulin, that is created by your myeloma cells.

All immunoglobulin proteins are comprised of two parts: a heavy-chain (so called because that part of the molecule is heavier in weight) and a light-chain (this part weighs less). The heavy-chain fragments of the molecule are known as IgA, IgG, IgD, IgE, or IgM. The light-chain fragments are known as kappa or lambda and are also known as Bence-Jones protein.

Your defective myeloma cells may produce a heavy-chain fragment only, a light-chain fragment only, a molecule with both heavy- and light-chain components (the most common), or none of the above (only about 1% are non-secreting, or non-secretory myeloma).

Therefore, your myeloma may be called something like IgG, or IgA lambda, or maybe just kappa light-chain. Don't worry about the difference in those names, at present, but be aware that it's a way for the medical people to classify your particular myeloma.

One more thing to note about the myeloma protein: the heavy-chain protein (beginning with the letters Ig) is quantified by testing your blood, and the light-chain protein (kappa or lambda) is usually quantified by testing your urine.

The stress to your kidneys from the excess protein can be measured and controlled (to some extent) by your doctor. Keeping the kidneys healthy with plenty of fluids is something that the patient has some control over. The light-chain fragments are more damaging to the kidneys than the heavy-chain fragments and lambda light-chain is the most damaging.

More Technical Stuff:

The immunoglobulin secreted by the myeloma cells is called m-protein, where the "m" can stand for myeloma or monoclonal. When the amount of myeloma protein is measured and shown on a graph, the excess protein forms a spike on the graph and is known as the "m-spike."

As previously mentioned, there are heavy- and light- chain fragments. In 57% of patients it is IgG, in 21% it is IgA, in 2% it is IgD, and only extremely rarely (>1%) IgM or IgE. In 18% of patients only a light-chain is secreted (Bence-Jones protein), which because of its low molecular weight is excreted in the urine, and in 1%-2% no immunoglobulin is secreted. This last category is known as non-secreting or non-secretory myeloma.

The supporting Cast

Simple Explanation:

We've talked about the myeloma cells and the protein that they secrete. But the myeloma cell also secretes other molecules that have a complex interaction with the many cells in the bone marrow environment. The result is a cycle of destruction whereby the myeloma cell creates other cells that destroy bone; but the cells that destroy bone secrete substances that cause the myeloma cells to proliferate. This cycle of destruction, unless broken by treatment, may result in severe damage to your skeleton.

More Details:

The myeloma cell secretes not only immunoglobulin but other molecules called cytokines that interact with the bone marrow microenvironment. Some of those secreted cytokines are called Osteoclast Activating Factors (OAFs), which cause a proliferation in the osteoclasts, which degrade bone. The osteoclasts in turn, along with other activated stromal cells, produce Interleuken-6 (IL-6), which is a major growth factor for myeloma cells.

To make matters even worse, the myeloma suppresses the osteoblasts, which are the bone builders in the remodeling that occurs in a person without myeloma.

More Technical Stuff:

Over the last several years, as more is understood regarding the interaction of the various players within the bone marrow matrix, new treatment ideas have become possible. In addition to treating the myeloma directly, protection of the bone matrix has become possible with drugs such as the bisphosphonates (e.g. Aredia and Zometa). Also, disruption of the "cycle of destruction" may be possible with drugs that suppress IL-6 and other MM growth factors; another treatment being investigated is the infusion of OPG in order to bind the RANK ligand that would otherwise bind to RANK, thus neutralizing the signaling chain that leads to osteoclast formation and ensuing bone destruction. In fact, there are an incredible number of molecular interactions, any one of which may turn out to be a solution to the dual problem of bone destruction and myeloma cell proliferation.

How Myeloma Affects Us

There are three typical ways that myeloma affects a person. First, myeloma suppresses the immune system, which leaves the person more likely to get sinus, respiratory, and other infections. A suppressed immune system may mean anemia (weakness, tiredness) and low platelets (slowness to heal).

Second, myeloma affects the skeleton. Lesions may lead to compression fractures in the spine, broken ribs, arms, shoulders, or legs. Bone pain is often a side effect of the disease.

Third, the myeloma protein may affect the kidneys to a significant degree. It is not uncommon for patients to have kidney damage and even kidney failure at diagnosis.

More Details:

There are a great number of cells, molecules, proteins, and enzymes that interact in the bone marrow. Every change within that population causes reactions, sometimes a veritable cascade of reactions. Myeloma changes the balance of the marrow and bone environments, but in ways that are unique to each individual. However, some of the changes are fairly typical.

There is only so much room inside the marrow-producing bones (e.g. pelvis, femur, humeris, rib, vertebra, clavicle, skull), and all the cells necessary for the care and maintenance of your body are found there. When a huge population of myeloma cells is produced inside those bones, there becomes less and less room for the "good" cells, which are crowded out. Therefore, it is typical that a person with myeloma has fewer red blood cells, white blood cells, and platelets. Those deficits often result in anemia, increased infection or inability to control infections, and a decreased ability for wounds to heal and an increased instance of bruising.

Bone destruction is a primary feature of multiple myeloma. In recent years, much attention has been paid to myeloma bone disease, especially after the development of a class of drugs (bisphosphonates) that greatly help that problem.

There is often some confusion about the role of the plasmacytoma and the lesion, as defined in myeloma. A plasmacytoma is simply an aggregation of myeloma cells – a soft tumor. A lesion is something that has made a defect on one of your bones. Often, a soft tumor has grown on and into one of your bones, thus forming a lesion. Sometimes, however, the plasmacytoma may grow either inside or on the outside of a bone without harming the bone (i.e. no lesion). But most of the time there is slow and steady destruction of the bone – unless the progression is slowed or stopped.

The large amount of monoclonal protein can clog up your bloodstream and cause lots of problems to your systems, which have a hard time eliminating it. The kidneys and heart are two of the primary organs that can get overwhelmed by this "sludge" created by the myeloma cells. People with light-chain-only myeloma create too much light-chain protein (kappa or lambda). This light-chain protein has a small enough molecular size that it passes into and through the tubules of the kidneys into the urine. In great enough

quantities, however, it can overwhelm the kidneys and cause kidney damage or even renal failure. Sometimes the light-chain protein combines with other proteins to form a substance called "amyloid" which is even more dangerous to the kidneys, spleen, liver and other organs.

More Technical Stuff:

Bone pain occurs in approximately 75% of patients and about 50% have radiologically detectable myeloma-related skeletal lesions at diagnosis.

Hyperviscosity sometimes occurs in cases of IgM myeloma (rare), IgA, or IgG$_3$ subtype.

Polyneuropathy is observed in 5%-15% of myeloma patients, but as many as 50% of patients may have subclinical neuropathy.

Hypercalcemia is found in about a third of patients at diagnosis and is usually associated with advanced disease and, in particular, with extensive osteolytic bone lesions. Such patients may develop acute nausea/vomiting or confusion due to hypercalcemia or uremia.

Different Types of Myeloma

Simple Explanation:

There are several different "varieties" of myeloma. One of them (you may hear the term MGUS) is not really myeloma, but only a benign condition that may, in time, become myeloma. All other varieties are malignant. The benign MGUS variety is usually not treated.

Another term you might hear is "Smoldering Myeloma." This term is used to identify a person with no bone problems, no anemia, no kidney problems, and a relatively low amount of myeloma cells in the bone marrow. This type of myeloma is usually not treated as long as it remains within the above criteria.

A third term used is "Indolent Myeloma." It is similar to "Smoldering Myeloma," but allows mild anemia and a few small bone problems (lesions). The amount of myeloma cells could be slightly higher than with Smoldering Myeloma. Treatment may or may not be used, depending on the treatment philosophy of the oncologist.

"Solitary Plasmacytoma of Bone" is a term used to describe a case of myeloma where the only evidence of the disease is localized in a single soft tumor on or in a bone. The significance of SPB is that radiation of that location may eliminate the myeloma from the patient's body.

"Extramedullary Plasmacytoma" refers to a case of myeloma where there is a soft-tissue plasma cell tumor. Such tumors usually arise in the upper respiratory passages.

Other than the above exceptions, Multiple Myeloma is given that name because it usually occurs in more than on location, usually associated with the marrow-producing bones in the body. When progressing from a lesser form of the disease, myeloma is sometimes referred to as "overt myeloma" or "frank myeloma."

