Myeloma–Expert Information About Diagnosis and Treatment

Asher A. Chanan-Khan, MD
September 27, 2011

Slide 1: Myeloma–Expert Information About Diagnosis and Treatment

OPERATOR:
Hello, everyone, and welcome to Myeloma–Expert Information About Diagnosis and Treatment. It is my pleasure to introduce your moderator, Lauren Berger, of The Leukemia & Lymphoma Society.

Slide 2: Welcome and Introduction

LAUREN BERGER:
Thank you. Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and a special thank you to Dr. Asher Chanan-Khan for sharing his time and expertise with us today.

We have over 1,700 people participating in this program from across the United States and international participants from Canada, Greece, India and Peru.

We'd like to acknowledge and thank Celgene Corporation, Millennium Pharmaceuticals and Onyx Pharmaceuticals for their grants to support today's program.

Slide 3: Asher A. Chanan-Khan, MD

I am now so pleased to introduce Dr. Asher Chanan-Khan, Chair of Hematology and Oncology at Mayo Clinic in Jacksonville, Florida.

Dr. Chanan-Khan, we're so privileged to have you with us today and I'll now turn the program over to you.

DR. ASHER CHANAN-KHAN:
Thank you so much, Lauren. It's a delight to be here and to be able to talk to so many people, the marvels of modern technology!

As a lot of you have known me at Buffalo for some time, I recently have joined Mayo Clinic in Florida and it has been a wonderful transition, with Mayo Clinic having a very, very long history of expertise in myeloma and plasma cell cancers.

Slide 4: Introduction to Multiple Myeloma

As most of you know, that today's topic, we're going to be talking about multiple myeloma, which is a disease unfortunately that remains incurable, but certainly it has come a long way over the last decade.

Multiple treatments have come forward over the last ten years due to increased understanding of the biology of the disease. Most encouraging is the fact that patients are living longer with this disorder, as the survival is improving in a positive manner and people are living longer, we are obligated to have a very strong focus on two important things:

One, to continue to fight against myeloma, continue to develop new therapies and come up with new options until the cure is in our hand. And the second important fact is that during this quest, you want to keep an eye on the ball and provide excellent care and supportive care to patients as they go through multiple treatments and multiple regimens.

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A lot of patients who have followed me and other myeloma experts know that there are regimens after regimens that we now employ to take care of this disease.

Now, trying to understand myeloma and bringing it into a nutshell in about 45 to 50 minutes has become difficult, but I'll try to go forward and try to section out the talk in about five topics and go through them so that I can address almost all aspects of myeloma and then be able to talk about where new therapies are and answer some of the questions that come to the audience's mind.

Slide 5: Pathogenesis

Multiple myeloma is a plasma cell cancer and plasma cells are an important component of the body. Their inherent job or their job dedicated to them normally has been to develop the immune system. There are two parts of the immune system. One is the cellular part, the other is the part that makes immune proteins. Plasma cells' normal job in the body is to make proteins against various culprits that invade our body. So think about the vaccine, when children get it or when we get it, the flu vaccine or something like that, these vaccines can contain antigens or proteins that are directly taken to cells like plasma cells, where they have a factory going on, making immune proteins. And these immune proteins then get back into the circulation in blood and able to target the bacterial or the virus that invades our body.

When plasma cells become cancerous, it turns into plasma cell cancer disorder, and there's a spectrum of these. The most common is multiple myeloma and we will focus our attention towards just multiple myeloma, although there are several varieties of plasma cell cancers that we can talk about.

If you look at this particular figure, this will tell you a plasma cell over here at the top and how a normal cell becomes a normal plasma cell versus a normal cell turns into a malignant plasma cell.

And the multiple myeloma spectrum is described in this particular figure. There are, on the right hand extreme, is the myeloma cell cell line and on the left is the MGUS, which is monoclonal gammopathy of unknown significance. This (MGUS) is just a benign, but pre-malignant condition where no treatment is necessary and a malignant plasma cell that was detected in the body remains so. Although there does remain a risk that this particular malignant cell may develop, at a later time, into full-blown disease. Think of it as a sleeper cell that we often deal with or hear about on the news in terms of terrorists. And clearly the myeloma cell is no friend to us.