More Details:

All of the types of disease with which we are dealing fall under the heading of "Monoclonal Gammopathies." They are characterized by a proliferation of a single clone of plasma cells producing a homogeneous (monoclonal) protein (m-component, m-protein, paraprotein).

MGUS is an acronym that stands for Monoclonal Gammopathy of Undetermined Significance. It means that there is relatively small monoclonal component in either the blood (IgG, IgA, etc.), or urine (kappa, lambda) and a relatively small infiltration of the bone marrow with plasma cells (< 10%). There are no symptoms of disease and the person is usually in good health. The disease is stable (until, or unless, it progresses to myeloma) and need only be watched.

Smoldering Myeloma (SMM) is characterized with IgG > 35 g/l or IgA > 20 g/l and/or Bence-Jones protein < 1.0 g/24 hrs. Bone marrow infiltration with plasma cells is > 10% but < 20%. There are no renal problems, anemia, hypercalcemia and no bone marrow lesions on skeletal survey.

Indolent Myeloma (IMM) is characterized with IgG < 70 g/l or IgA < 50 g/l and/or Bence-Jones protein < 1.0 g/24 hrs. Bone marrow infiltration with plasma cells is > 20% but < 30%. There are no renal problems or hypercalcemia, no more than mild anemia, and no more than two or three small lytic lesions (but no compression collapse).

Multiple Myeloma (MM) is characterized by the presence of one or more of the following major criteria: plasmacytomas, infiltration of the bone marrow > 30%, monoclonal IgG > 35 g/l, monoclonal IgA >20 g/l, and Bence-Jones protein > 1 g/24 hrs. Also, one or more of the following minor criteria: lytic bone lesions, suppression of the normal immunoglobulins.

More Technical Stuff:

There are many other factors that can lead to a diagnosis of multiple myeloma, such as the markers Beta-2-Microglobulin (B2M), C-Reactive Protein (CRP), hypercalcemia due to bone destruction, and Plasma Cell Labeling Index (PCLI).

These will be discussed further in the section on "Staging Myeloma."

There will continue to be advances in understanding the genetics of myeloma. There has already been important work done to categorize different kinds of myeloma according to specific gene translocations. One of those genetic variations, known as "chromosome 13 deletion" is known to have a less favorable outcome than others. For now, however, the science of differentiation doesn't lead to better, or more selective, treatment for any given genetic variation of myeloma.

Staging Myeloma

Simple Explanation:

Staging for a disease has two purposes. First, it tells the medical team, and the patient and caregiver, how far the disease has progressed. Generally, the lower stage number is better news for you and the medical team. Knowing the stage can be a mixed blessing for you. Hearing that your myeloma has a relatively low stage number can make you feel better about your future, while hearing that it's a high number can be frightening. This is deceptive, because it's often not the stage that's important but rather the aggressiveness or trend of the disease. For the most part, knowing the stage does little for the patient and the family.

Second, the stage can sometimes determine the treatment you will receive. Some clinical trials might allow only, say, stage 3 patients. Sometimes the lowest stage patients might be given a fairly benign treatment rather than a harsh one. Quite often, however, patients will be treated pretty much the same, by a given oncologist, regardless of the stage.

An additional point: staging can be somewhat an "art" as well as science. Although most staging systems have fairly strict criteria, there is some gray area between stages. One oncologist might stage a patient as stage 2, while another might call it stage 3.

One final point: Knowing a stage number doesn't mean much unless you know which staging system is being used by the oncologist. There are four different staging systems in use at this time (although only one is most commonly used), so you might get two different stage numbers from two different consultations, even though they really mean the same thing.

More Details:

There are four usual staging systems in use as of this date. In order of usage, they are:

- The Durie/Salmon Staging System
- The SWOG (SouthWest Oncology Group) Staging System
- The Durie/Salmon Plus Staging System
- The new International Prognostic Index (IPI) Staging System

At this date, most patients have been staged with the Durie/Salmon Staging System. This system has three stages (I, II, and III) and each stage has a sub-classification indicating renal (kidney) function. The factors weighed for the three stages are hemoglobin value (anemia), serum calcium value (bone destruction), bone x-rays results (lytic lesions), m-component production rates (IgG, IgA, etc. and kappa, lambda), and myeloma cell mass (tumor burden) from a bone marrow biopsy and aspiration. Sub-classification ("A" or "B") refers to the serum creatinine value (renal function).

The SouthWest Oncology Group (SWOG) Staging System is a simple prognostic classification system that has four stages (I, II, III, and IV). This system weighs only two factors: serum beta-2-microglobulin (b2m) and serum albumin. Stages I and II result

from normal or higher b2m, respectively. Stages III and IV result from high b2m, and normal or low serum albumin, respectively.

The Durie/Salmon Plus Staging System uses the factors used in the standard Durie/Salmon Staging System for stages IB, IIA and IIB, IIIA, and IIIB, although it adds the criterion of number of focal lesions to the I, II, and III stages. Stage IA is reserved for smoldering or indolent myeloma if there is a single plasmacytoma and/or limited disease seen on imaging studies. The sub-classification (A or B) weighs the factors serum creatinine, platelet count, and presence or absence of extramedulary disease.

The International Prognostic Index (IPI) Staging System is a simple system similar to the SWOG system. Like the SWOG system, it weighs only the two factors: serum beta-2- microglobulin (b2m) and serum albumin. Stages I results from normal-to-low b2m and normal-to-higher serum albumin. Stage II results from either normal-to-low b2m and low serum albumin, or low-to-medium b2m. Stages III results from high b2m. There is no Stage IV in the IPI Staging System.

More Technical Stuff:

Durie Salmon Staging System:

Stage I

- All of the following:

- Hemoglobin value > 10 g/l

- Serum Calcium value normal or < 10.5 mg/dl

- Bone x-ray shows normal bone structure or solitary bone plasmacytoma

- Low m-component production rates (IgG < 5.0 g/dl or IgA < 3.0 g/dl, urine light-chain < 4 g/24h)

- Myeloma cell mass (in the whole body) 600 billion cells/meter squared or less

Stage II

- All of the following:

- Fitting neither Stage I or Stage III

- Myeloma cell mass (in the whole body) 600 to 1,200 billion cells/meter squared

Stage III

- One or more of the following:

- Hemoglobin value < 8.5 g/dl

- Serum Calcium value > 12.0 mg/dl

- Advanced lytic bone lesions

- High m-component production rates (IgG > 7.0 g/dl or IgA > 5.0 g/dl, urine light-chain > 12 g/24h)

- Myeloma cell mass (in the whole body) > 1,200 billion cells/meter squared

Sub-classification (either A or B)

- A: relatively normal renal function (serum creatinine value) < 2.0 mg/dl

- B: abnormal renal function (serum creatinine value) > 2.0 mg/dl

Testing - Blood Tests

Simple Explanation:

There are two different reasons for testing in myeloma. The first is to confirm a diagnosis of the disease and determine the severity of the patient's condition. The second is to monitor the patient through periods of treatment and plateau (remission).

Basically, there are three kinds of tests for myeloma:

- **Blood tests** (we will include the bone marrow biopsy in this group)

- **Urine tests**

- **Imaging tests**

In order for your doctor to know the extent of the disease and, subsequently, the success of a treatment, there are a variety of blood tests that, together, create a picture. It's much like putting together a jigsaw puzzle; any given piece of the picture puzzle is, by itself, inadequate. But when you've assembled all the pieces, the picture becomes clear.

Having said that, I've met many MMers who simply want to understand, and follow, their "**myeloma count**" and their "**blood counts**." When they refer to the "myeloma count," they really mean the number their oncologist mentions when he's talking about the amount of **myeloma protein** in their blood. Remember that myeloma cells produce lots of myeloma protein and that's what can be measured in the blood. However, that's only true for about 80%-85% of MMers, as the others only create a myeloma protein that can be measured in the urine. If you're among the majority (the 80%-85%), then that protein value is the "**myeloma count**" for you.

The "**blood counts**" refer to the test called the **CBC** (**complete blood count**). You might be told that your **red blood cells** are too low, or your **white blood cells** are too low, or you don't have enough **platelets**. That may delay your next treatment. It might also cause your oncologist to order something to stimulate more of the cells that are lacking (e.g. Procrit, Neupogen).

More Details:

One of the fortunate aspects of myeloma is that for most of us there is a myeloma "**marker**" [a **marker** is a test result that can tell the physician, and you, how your disease is behaving]. The marker for myeloma is either the myeloma protein (m-protein) in your blood or the m-protein in your urine, or both. Only a few people (1% - 2%) have a rare variant that has no such marker. The primary blood test for both diagnosis and monitoring is called **serum protein electrophoresis** (sometimes called **SPEP**), which tests for the myeloma marker in the blood.

The **bone marrow biopsy** can be important, because it can show the actual myeloma cells and the sample retrieved can be examined to determine the type of myeloma and may suggest how to treat the disease. Your oncologist might say, for instance, "Your

latest bone marrow biopsy shows that the plasma cells in your marrow have dropped from 60% to 15%."

The **complete blood count** will often show how the patient has been affected by the disease (e.g. lowered red cell, white cell and platelet counts). Those lowered counts often correlate to the patient's being tired, prone to bruising, slow to heal, and open to infections.

The **chemistry panel** shows a variety of important counts, which may have been affected by the disease (e.g. **calcium**, **creatinine**). These may indicate that your bones are being degraded, that your kidneys are stressed, or other ways in which the myeloma is affecting your body.

Several secondary markers that can be elevated when a disease is active in the body are also usually checked and tracked: **beta-2-microglobulin (B2M)**, **C-reactive protein (CRP)**, and **lactate dehydrogenase (LDH)**.

A new blood test, which is growing in usage, can be very important to patients who have only urine myeloma protein or have no myeloma protein. This test is called the **FreeLite Test** and it measures free monoclonal light chains in the blood. Everyone has a certain level of these free light chains in their body, but those of us with myeloma will often have an excess, indicating that the disease is active.

More Technical Stuff:

The most important marker for MMers is the excess protein that is created by the myeloma cells. But not all oncologists follow that marker the same way. Most will use the **serum protein electrophoresis** or the corresponding test against the urine (for those with light-chain-only myeloma). In some cases, in order to save money, the oncologist will only look at the **total protein** number that is available from the **chemistry panel**. When there is myeloma protein in the serum, the total amount of protein is elevated above normal by that "abnormal" amount. Therefore, it is possible to track the progress of the disease, and/or treatment, by the total protein. It is not, however, possible to know if there are other problems that might be elevating the "good" protein, thus making **total protein** a poor way to track the myeloma.

The **serum protein electrophoresis** test does not tell the doctor which of the immunoglobulins (IgG, IgA, etc) is the culprit. In order for him to determine which of the immunoglobulins is your myeloma protein, a test called **immunofixation** may be performed. Still another test (either **radial immunodiffusion** or **immunonephelometry**) can quantify the amount of the monoclonal immunoglobulin. Obviously, cost is a factor in testing, and you and your oncologist must decide how much information about your myeloma is enough.

The **bone marrow aspirate and trephine biopsy** (the more complete name of the test) can be very important if testing is going to be done with your actual myeloma cells. **Cytogenetics**, **immunophenotyping**, and **plasma cell labeling index** are among such tests. The bone marrow test has long been used as a confirmation of diagnosis

and to quantify the amount of "tumor burden" (the degree to which myeloma cells have infiltrated the marrow). The limitation of this test is that many myeloma patients have "focal" (myeloma clusters here and there) rather than "diffuse" (myeloma cells homogenously spread through the marrow) disease. In the case of focal disease, it's difficult to assure that the aspirate and biopsy will always hit an area representative of the patient's disease. Many oncologists no longer rely as much on this test unless there is a need for the marrow for further testing.

Complete blood count is very important to MMers with active disease, especially the red cell (RBC), white cell (WBC), and platelet counts. Anemia is a frequent problem with myeloma and the RBC correlates well with that problem. The risk of infection will correlate to the WBC value. Lowered platelets can mean a risk of bleeding and bruising. As the myeloma cells are controlled, the immune system can make for good cells and those counts will improve.

Chemistry panel shows many important values, but often MMers are most interested in the values that indicate whether or not their bones are being "eaten" by their disease (**calcium**), and whether or not their kidneys are being affected by the myeloma (**creatinine**). When myeloma is active, cytokines are created that cause bone resorption. As the bone is resorbed, lytic lesions form and calcium is a byproduct that may be detected in the blood. Although creatinine is a good general indicator of kidney health, some oncologists order another test called the **creatinine clearance** in association with the 24-hour urine testing.

Beta-2-microglobulin (B2M) is most effectively used at diagnosis. This marker is affected by treatment and is, therefore, of limited value after diagnosis. In addition, B2M, CRP and LDH may all be elevated in the course of problems other than myeloma.

There are, of course, many **other values** that may or may not be important on your blood tests. The important things are to understand the reason why any value is not within the **reference range** (that lab's "normal" range) and to track each value over time, as with a spreadsheet. **Trends** are more important than just the **values** at any specific time.

Remember that the **reference range** for your lab values may differ from the reference range for another MMer's values. Also, **measurements** may vary; one person's reading might be in g/dl (grams per deciliter), while another person's lab may use mg/dl (milligrams per deciliter).

Testing - Urine Tests

Simple Explanation:

Testing of the urine is particularly important for MMers who have been diagnosed with a type of myeloma that only shows in the urine. It can also be important for those who show myeloma protein in both the blood <u>and</u> the urine. But for those whose myeloma protein can <u>only</u> be found in the urine, the urine test can give them their "**myeloma count**." That count will enable the patient and the doctor to see if the myeloma is progressing and it can show whether or not a treatment is working.

Remember that the "**trend**" is more important than the "**number**." In other words, if the amount of myeloma protein in the urine is increasing, that's not so good; on the other hand, if the amount of myeloma protein remains stable, that's much better. The best trend, of course, is a steadily decreasing amount of protein.

There are several methods by which the protein in the urine can be tracked. Whichever method is used by your oncologist, the important thing to remember is that you and your oncologist should understand the <u>direction</u> of the **trend**.

Since myeloma protein in the urine is usually a sign that the kidneys are threatened, it's important that you know whether or not you have such protein in your urine. Even if you did <u>not</u> have any myeloma protein in your urine when diagnosed, that can change over time. Make sure that your oncologist tests your urine at least once a year even though there wasn't any found in the past.

There is another test associated with urine testing: it's called **creatinine clearance** and it is a more sensitve measurement of kidney function than the **serum creatinine** test done with the blood. The serum creatinine test is usually sufficient unless the kidneys are being damaged. Then, your oncologist might order the creatinine clearance test.

Another important point about urine testing for MMers is that the oncologist will usually order a "**24-hour urine collection**." Often, urine testing for problems other than myeloma will be done with the "urine in a cup" {a method called "**dipstick**") with which we're all familiar. It's important that MMers have a full day's worth of urine tested rather than using the "urine in a cup" method.

More Details:

There are several tests that can be performed with the urine collected for your "**24-hour urine**" testing. The tests ordered will depend on how much information about your myeloma protein you and your oncologist need.

The most basic test gives the **total protein** value. But the total protein includes the albumin protein, which does not have any significance, usually, for MMers. Therefore, by itself, the total protein value is not very informative and would usually not be the only test performed. Normally there is no, or only a small amount, of protein in the urine. When there <u>is</u> protein in the urine, it usually consists primarily of urine albumin

The most common test performed with the 24-hour urine collection is the **urine protein electrophoresis**. For those MMers who are "light-chain" only, this test will result in a value that will show whether or not the urine immunoglobulins are increasing, staying the same, or decreasing. However, this test will only show the immunoglobulin proteins as a group, rather than identifying specific immunoglobulins, among which would be that particular protein of importance to you – your "**marker**" [remember - a **marker** is a test result that can tell the physician, and you, how your disease is behaving].

Assuming that the urine protein electrophoresis does show a higher-than-normal value for the area containing the immunoglobulins, a further test is helpful in separating that area (called the "gamma band") and identifying the individual immunoglobulins. This test is called **urine immunofixation**. It is similar to another test called **urine immunoelectrophoresis**, but that older test is less sensitive and most doctors will prefer the urine immunofixation, which identifies and monitors the monoclonal proteins (that is, lambda light-chain, and kappa light-chain).

Finally, if it is desired to quantify the kappa and lambda light-chain (Bence Jones) m-protein, a **quantitative Bence Jones protein** test may be performed. This test will give specific quantitative measurements for the kappa and lambda protein.