As the disease grows further or the cancerous cell becomes a little bit more aggressive, we call the term smoldering myeloma. And then, even at the stage of smoldering myeloma, we usually try not to do anything until the disease becomes a multiple myeloma, involving various sites in the bone marrow, causing a lot of bone damage and so forth.

A more aggressive stage is extramedullary myeloma, where the disease that was initially growing in the bone marrow no longer finds its interest or support necessary in the marrow and can now go outside the marrow and develop wherever it wants to go. Now, you can understand that evading the dependency on marrow cells is not a good phenomenon. And this extramedullary or multiple tumors anywhere in the body is a very troublesome disease and usually present in an aggressive form of disease.

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The therapy for extramedullary myeloma coming out of multiple myeloma are more or less lumped up as myeloma. And then the myeloma cells present a phase of this cancer cell, where the disease is completely autologous, develops in itself rapidly, divides even in a Petri dish, and these are the tools that we use to identify biology and new therapies and so forth.

Multiple myeloma or intramedullary, where the disease is inside the bone marrow, is one of the most common forms of disease that we usually see in the clinic when they require therapy. Other forms, smoldering and MGUS, are usually seen less frequently, just because less monitoring is necessary for them.

Slide 6: Epidemiology of Multiple Myeloma

Myeloma is fortunately not that common a disease, it's only about 20,000 or so cases that are detected in the United States. Although about 11,000 or so of these patients do die from this disease, presenting a very aggressive kind of blood cancer.

There is some information that has been available over the last several decades in terms of what kind of patients are – it seems to be a little bit more common in Afro-American folks, it's a little bit more common in men. The usual age at which this disease is diagnosed is around 70 years or so in general. And 75% of the men are older than the age of 70 years and 79% of the women are over the age of 70. So it happens a little later in life, although I have had patients in their 30s and in 40s where myeloma has been detected, and clearly baffles our mind in terms of the etiology of disease.

Nobody knows exactly what are the real culprits that result in development of multiple myeloma. But there are hypotheses including viruses and chronic exposure to radiation or chronic infections and so forth, have been talked about. Benzene has been identified as one of the risk factors and so forth. But truly we don't necessarily know what is the exact cause of this disease.

Slide 7: Major Symptoms at Diagnosis

Major symptoms that people need to be aware of, (and I understand a lot of people on the line today are caregivers as well as those who may know somebody or may have multiple myeloma), is involvement of the bones resulting in bone pain almost is seen in over half the patients. Fatigue is a major problem with this disease because it causes a lot of anemia. Weight loss is seen in a quarter of patients. And then nerve damage, very rarely resulting in neuropathy and so forth, can also be seen in these patients.

Sometimes patients will have no symptoms and will be picked up completely asymptomatic on routine medical evaluation and they will then be worked up to have found multiple myeloma. And this is very important and this highlights an important feature of regular medical evaluation.

There are no tests that should be routinely done to rule out this disease because of its rarity and nobody has ever shown that that would be of any benefit. So just a physical examination should be good enough in the current time.

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Slide 8: Clinical Manifestations

Clinically patients can have very high calcium levels because of bone resorption, kidney dysfunction or anemia or bone lesions just can be. And this particular group of symptoms is called CRAB symptoms. When these symptoms happen, repeated infections or bone pain or bone lesions or kidney insufficiency, not necessarily always kidney failure, this results in a particular kind of a syndrome that we then would want to treat these patients.

Slide 9: Clinical Presentation

Now if you look at the next slide you will see how actually the myeloma cell looks like in terms of when we do a bone marrow biopsy, several of these cells are round, blue color and shape, and these cells often produce a lot of immunoglobulin. In the second picture on the right side you will see bones that show a lot of lesions in them and this gives you an idea how when the calcium is eroded out of the bone, how the bones look. And the bones can be really, really soft and very fragile. And clearly this is a reason that caution should be taken by myeloma patients not to do physical activity that can actually have too much stress. Now that doesn't necessarily mean that no exercise or healthy things should be done, it only means that you should be aware of how your bones are before you indulge in heavy exercise or sports that are associated with trauma to the bones.