More Technical Stuff:

Normally, protein is not present in the urine when measured by routine dipstick qualitative tests. This is because the glomerulus (which is the part of the kidney nephron which filters fluid from the blood) generally prevents large molecules (which includes most proteins) from entering the renal filtrate. Even if small amounts get through, they are normally taken up by renal tubular cells which then metabolize the proteins as a source of energy. However, even if both the glomerulus and renal tubules are completely normal, some proteins will appear in the urine if plasma (blood) concentrations exceed the threshold value. If the kidney is diseased, protein will appear in the urine even if the plasma concentrations are normal.

Urine Immunofixation is a laboratory technique that is used to enhance the results of standard **urine protein electrophoresis**. With the urine protein electrophoresis, the urine is placed on specially treated paper and exposed to an electric current. The various proteins migrate (move on the paper) to form bands that indicate the relative proportion of each protein fraction. Immunoglobulins (antibodies) appear as a "gamma" band. The **urine Immunofixation** test is a technique to separate this "gamma" band and identify the individual immunoglobulins. It is similar to **urine immunoelectrophoresis** but may give more rapid results and is slightly more sensitive. The primary use of immunofixation is the identification and monitoring of monoclonal immunoglobulins (that is, IgG, IgM, IgA, lambda light- chain, and kappa light-chain), including those that are present in multiple myeloma and Waldenstrom's macroglobulinemia. The absence of monoclonal immunoglobulins is normal.

Urine Immunoelectrophoresis Is a test that detects the presence or absence of immunoglobulins in the urine and assess the qualitative character (polyclonal vs. monoclonal) of the immunoglobulins. Immunoelectrophoresis is a laboratory technique. Electrical charges are used to separate and identify the various immunoglobulins. This test is used to roughly measure the amounts of various immunoglobulins in urine. Most often, this is used as a screening test,

particularly in people who have protein in the urine (demonstrated on urinalysis or other test) when urine protein electrophoresis indicates a significant amount of globulin proteins (antibodies). It uses a combination of protein electrophoresis and an antigen-antibody interaction. Protein electrophoresis indicates the presence of immunoglobulins as a group. Immunoelectrophoresis enhances the ability to identify the specific immunoglobulins through the use of antibodies that only react with the proteins of interest.

<u>Bence-Jones Protein (quantitative)</u> is a test to measure the presence of Bence-Jones proteins (free immunoglobulin light-chains) in urine. Normally light-chains (a small group of antibodies) are produced in excess of heavy chains (a large group of antibodies), so free light-chains are normally present in a small amount in urine. Increases in free light-chains (polyclonal) may occur with increased immunoglobulin synthesis or catabolism (a destructive change in cells). These light-chains do not exhibit the thermal characteristics of Bence-Jones proteins (monoclonal free light-chains). Not all monoclonal free light-chains exhibit Bence-Jones behavior, but all are abnormal. Urine immunofixation is the best test for detecting free monoclonal light chains. Since Bence-Jones proteins are relatively small, they can be filtered by the glomerulus of the nephron. When urine protein is elevated, analysis and other clinical features suggest multiple myeloma, a Bence-Jones proteins test may be ordered. These proteins have an unusual thermal property that allows them to be identified; they precipitate from urine when heated between 45 degrees and 60 degrees C and re-dissolve on boiling. Unequivocal identification is made by immunoelectrophoresis.

Creatinine is a protein produced by muscle and released into the blood. The amount produced is relatively stable in a given person. The creatinine level in the serum is therefore determined by the rate it is being removed, which is roughly a measure of kidney function.

<u>Creatinine clearance</u> is technically the amount of blood that is "cleared" of creatinine per time period. It is usually expressed in ml per minute. Normal is 120 ml/min for an adult. It is roughly, inversely related to serum creatinine: If the clearance drops to one half of the old level, the serum creatinine doubles (in the steady state). So for an adult, serum creatinine of 2 is roughly a creatinine clearance of 60 ml/min; creatinine 3 is roughly a clearance of 30; creatinine of 4 is roughly a clearance of 15, etc. So why didn't the creatinine rise to only 2 when a kidney was removed? (I said it would rise to 1.8) The answer is that the remaining kidney "hyperfilters" and seems to work harder, therefore kidney function is not quite halved..

Testing – Scans

Simple Explanation:

We are all familiar with the x-rays of our skeleton that are usually ordered, when diagnosed, by our oncologist. The x-rays are called a **skeletal survey** and usually include views of all the bones that are typically involved with myeloma. That means x-rays from the head down to the legs above the knee. It will usually exclude the hands, lower legs, and feet.

The skeletal survey is the primary method for the detection and staging of skeletal involvement in myeloma, but it does have limitations. That limitation might only be apparent when the patient has bone pain even though their x-rays are normal.

It's true that some 10-20 percent of patients with multiple myeloma have no bone involvement at all. Those patients have other consequences of the disease; for example, anemia or kidney problems. They might have myeloma in the marrow of their bones, but no actual damage to the bone. Alternatively, however, they might have some bone destruction that is not visible on x-rays. For instance, almost 50% of a vertebra may be lost before that damage can be seen on an x-ray.

Therefore, several other scans are often used to detect the myeloma or the damage done by myeloma. These are:

Bone scan - A "nuclear medicine" scan that shows bone growth due to tumors. This scan is not very effective for myeloma, and is rarely used.

CT scan (also called "**CAT scan**") - Will show connective tissue problems or plasmacytomas (soft myeloma tumors).

MRI - Will show suspect areas in 3-D and can also show plasmacytomas. This method can show the composition of the bone marrow and any myeloma infiltration into it. There is also a special technique called a **Screening MRI**, which was developed at Cedars-Sinai just for myeloma patients.

Setamibi nuclear medicine scan (also called "**MIBI**") - Can show "hot spots" of myeloma. Can show active myeloma tumors.

FDG nuclear medicine scan (also called "**PET scan**") - Also shows active myeloma disease and is somewhat more sensitive than the MIBI scan.

Dexa scan (also called "**bone density test**") - Can show if there is generalized bone loss due to myeloma. This test is useful as a baseline as treatment progresses.

More Details:

The **Bone Scan** is a test that's very valuable in diagnosis for cancers that cause tumor growth in and on bones. That is, cancers such as metastasized breast cancer, melanoma, and prostate cancer. Myeloma, however, does not cause growth on bones, but rather bone resorption or lesions (the bone is eaten away). Therefore, the bone scan is not a useful diagnostic tool for myeloma.

MRI, or **Magnetic Resonance Imaging**, works by the detection of radio waves given off by the water protons in the variety of bodily tissues (which include bone) when subjected to magnetic fields. Therefore, fat (high water content) will give off a different signal than muscle (less water), and so forth. There are also several different techniques used (such as STIR, T1-weighted, T2-weighted) and different perspectives (sagittal, axial, coronal). Thus, the same body area can be viewed different ways and give different perspectives in hopes of more clearly identifying the anatomy.

The **Screening MRI** was developed by Dr. Waxman at Cedars-Sinai especially for patients with myeloma. What makes this technique different from the "usual" MRI is that it relies on the use of **sagittal imaging** only (side-to-side scanning). Another significance of this technique is that the technician is looking for something with known characteristics - that is, myeloma. They can set the machine to scan for the myeloma characteristics and eliminate most of the "in depth" iterations, which make most MRI studies very expensive.

The **CT scan**, or **Computed tomography scan** (also known as a **CAT scan**, or **Computed Axial Tomography scan**) is a method of body imaging in which a thin x-ray beam rotates around the patient. Small detectors measure the amount of x-rays that make it through the patient or particular area of interest. A computer analyzes the data and constructs a cross-sectional image. These images can be stored, viewed on a monitor, or printed on film. In addition, the computer can create three-dimensional models of bodily areas by stacking the individual images, or "slices."

Sestamibi scan (also called **MIBI scan**) has only been used for myeloma since the late 1990s. It was pioneered for MMers at Cedars-Sinai in Los Angeles. The MIBI scan uses **SPECT** technology with the pharmaceutical **Sestamibi** tagged with the tracer **Technetium-99**. This scan has been used for cardiac perfusion and parathyroid studies, as well as for breast cancer. The Sestamibi is preferentially taken up by malignant tumors, including myeloma. It can indicate active myeloma disease.

The **FDG PET scan** was also first used for myeloma in the late 1990s. The radio-pharmaceutical **fluorine-18-fluorodeoxyglucose** (or, **FDG**) is used. The FDG is tagged with the tracer fluorine-18, chosen because of its affinity for, and metabolism with, certain biological targets. It gets "trapped" in the target for the duration of the imaging study, allowing the image to be recorded. The image contrasts (which are shown in colors) come about because various biological entities have different uptake characteristics. Some tumors may have higher metabolism rates than normal tissue or may take up the radio-pharmaceutical by a mechanism different than normal tissue. Unlike MIBI, which is taken up in the tissues surrounding the tumor, FDG is associated with the metabolic activity of the tumor itself. It may have prognostic significance where MIBI is negative.

DEXA Scan is a bone density test. The **DEXA** acronym stands for **Dual Energy X-ray Absorptiometry**. It is a relatively new x-ray technique that can see beyond the surface of the bones. Data has been compiled so that results can be expressed in terms of comparative density with respect to others of the same age and sex. The method is most commonly used for osteoporosis. The scan looks at the frontal and side views of the lumbar spine (the side scan is much more accurate), and the neck of the femur. Sometimes the dominant wrist is also used.

More Technical Stuff:

MRI: An interesting concept is the "slice." Depending on the power of the magnet and the desire of the radiologist, the body part can be viewed in slices. Therefore, you can view the head of a femur in slices down to 1.5 mm in thickness and see the entire bone in slices from one side to the other. And you can do that at various angles as well as front to back, side-to-side, or top to bottom. Therefore, you can image the inside of the bone and see veins, marrow, bone matrix, and so forth.

Another part of the MRI is the coil - or, more properly, coils. For some studies you might not know it's there because it's what you're lying on. But for an MRI of the head they will most likely put a helmet-like device on your head. For your cervical spine you will fit your neck into a U-shaped coil; sometimes another part of the coil will fit on the front part of your neck, also. There are also special coils they might use for your shoulders, hips, knees, and so on.

Some MRI studies use contrast, but contrast is not really necessary for myeloma, which can be visualized just fine without it. The contrast for MRI, however, unlike the contrast for x-rays and CT scans, is not especially toxic to the kidneys and doesn't have to be avoided for those with renal impairment.

Limitations seem to be few. Motion can really mess up imaging. Both the respiratory system and the digestive system give real problems when imaging is for something in those areas. Since the MRIs for MMers is almost always skeletal, that's not much of a problem in our cases. Also, metal can cause problems. A port and wedding ring will be quite evident in some views. Harrington rods can cause distortion and make studies of the spine difficult.

The size of the object being sought may be a limitation as well. You might well miss a 2mm lesion if you're doing 5mm slices. Therefore, tiny anomalies can be missed. Also, small aggregations of myeloma in the marrow may not be imaged if there's not enough to change the signal.

Sestamibi or **MIBI**: This is done using SPECT technology. SPECT stands for Single Photon Emission Computed Tomography and it uses one or more gamma cameras heads that detect gamma ray photons that pass through a collimator. The gamma camera is called an Anger camera (named for a person named Anger). Depending on the size of the camera, SPECT can image body areas, organs, or tumors. The SPECT image acquisition protocol is under the control of the nuclear medicine technician. The camera moves around the patient. The resolution and sensitivity is specific to the camera manufacturer. SPECT uses radionuclides such as Technetium-99m and Thalium-201, which are among the long-lived, heavier isotopes used in nuclear medicine scanning.

FDG PET Scan: PET stands for Positron Emission Tomography. It features shorter-lived isotopes for which a cyclotron is required very close by (the radioactive fluorine atom has a half-life of only about 100 minutes). It has higher sensitivity than SPECT, but the cost can be higher.

PET uses a ring of detectors that pick up the photons emitted when positrons are annihilated from the tracer coupled with the radiopharmaceutical that has been transported to and metabolized by the biological target. This means that the purpose of the radiopharmaceutical is to get the radionuclide to the proper target and to be a means by which a biological "function" takes place; the radionuclide is the means by which that function will be "seen" by the detectors and can be "recorded" and analyzed.

Hence, the FDG scan identifies "hot spots", that is, areas of active tumor activity (in our case active myeloma activity). It can actually indicate the level of disease activity, not just a reading of the damage that has occurred".

DEXA Scan: These "partial" scans are sufficient to measure the bone density because they are looking at areas that are frequently the first sites of bone problems. If the density is low in these areas it is probably low everywhere else.

You should get a report that compares your bone density to a statistical norm. If your value is less than one standard deviation below normal, there is no reason for concern. If it's more than that, then your scan not only becomes your baseline scan but diagnostic as well.

Testing – Other

Simple Explanation:

The **Freelite**® Serum Test can be very important for MMers who have no protein marker in their blood. Remember those IgG and IgA things that we've talked about? Well, some people with MM don't have that in their blood and they have either had to track their myeloma by testing their urine, or with bone marrow biopsies (in the case of a small percentage who have no protein in <u>either</u> their blood or urine).

Now, however, there is a new test known as the **Freelite** serum test that can provide a marker for those MMers. For Bence-Jones MMers (people who only have myeloma protein in their urine), it can provide an even more sensitive marker than the 24-hour urine test. For the non-secretory MMers (no protein in either blood <u>or</u> urine), it can provide something they've never had before - a reliable myeloma marker.

What this test does is find and quantify the free light-chains given off by the myeloma cells into the blood. Those light-chains are kappa and lambda. Usually, one or the other of those classifications will be above normal and can be tracked as a marker. Therefore, only another vial of blood needs to be taken when the blood is drawn for the MMer's lab tests.

More Details:

As early as December of 2001 the IMF reported that a new test called the **Freelite**® Serum Test could be used for serum monitoring of free Bence-Jones light-chain levels in cases of Bence-Jones [light-chain only] myeloma. The **Freelite** Serum Test was helpful in identifying 30-40% of all myeloma patients not showing abnormal results by other mechanisms and over 90% of non-secretory patients.

About 1-3% of myeloma patients do not make enough abnormal (monoclonal) protein to be monitored by standard blood and/or urine tests(non-secretory MM). This group of patients is difficult to diagnose and to monitor. The **Freelite** test may also be useful for the monitoring of patients with amyloidosis.

Approximately 70% of the patients formerly thought to have non-secretory myeloma test positive for the presence of free light-chains (Bence-Jones protein) in the blood with this new test. What this means is that the majority of patients with non-secretory myeloma actually have low-level Bence-Jones myeloma that has gone undetected with previous tests. The very sensitive **Freelite** test enables doctors to diagnose those patients and to monitor them with greater accuracy during treatment, remission, and relapse.

The **Freelite** test should not be confused with an older test called "Serum Light Chain Analysis." The older serum light chain test is rarely if ever administered because it is not particularly useful. The new **Freelite** test will have the name "Ultraquant" on the lab report.

However, 30% of non-secretory patients do not produce free light-chains that can be picked up by a **Freelite** test. In such a case, such a person's myeloma may be assessed by more traditional means: full skeletal x-rays as well as by whole body PET

scan, or by wide field MRI screening of the spine, thoracic area, lumbar region, and pelvis.

Although myeloma patients cannot, of course, do away with bone marrow biopsies altogether, the above tests make it possible to monitor non-secretory disease without relying upon a biopsy that can be painful and invasive. Because myeloma tends to "clump" in the bone marrow, a bone marrow biopsy is not always the most reliable way to monitor response to treatment.

More Technical Stuff:

Approximately 15% of all cases of MM are Bence-Jones (light-chain) myeloma. These are not readily detected on serum protein electrophoresis and most will **not** be identified. Between 1% and 3% of MM cases are non-secretory myeloma. Such patients are negative by serum protein electrophoresis and immunofixation on both serum and urine. Consequently, if serum alone is tested, up to 18% of MM patients can be missed.

In order to exclude Bence-Jones myeloma, 24-hour urine specimens should be tested. These samples must be sent to the laboratory, where they are concentrated x100, before being tested by electrophoresis and examined for the presence of free light-chains. Unfortunately, problems of patient compliance with urine collection, and the transportation of large volumes of urine to the laboratory, means that urine samples are not always tested. Even when urine samples are received, many laboratories are not able to identify the presence of Bence-Jones protein. Consequently, Bence-Jones myeloma patients are frequently not diagnosed on first presentation.

Freelite is a new immunodiagnostic assay system permitting, for the first time, the accurate and rapid quantification of free kappa and free lambda light-chain concentrations in serum, urine and cerebrospinal fluid.