Bones remain a very important concern to myeloma experts as fractures of the bone are associated with significant pain and comorbidities that can limit and compromise quality of life.

And rarely does abnormal protein called amyloids gets deposited and that's the bottom picture that shows a man sticking out his tongue. Now actually this person is not sticking out a tongue, the tongue is so huge that it cannot be kept inside the mouth and it's actually protruding because of abnormal protein. And this particular protein can be deposited in any part of the body, whether it be heart, lung or any of the arteries or so forth. And this results in a very abnormal function of these organs, causing compromise and often death. The only way to stop this particular feature is to treat multiple myeloma.

And lastly, but not the least, is a very important complication and that's infection. As you may recall that I mentioned this is a cancer of the immune system and therefore compromise of the immune system exists in myeloma patients. In fact, the reports continue to be the same, that most important cause of death in myeloma patients remains infection. And this is one of the reasons that active treatment should be sought when fever or other sign/symptoms of infections are happening in these patients.

Slide 10: Diagnosis and Staging Myeloma

In terms of staging and diagnosis, one of the most important things that I would warn the audience here to learn in this second section is to know about M protein. Not only does that allow you to understand how to follow or diagnose your disease, but how to monitor response to therapy.

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Slide 11: Serum Protein Electrophoresis

On the left hand side you will see a normal protein electrophoresis of the blood, which basically is a blood or serum samples taken from the blood, put in a machine and electricity passes through it, and then this protein that carries charge, usually a negative charge, will proceed in one direction and based on their weight they will migrate slowly or faster. So albumin is fast, as you can see on the far left side, and gammoglobulins are slow and so they're huger, larger proteins and they are on the right hand on the first figure. But this pattern is very, very normal, on the left side.

On the other hand, in myeloma patient, where there's a lot of one cell, plasma cell producing one kind of protein, you will see a peak. That peak is identified over here in the far right corner. And this abnormal peak is called the M protein or M spike. You'll often hear your physician referring to your M spike or M protein is increasing and that basically implies that the cell that's cancerous is growing more in the body. And that is often a sign of disease progression or relapse and so forth.

Slide 12: Monoclonal Proteins in Multiple Myeloma

Almost 80 to 90% of the patients will produce some kind of an M protein and therefore you should know about this and you should know these numbers when you see your physician.

There are different kinds of M proteins, so there's no need to get alarmed because there are different kinds of proteins produced by the plasma cells normally. These can be IgG type, M type, A type, B type and so forth. Typically in my experience IgA seems to be a little bit more aggressive myeloma than IgG, but fortunately in this particular situation IgG seems to be a much more common disease than IgA.

If you do immunofixation test, which is a much more sensitive version of this particular test that I just showed you, over 90% will be able to have detection of some kind of a protein in their blood. Now this protein can also come in the urine and the test is more or less the same, but done in the urine collected, and that is what will develop, a patient is a urinary secretor, a blood secretor or both. Patients who are producing urine secretion tend to have a higher chance of kidney insufficiency.

One of the things to remember and probably somebody will ask that, is the light chain. There are different parts of the immunoglobulin produced by the plasma cell and one part is called a very small protein, which is called a light chain. And sometimes these light chains are detected by themselves, they're not a huge protein. And these light chains are like spikes that can entangle inside the tubules of the kidney and cause kidney damage. Very important to know about that and very important to deal with them from a clinical perspective because of very high propensity to develop kidney failure.

Slide 13: Initial Diagnostic Evaluation

Initial diagnostic work-up is listed here. I will not go on all the tests here because you will have access to them. Usually blood counts and kidney function tests are important for diagnosis as well as X-rays and MRIs sometimes and I'll show you some pictures of these. And these tests will help us diagnose whether an abnormal protein is present in the blood or the urine, if it is causing anemia, kidney failure or so forth, or if there are lesions present in the skeleton system or there are, using a bone MRI or PET scan, you will be able to detect if there is more lesions or more disease present.

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Slide 14: OS according to the Presence of PET Criteria

Now this particular figure that you see is a PET scan of a patient that shows a lot of "hot spots". Now PET scan is a radioisotope type test, which is taken up by the growing cancer cells, and as you can see there's a lot of lesions in the body. And after treatment, in this far right corner, the lesions have cleared up with treatment.