Certain diseases can affect the production of free light-chains by the plasma cells in the bone marrow, resulting in abnormal levels in the serum, urine or cerebrospinal fluid. **Freelite** may be used as a screening test to measure the free kappa and free lambda levels, as a tool for monitoring the response to therapy and as a serum marker of progression/relapse.

The finding of Bence-Jones protein in the urine of MGUS patients is associated with an increased risk of malignant evolution to MM; therefore, the serum free light-chain levels in MGUS patients may provide useful prognostic information.

Primary amyloidosis (AL) is characterized by fibrillar deposition of circulating free light-chains in a wide range of organs. In Light Chain Deposition Disease (LCDD) the light chain is deposited largely in the kidneys. In a recent study the rate of detection of serum or urine free light-chains in a group of AL and LCDD patients was significantly improved using the **Freelite** assays over conventional techniques.

In the USA, **Freelite** *is FDA-cleared as an aid in the diagnosis and monitoring of multiple myeloma*. Clearance for AL and LCDD is pending.

Treatment – Overview

Simple Explanation:

Multiple myeloma is an incurable (at this date), but very treatable disease. For all of the years until very recently, there were only a few treatments available to a person with myeloma. As a matter of fact, the "old" treatment of melphalan and prednisone wasn't even introduced until the 1960's. Even as recently as 1994 [when this author was diagnosed], there were only a handful of treatment options. In the ten years since then, many effective treatments have been introduced, including Aredia and Zometa, thalidomide, and Velcade. The art and science of the transplant has been advanced greatly and new, innovative methods of subjecting myeloma cells to lethal radiation have been made available.

When a person is diagnosed with myeloma, he [or she - I will use the masculine pronoun for patient and doctor, but that's only for journalistic convenience] may be in serious physical condition. There may be painful fractures, seriously elevated calcium, kidney damage, depressed red, white and platelet cells, and almost always an excess of protein in either the blood or urine. In such a case, the newly diagnosed MMer must have treatment in order to bring him out of the crisis. Such treatment may also include a strong anti-myeloma agent in order to get the source of those problems under control. Such a patient has no choice but to put himself into the hands of medical people with few or no questions. Time, in such a case, is of the essence.

Other newly diagnosed MMers may be more fortunate. They are the ones who are diagnosed fairly early in the disease progression and they may have few, if any, serious problems besides the myeloma itself. Such people have some breathing room before undertaking treatments that they've not yet had a chance to investigate. Even the patient who is in crisis when diagnosed will have that breathing room once his condition has been stabilized.

There are three stages of treatment during the patient's journey with myeloma: **crisis intervention** (when necessary) in order to stabilize him, **short-term treatment** in order to get the myeloma into remission, and **long-term treatment** in the event of future relapses.

The MMer must have an oncologist he trusts and with whom he feels comfortable. If the oncologist and patient are not a good fit, a change should be considered. Remember, it's your life that's at stake! Every oncologist has a "treatment philosophy" for myeloma. Some are conservative, some aggressive, some have good bedside manner, others want no questions or interference from the patient and caregiver … there are all kinds. You must find someone who fits with you.

Quality of life should be as important an issue as killing myeloma cells. If it is, then don't agree to treatments that will ruin your life along with the myeloma, unless the oncologist can convince you that there is no other choice. There are almost always other options. You must learn to communicate with your oncologist. It doesn't matter whether it's you or your caregiver, a family member or a friend, but somebody must ask the hard questions and make sure that your wishes are considered.

A second opinion is very helpful and might even be considered essential. The best second opinion is from a myeloma specialist. A myeloma specialist is someone who treats only myeloma (not 100+ cancers) and usually does both clinical and research work with myeloma. No ordinary oncologist or hematologist has the time or energy to keep up with the rapid developments in the field of myeloma. The myeloma specialist can give you the assurance that your oncologist in taking you in the right direction. He can also talk one-on-one with your oncologist, giving him the benefit of his specialized insight into your treatment.

Some treatments are not yet approved for general clinical use and are in **clinical trial**. Remember that those trials have both an upside and a downside to them. They are very important for future patients and for the medical people. They may or may not benefit you. They are experimental and their value has yet to be proven. On the upside, they may be free and you may only be able to get that treatment by being in the clinical trial.

Your insurance coverage may override all other considerations when it comes to who treats you and what treatment you may have. Make sure that you understand what coverage you have and what recourse you have for appealing any insurance company decisions.

Lastly, remember that no treatment is without some risk in terms of side effects or even death. Most treatments are toxic or otherwise harmful to all the good cells in your body. You may have to accept that risk, but make sure you understand exactly why you must take that risk and for how long.

More Details:

In past topics we have discussed the concept of "staging" myeloma. In addition to staging, we've also described the types of myeloma, from the benign MGUS to smoldering and indolent myeloma to the overt myeloma to which the stages apply. Those differences often form the basis for treatment by your oncologist. When your oncologists determines that you have, say, Stage II myeloma, he might tell you that it would be best for you to have such-and-such a treatment protocol. There has been much written about the appropriate treatments for various stages of the disease, based on statistics and studies and trials, and that information is what most oncologists will use in determining your treatment. You might think of this method of matching patients to treatment as "doing it by the book."

Statistically speaking, that's a very good method, especially for the medical people. Over time, they will probably do the most good for the most people. Some of the MMers, however, will not fare so well with this method. Since we are not all in the "middle of the statistical curve," some will do very poorly indeed. One of the best methods would be for each of us to be evaluated by the best myeloma minds in the country and have them assess what treatment would work best for us – as individuals. For most of us, however, that's impractical. But it points out the value of an assessment by a myeloma specialist.

Also, a treatment protocol will usually specify dosages and limits of treatment, which have been determined from studies and clinical trials. But just as the treatment choice

itself is <u>statistically</u> effective for a large population of myeloma patients, so too are the dosing and limits <u>statistically</u> derived. Therefore, you as an individual patient might be under-dosed or over-dosed, and you may be treated for too long or too short a time. True, some oncologists may choose to alter those variables, but many will choose not to vary from what they see as proven and defensible – statistically.

Another consideration that goes into your treatment choice is concern for litigation on the part of the physician. We live in times of lawsuits for malpractice and the specter of such suits will cause many physicians to lean toward conservative treatment. Bold and innovative treatments will be seen as risky, unless the patient asks for, or insists on, those treatments. Most patients are not knowledgeable enough about myeloma or treatment to make such requests, at least early on.

Some MMers wish not only to consult with a myeloma specialist but also to have their treatment done at a myeloma center under the direction of the specialist. Those of us who live in the north Texas area have two major centers with myeloma specialists within driving distance: **Arkansas Cancer Research Center** (ACRC) in Little Rock, Arkansas and **M. D. Anderson Cancer Center** in Houston, Texas. Such centers have the advantage of experience with a great number of myeloma patients, cutting-edge technology and, of course, the myeloma specialists.

But it's important to remember that just as individual oncologists have "treatment philosophies," so do myeloma specialists. It's not unusual for an MMer who consults with his oncologist and two specialists to get three different opinions about the best treatment for him. Often, the myeloma specialists are involved in clinical trials in which they would love to place you. Good for them, maybe not so good for you. They may also be involved in studies and technical papers that need MM bodies for completion.

So what is a myeloma patient to do? You or your caregiver, family member, or friend must become educated about myeloma and treatment options. You cannot get answers if you don't know the questions. One of the best ways to do this is to join an active myeloma support group. Listen, learn, ask questions, and become an expert. Another way is to join the IMF's Internet support group, which has well over 1,000 members online from all over the world. You can begin by "lurking" and reading what the experienced members say and then slowly begin posting questions. Even the myeloma specialists cannot match the experiential information that is available through a support group. In a good-sized group, such as the North Texas Myeloma Support Group, there is always at least one person who has had the very treatment that the newly diagnosed patient is considering and can tell that person exactly what his experience was with that treatment.

Treatment – Standard/Frontline

Simple Explanation:

The word **frontline** refers to the first treatment after diagnosis, and the purpose of frontline treatment is to get the patient's myeloma under control and, hopefully, achieve a **plateau**. The word plateau is used to describe a state where the patient is stable. The word **standard** refers to the treatment for myeloma that has been proven by clinical trial and experience to reliably help patients with minimal risk.

For many years, the standard frontline treatment for multiple myeloma was **melphalan** (also known as **Alkeran**) and **prednisone**. That combination is still used, especially for patients who are over 70 years of age. The treatment has, for years, been known as the "**gold standard**" of myeloma treatment. One of the positive aspects of this treatment is that both drugs can be taken as pills.

In more recent years, after other myeloma drugs were found to be effective, several alternatives started to be used by oncologists as frontline treatment. A variety of chemotherapy drug **combinations** became popular, especially a combination called **VAD** (**vincristine**, **Adriamycin**, and **dexamethasone**). A disadvantage of VAD is that it requires the installation of a temporary "port" in the patient's chest, and a "pump" that dispenses the Adriamycin. Although a nurse can infuse the vincristine in the doctor's office, the dexamethasone can be taken in pill form. This combination of drugs does not damage the patient's stem cells and is often prescribed as frontline treatment for patient's for whom a transplant is being considered.

Other chemotherapy combinations feature a drug called **Cytoxan**. Cytoxan is less damaging to a patient's stem cells than melphalan, thus allowing a stem cell transplant in the patient's future. Like melphalan, Cytoxan is also usually taken in pill form. Sometimes, Cytoxan is simply used in place of melphalan along with the prednisone or, in some cases, dexamethasone.

Around the turn of the millennium (2000), oncologists began to use **thalidomide** as frontline treatment, sometimes in combination with other drugs. One of the combinations seen in the late 90's was **Biaxin**, low dose thalidomide and dexamethasone (**BLT-D**), but for the most part, thalidomide was initially used as frontline therapy either by itself or with one of the steroids, prednisone or dexamethasone.

Another change to frontline treatment occurred in the very late 1990's and early 2000's as the **transplant** (**peripheral blood stem cell transplant** [**PBSCT**]) began to achieve statistical results that prompted oncologists to recommend that treatment as frontline therapy. In reputable transplant centers, mortality associated with the procedure had become very, very low. Usually, a chemotherapy that wouldn't damage the stem cells was given prior to the transplant in order to lower the amount of myeloma in the patient's body, so that the procedure would have the best chance to achieve remission.

As new drugs are proven effective, in clinical trials, those drugs are prescribed by oncologists for initial treatment. One very noteworthy, recent (in the early 2000's)

treatment is **Velcade**, which is the first drug specifically approved by the FDA for multiple myeloma.

One other standard treatment is worth mentioning at this point. If the patient has plasmacytomas (myeloma tumors) that have been identified by CT scan, MRI or PET scan, those tumors can sometimes be shrunk or even eliminated with **radiation** treatments. Because most chemotherapy will negatively affect the patient's blood cells, radiation and chemotherapy are usually not done at the same time, as radiation also has that same negative effect on the patient's blood.

More Details:

It's an unfortunate fact of our lives that most of us are in need of treatment when we are diagnosed. Having just been told that we have an incurable cancer and that we need treatment, we're not in a position to discuss the merits of a treatment about which we haven't a clue. We just say, "Okay, when do I start."

Your oncologist is going to start you on a frontline treatment (also called **induction** treatment) that has been found to be statistically successful for a large number of patients. He's going to monitor your progress to make sure the treatment is working, while not damaging you too badly. But all treatments have side effects and some of those have serious implications to your well-being, both now and in the future.

Melphalan (or **Alkeran**, which is a brand name for the generic drug melphalan) and **Cyclophosphamide** (or **Cytoxan**, which is a brand name for the generic drug cyclophosphamide) are what are known as **alkylating agents**. They are very toxic to rapidly dividing cells, which include, of course, cancer cells. But they also damage good cells, causing mutations that can result, in some cases, in other cancers.

The combination chemotherapy called **VAD** is comprised of three drugs. The drug **dexamethasone** (or **Decadron**, which is a brand name for the generic drug dexamethasone) is a powerful **steroid**, which accounts for about 85% of the efficacy of the VAD. The **Adriamycin** (the generic drug name is **doxorubicin**) is the drug that accounts for the rest of the anti-myeloma effect, but it can affect your heart to the extent that you might have problems with your heart in the future. Until VAD came along, Adriamycin had been reserved for use when other drugs stopped working. The **vincristine** is a drug that probably has little or no useful effect on the myeloma cells; yet it causes neuropathy. [Author's note: In spite of the evidence that the dexamethasone alone (which can be taken as pills) has almost as good an effect as the combination that requires a pump, VAD is still widely prescribed by oncologists. But the patient, early in his myeloma journey doesn't know enough to question whether or not that combination is in his or her best interest.]

Another drug that has presented problems for the newly diagnosed MMer is **Thalidomide** (the brand name is **Thalomid**). Early tests with thalidomide called for dosages up to 800 mg/day – a huge dosage. After some of the initial tests showed serious problems with neuropathy, rashes, and DVT (deep vein thrombosis), the protocols dropped to 400 mg/day. Even though some of the myeloma specialists suggested that lower dosages worked well for those patients for whom thalidomide

would work at all, oncologists were still starting patients at 200 mg/day and increasing it to 400 mg. Savvy patients who had been around for a while were able to request (or demand) lower dosages, but the newly diagnosed patient simply took what was given. The result has been a great deal of neuropathy, at least some of which was probably not necessary.

There are no benign treatments, and **Velcade** (the generic drug name is **bortezomib**), which is the first treatment approved specifically for myeloma, is no exception. Quite a list of side effects has been recorded. With limited trial experience in the early 2000's, the ideal dosage is, at this point, still unknown.

Getting a **transplant** (**PBSCT**) early in the MMer's journey has proven effective for some MMer's, but for others it's been a harsh protocol with little relief. The transplant is simply a treatment: it is **high-dose chemotherapy** with **rescue** by the harvested and frozen stem cells from the patient's own body. When used as a frontline treatment, however, the MMer has little knowledge for discussing the wisdom of this or any other treatment. While transplant studies have shown a statistical benefit for patients, there is no way of knowing where a given patient will fall on that statistical curve.

Radiation treatment can be very effective against myeloma tumors (plasmacytomas). All radiation is not the same, however. Some of the more recent technology allows for much better targeting, with less collateral damage to good cells. Even so, radiation has its drawbacks, especially when the targeted tumor is near vital systems. [Author's note: In our group, we have seen some serious long-term problems that resulted from radiation damage to lungs and other systems.] Like all treatment, radiation should be used when necessary, but patient and family must always learn as much as possible about the downside of the treatment.

Many savvy MMers say, "The various treatments available to the MMer are like bullets, and you don't want to fire all of your bullets too early. Then you'd have none left later when you really need them." Remember that myeloma cells become resistant to treatments. Once that happens you can't use that treatment anymore. If you become resistant to enough of the treatments, then you have no more bullets.

Offsetting the above philosophy of treatment, there are oncologists and patients who believe in the "hit it hard and hit it fast" treatment philosophy. The idea is that if you treat the myeloma as early as possible and with the most powerful agents available, then the result will be longer-term remission or plateau.

Treatment – Maintenance

Simple Explanation:

The term **Maintenance** refers to treatment aimed at keeping a patient's myeloma in remission (or plateau). This usually follows a course of treatment that has brought the patient's myeloma under control.

Let me explain maintenance this way. The MMer is like a small boat with a hole in it. The boat is leaking – taking on water. The water coming in became serious enough that a pump had to be used to suck the water out of the boat so that it would stay afloat. After such serious action, the boat is stable, but the hole is still there and water is still trickling in. The MMer no longer needs a pump, but does need <u>something</u> so that the water won't become a serious problem again. So, let's suppose that a small bucket is available and the small amount of water can be scooped up with the bucket and thrown over the side. The boat can remain stable for a long time with very little effort. The bucket is the "maintenance" that's used to make sure that the situation will remain stable.

With myeloma, the "pump" might be melphalan and prednisone, or Cytoxan or VAD or a transplant. The "bucket" might be interferon or low-dose prednisone or a small amount of Cytoxan. The philosophy is what's important: prolong the stable condition as long as possible so that the "pump" will not be needed.

More Details:

It's important to be aware that there are two schools of thought among oncologists about what to do once the myeloma becomes stable. The first group thinks that maintenance is a good idea because it will prolong the plateau period. The second group believes that the best thing to do is let the MMer's body rest and recover from treatment. Since <u>all</u> treatment does at least <u>some</u> harm to the body, the "rest and relaxation" group feels that the better quality of life during maintenance-free plateau is more important than the additional (if any) plateau time gained with maintenance.