The group at Arkansas, have demonstrated that the number of lesions on PET scan correlate with the number of the disease outcome in terms of survival and so forth. So this is becoming an important tool, but not everybody should need to have a PET scan. I usually do a PET for patients where I suspect extramedullary or outside the bone marrow myeloma. And remember there's no end in doing testing and after a while the testing becomes cumbersome. We are fortunate to say nowadays that the survival has increased to anywhere from seven to ten years, on an average about seven or eight years, compared to a decade ago when we were talking about two to three years. And so for patients who are living that long, going through extensive testing again and again and again, month after month, can be very, very tedious.

Slide 15: Criteria for Diagnosis of Myeloma

The criteria to diagnose myeloma versus a less aggressive form, smoldering or MGUS, is listed here. And basically it depends upon the quantity of cells. If there are more than 10% plasma cells, listed as PCs here, or a spike that's really high M spike, as I showed you, or there are symptoms of anemia, bone lesions or calcium that is high, that is associated or that's diagnostic criteria for multiple myeloma.

Slide 16: International Staging System

In terms of bone marrow MRI, it's a relatively new thing and I'll show you that. But before that you can see the staging system. The staging system is typically done on the blood test that is beta-2 microglobulin and albumin. Very simple, stage 1, 2 and 3. Of course, the outcome for patients with stage 3 disease seems to be less favorable than those who are limited stage. But there are multiple other factors, as I mentioned, that contribute to the outcome.

Slide 17: Magnetic resonance Imaging of MM

Another way to stage disease that we have found over the last several years is to do MRI. And patients who have limited stage disease will have a bone marrow MRI like that on the left side, very sparse lesions seen on the bone marrow MRI. And the bone marrow MRI seems to be a much more sensitive tool for me because it picks up the whole marrow in the spine, which is usually the site of this particular disease. By doing MRI of the thoracic number and iliac bones, bone marrow, we're able to actually determine how much of the bone, adult bone marrow may be involved. And the extent of involvement actually does correlate with patient outcome.

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Slide 18: Magnetic Resonance Imaging of MM (Cont.)
And this particular figure you will see that complete effacement of bone marrow happens in stage 3 or 4 of patients as noted in this particular slide. On the left hand side there's still some patchy white areas, where on the right hand side there's a complete color that's gone completely gray, representing very packed and aggressively growing cells in the bone marrow.

And so I rely a lot on bone marrow MRI. And it is also nicer to do that instead of bone marrow biopsy, which only looks at a very small spot, versus MRI that looks at the whole big area.

Slide 19: Not all Myeloma are the same! Prognostic Factors
In section 3 we'll talk about – or section 3 will talk about prognostic factors a little bit.

Slide 20: Major Adverse Prognostic Factors
And prognostic factors basically talks about what we know a particular patient may have. And are all myelomas the same or are there inherent differences in myeloma that should be kept in mind when treating patients. And there are, there are some tests done, that is called cytogenetic testing, there are plasma cell labeling index. I have not done plasma cell labeling index, but I know that my new institute, Mayo Clinic, has done extensive work and has reported that high plasma cell index basically defines high or rapid plasma cell division, and aggressive disease.

Molecular genetics, so testing various chromosomes such as lesions in the chromosome 4, 14 or 16, and especially 17 (fortunately rarely seen), is very aggressive disease.

Now there's a lot of controversy about how to treat aggressive disease versus how to treat the normal or not so aggressive disease. And we can talk about that a little bit in the question and answer session.

High LDH and plasmablastic morphology or low albumin are all identified as factors that should be kept in mind. And I'm not going into all of them because you have access to these slides and you can use them to induce a conversation with your provider, to ask them about your prognostic factors.

Usually these prognostic factors will tell you what kind of a beast you are dealing with or your patient is dealing with in terms of treating. And that could in the future help us, strategizing various therapies and so forth.

Slide 21: Treatment Approaches
We'll now move on to therapeutic strategy. Now treatment of multiple myeloma, as I mentioned earlier, is usually embarked upon when symptoms start to happen or where you will anticipate end-organ damage. What I mean by end-organ damage is fractures or large lesions in the bones or kidney failure or impending kidney failure, severe anemia and so forth. Things that we know are factors that we know are compromising the overall outcome of patients or causing symptoms to patients, warrant treatment.

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And there are various approaches to treatment, so I have picked out the most generally acceptable treatment approach. There are philosophical differences in terms of what is the best approach to treat a myeloma patient, among various myeloma experts. And what I have to say about that or for patients especially on the line, a good debate is actually a good thing for us. Different minds, different techniques to tackle disease are important because that will result in much more robust responses for us in the future than if everybody was trying to do the same thing and not identifying novel new ways to tackle disease.

Slide 22: Initial Approach to Treatment of MM

But by and large most myeloma experts will agree with this particular strategy, which is to once a myeloma is diagnosed, based on age, performance status, organ function and all these parameters of somewhat healthy body that can tolerate aggressive therapy, patients are usually divided into those that can undergo transplant or no transplant. And in this particular case we're talking about bone marrow transplant, also known as stem cell transplant.

For those candidates who are transplant eligible or stem cell transplant eligible, and usually eligibility depends on tolerability. Remember in transplant the whole process, to give very high doses of chemotherapy, and then rescue the patient while giving his or her own transplant.

There are two different major kinds of transplants and one is called allogeneic transplant, meaning somebody else's stem cells are taken, matched by the patient, and then given to patient after chemotherapy. Or the most commonly used transplant is called autologous or your own transplant, where your own stem cells are collected at the time of remission, then a very big dose of chemotherapy called melphalan is given, and then stem cells are poured back.

By and large research has shown autologous or your own stem cells are favorable, that the regimen that has proven to be relatively safer and tolerable, and has resulted in survival outcome benefit to patients. Allogeneic transplant is a far more different thing, a very cumbersome process, a very high chance of death in the first hundred days of treatment, and therefore it has remained experimental to date.

If you look at this particular strategy, you'll see that on the left side transplant candidate goes through four steps in my mind. And step one is induction treatment; two, stem cell harvesting, collecting the stem cells; three is stem cell transplant, where you get the chemotherapy and get the stem cells back; and four is maintenance therapy. These are the four important steps that are recognized and more or less accepted by most myeloma experts.

If patients are transplant ineligible, for whatever reason, they usually get step one, which is an induction, and then they may or may not get maintenance treatment. And these are the two major differences in terms of treatment approach.

There's a lot of controversy about maintenance therapy, what to use, and we'll get into that a little bit later.

What I want to share with you is not every single regimen or clinical trial information that is available, because you can all access it (this information), but a basic understanding of what goes through my mind and hopefully most myeloma experts' mind in terms of when we start going to treat a myeloma patient.

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Slide 23: "Tools" to Treat Myeloma

The first important thing to remember in step one, which is induction treatment, induction means the first regimen you will get, to get the myeloma under control and in remission.

Two, know your tools well. These are the tools that a myeloma expert has and the tools that I've identified in this particular slide are those that are approved and does not require a clinical trial. They're available, they're FDA approved and anybody can prescribe it in and around this country as well as internationally. So steroids and melphalan and cyclophosphamide and novel molecules like bortezomib and doxorubicin and thalidomide and lenalidomide . And these are all available for us, these are the agents, the drugs that I think about when I'm not thinking about a clinical trial.

And then there are multiple clinical trials that have investigated them alone or in combination with each other. And when you combine them there are various regimens that have come across, listed on the right side. Although there are a ton of them, I've only listed a few.

As you can see, patients can either get one drug, they can get a doublet or two drug combination, or they can get a three drug combination or a triplet. People have combined four drugs also, but to date I think a regimen containing three drugs is able to deliver 90-plus percent response rate.

The question, the philosophical question that we tackle, is does everybody need that aggressive approach. If somebody has stage 1 disease (very limited disease), good performance status, no major symptoms, but need therapy, do we need to kill their disease and waste all the options up front or should we start with one or two drugs and see how we do at the time and they need more therapy, we can go further with larger or more drug combinations. And these questions remain unanswered.