To be honest, there is probably no choice that's <u>better</u> than the other, but it may be very important for the patient to have that choice.

More Technical Stuff:

According to the text, "***Multiple Myeloma***," edited by Dr. Brian Durie, a variety of studies were done to determine whether or not maintenance treatment showed any benefit. The conclusion (on page 119) said: "None of these studies therefore indicate any benefit from continuing chemotherapy once stable plateau is reached."

More recently, in the "***Myeloma Management Guidelines: A Consensus Report from the Scientific Advisors of the International Myeloma Foundation - May 2003***," the following conclusions were reached:

- ➢ The role of anti-myeloma maintenance therapy following frontline therapy and/or stem cell transplantion is unclear.
- ➢ Maintenance therapy isn't definitely helpful in any disease setting.
- ➢ The only two maintenance protocols with any benefit were:
  - Low-dose prednisone (50mg every other day), which showed benefit in one study of prolongation of remission from 5 to 14 months and median survival from 26 to 37 months, although there can be side effects that affect quality of life.
  - Alpha interferon has proven to provide only marginal benefit overall. Remission duration was prolonged by 4-7 months and there is no statistical significant impact on overall survival.

The overall recommendations of the Scientific Advisors regarding maintenance therapy were:

- ➢ No strong recommendations can be made for any particular maintenance strategy.
- ➢ The pros and cons of specific maintenance therapy such as prednisone or alpha interferon must be assessed in the individual patient, based upon the level of residual disease and the anticipated potential for renewed disease activity. Steroids in some fashion are the simplest agents for maintenance if some therapy is deemed necessary. Also, alpha interferon can be considered, starting with a trial for tolerance, especially in settings in which benefit has been observed in some studies, including post auto stem cell transplantion, IgA myeloma, and in the setting of concomitant viral infection such as hepatitis. Although no trial data exist, thalidomide with or without steroids is an option for maintenance, especially in high-risk settings. The potential for neuropathy can temper such use.

Treatment – Transplants

Simple Explanation:

For patients with myeloma, the term **transplant** refers to a type of treatment whereby a relatively high dosage of chemotherapy is given to the patient in order to kill as much of the myeloma as is possible. Shortly thereafter, a large volume of a certain kind of cell called **stem cells** (either the patient's own or a donor's stem cells), which were previously collected and stored, are infused back into the patient in order to restart the patient's immune system.

Think of it this way. If your body was to be represented by a large office building and myeloma cells were ping-pong balls, then a typical patient might have every room in the building fairly well filled with ping-pong balls. After conventional chemotherapy, perhaps a half to two thirds of the ping-pong balls in the building might be removed. But after the high-dose chemotherapy used with transplant, only one room, or maybe just a closet in one room, might have ping-pong balls left (we can never get rid of all of them – the disease is still incurable). The problem is, however, that the high-dose chemotherapy not only gets rid of ping-pong balls but it also destroys the patient's immune system. Fortunately, we know how to grow a new one. If we save a whole lot of stem cells ("building block" cells from which all of the immune system cells are derived), we can infuse them after we've done all that damage and grow a new immune system. Those stem cells can come from either the patient or from a **donor**, as long as the donor's blood closely matches the patient's blood.

Therefore, a more accurate description of the term "transplant" would be "**high-dose chemotherapy with stem cell rescue**," because the infused stem cells rescue the patient from the death that would otherwise follow such a high dosage of chemotherapy.

There are several types of transplants for myeloma patients that you might hear about.

Autologous Transplant uses high-dose chemotherapy followed by rescue with either the patient's bone marrow or the patient's peripheral blood stem cells.

Allogeneic Transplant (sometimes called "**Allo Transplant**") also uses the high-dose chemotherapy followed by rescue with either a donor's bone marrow or a donor's stem cells.

Syngeneic Transplant is a special allogeneic transplant that occurs only between **identical twins**. Because the twins immune systems are almost identical, the "graft-versus-host" is minimized and there is the possibility of cure with this transplant.

Mini-Allogeneic Transplant (sometimes called "**Mini-Allo Transplant**") is a recent attempt to find a balancing point between the good of the allogeneic transplant's ability to fight the patient's myeloma and the problem of the graft-versus-host disease. A lower dosage of chemotherapy suppresses the patient's immune system but does not destroy it. Then, the donor stem cells are introduced and grow a donor immune system alongside the patient's immune system.

Stem Cell Collection or **Harvesting** refers to the process where the patient's or donor's stem cells are collected and stored (frozen) for use in an upcoming or future

transplant (rescue). Sometimes, stem cells are collected for later use if and when the patient and his medical team decide that the transplant option is suitable. Enough stem cells may be collected, in separate bags, for multiple transplants.

Second, or **Tandem Transplant** – The **tandem transplant** refers to an approach where the transplant center plans to carry out two transplants in succession, and is an option that should be carried out at centers that specialize in this approach. Experts feel that a **second transplant** in a patient who has responded well with a first transplant and relapsed after two years is a useful and viable option.

More Details:

If the **autologous transplant** uses the patient's bone marrow it would be called a **bone marrow transplant** (**BMT**) and if it uses the patient's own stem cells it would be called a **peripheral blood stem cell transplant** (**PBSCT**). Both would be autologous transplants, however, because both use material saved from the patient, rather than from a donor. Autologous transplants may be done with or without **total body irradiation** (**TBI**), an additional means for trying to kill as much of the myeloma in the body as possible.

The **allogeneic transplant**, like the autologous transplant, can be done with either bone marrow or blood stem cells. The donor is usually a person related to the patient by blood type. A very close blood type relationship is necessary. The allogeneic transplant has two factors in its favor that the autologous does not have: the stem cells will not be contaminated by any residual myeloma cells and the stem cells will create a new immune system in the patient that will recognize the myeloma as an "enemy" and work to kill the myeloma in a way that the original immune system was not able to do. A downside of the allogeneic transplant, however, is that the donor's immune system will also recognize the patient as "enemy" and will fight against the organs and systems in the patient's body unless the donor's immune system is kept under tight control with drugs. That conflict is the dreaded "**graft versus host**" problem.

The **mini-allo transplant** is sometimes called a "**mixed chimera**" or a "**non-myeloablative**" transplant, with the dual immune systems being the two-headed creature meant to keep you alive and fight the myeloma. There is less graft-versus-host, lower transplant-related mortality, and still the benefit of the donor immune system fighting the myeloma.

The high-dose chemotherapy used most of the time is melphalan at 200 mg/meter squared of body mass. Other high-dose treatments are cyclophosphamide (Cytoxan) and Busulfan. Pre-transplant regimens that are used to reduce the myeloma prior to transplant include VAD, dexamethasone, thalidomide/dexamethasone, and Cytoxan.

At the time of this writing, TBI is not recommended by consensus of the scientific advisors of the International Myeloma Foundation.

Stem cell purging is a technique that aims to minimize the residual myeloma that remains in the stem cells harvested prior to an autologous transplant. At the time of this writing, stem cell purging is not recommended by consensus of the scientific advisors of

the International Myeloma Foundation because of the added expense without additional clinical benefit.

At the time of this writing, peripheral blood stem cells are recommended over bone marrow by consensus of the scientific advisors of the International Myeloma Foundation both because of ease of collection and more rapid engraftment.

More Technical Stuff:

The allogeneic transplant, even with a perfectly matched family member donor, is a high-risk procedure. The initial treatment-related morbidity and mortality is high. Even at centers with the greatest experience, and in the best risk settings, initial mortality is at least 20%. In other centers, 20-30% or higher mortality is frequently reported.

In spite of the advantages of the **graft-versus-myeloma** effect and myeloma-free stem cells, long-term cure is rare with allogeneic transplant. Relapse continues at a rate of approximately 7% per year and graft-versus-host disease can require therapy and may impair quality of life.

The graft-versus-myeloma effect can be enhanced with **donor lymphocyte infusions**, which have been clinically beneficial in some cases.

Thus, according to a consensus of the scientific advisors of the International Myeloma Foundation, conventional full-match allogeneic transplantation is rarely recommended as a primary strategy because the risks of transplant-related complications are too high. However, risks are lower in younger patients, especially those with an HLA-matched, CMV-negative, sibling donor of the same gender.

The consensus of the scientific advisors of the International Myeloma Foundation find that the mini-allogeneic transplant is a promising new approach, but that it requires further evaluation as part of well-planned clinical trials.