Some myeloma experts like to use three drugs in every single patient or four drugs in every single patient because they want to get to remission faster. Others will argue that we should look at each patient individually and pick out single, double or triple combination, depending on what kind of a beast we are dealing with. And that allows us to save the other agents for a later day when the disease will relapse.

One of the things that patients online and caregivers need to remember, this disease is all about strategy now. It's a long haul, several years of therapy, in and out, several remission and several relapses patients will suffer. And that is just the truth. When you go through this unfortunate roller-coaster, you will see there will be times where we are high, when the remission is there, and times that our spirits we will be low, when relapses happen. The trick is that we should always have something in our back pocket to be able to get the disease into remission. And believe me, there are multiple regimens and treatments now that have – many years ago, when I started, I was afraid of myeloma because I knew after two years I will lose a lot of friends. But now I know that if I strategize fairly intelligently, look at the disease carefully, and use my tools carefully, I'll be able to deliver long-term remissions and long-term survival for these patients.

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Slide 24 Know Your Tools
Therefore I say know your tools better.

The two most important drugs that are used, or class of drugs I would say, that are used, I'll share with you how they work.

A lot of presentations will talk about numbers and remission rates. What I would like to share with you today, how the drug works. And that's important in my mind because then I know how to use that tool.

So proteasome inhibitors and IMiDs what we will talk about in a few slides to see how they work and when they should be combined, how our clinicians think. It's just not an alphabet soup in my head, that we should just give this regimen and that regimen and it's done with. No. We should know when a drug and how a drug works and when we should use it.

Slide 25: Targeting the Proteasome
Now proteasome is an important part of every cell in our body, normal or abnormal. Proteasome is like a garbage disposal. Its function is to take about all redundant proteins, chop them into small pieces and get rid of them. This is normal protein metabolism in our body. Think of it as the digestive system of the cell. When you eat, the food that we eat is broken up into small chunks so that it can be absorbed. And here the cell, what it does, has a long digestive system, that proteins are pulled in, and they are broken down by the cylinder into smaller chunks and can be used again.

Slide 26: Bortezomib and Proteasome Inhibition
If you stop this proteasome cylinder or garbage disposal – and this was done by this particular drug, on the right side you will see on beta-5, there's a drug named bortezomib. When this proteasome was stopped by this particular drug in preclinical or laboratory testing, it was found that myeloma cells were very, very sensitive to this and they immediately died. And the reason is myeloma cells all, their job depends upon protein production and protein metabolism. They produce a lot of proteins. That's what immunoglobulins are. So when you shut off their major function, they become very sensitive to this kind of treatment. So proteasome is an important ingredient in their day to day life. And when we shut it off these cells die.

In fact, proteasome inhibitor is one of the most potent single agent drugs. This is a drug that you can give alone and expect at least 10% of the patients to go into complete remission, don't need a second drug. But if we add a second drug, 90% will go into remission.

Slide 27: Bortezomib Inhibition of NF- B Activation and Signaling
But it does work in various ways. So this is a much more complicated figure and it basically shows how the signal coming from outside that gives survival advantages to myeloma cells can be interrupted by this particular drug. And when this happens, the internal mechanism or machinery of the cancer cell stops. Now not all cancer cells respond so sensitively to this particular drug. Myeloma seems to be one of the very few. And therefore this drug was first approved in this particular disease because it made a major impact in myeloma patients.

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Slide 28: Proteasome Inhibitor-Based Therapies in Transplantation
If you look at this particular slide it'll just give you some numbers. If you use bortezomib alone you'll see about 60% of the patients may respond in some way, but by and large about 40% of patients have a major response to it. If you combine it with steroids the number jumps up and I'm reading the left, the second left column, the numbers jump up to 80 or 90%. And if you go all the way down and combine these drugs with a third drug, called ImiD, which we'll discuss in the next slide, thalidomide or for that matter lenalidomide, 90 to 100% of the patients will respond. That means independent of what kind of disease they have, whether they have aggressive cytogenetics, low albumin, high albumin, IgA, IgG, whatever they are, they will respond if you put three drugs together.

However, it can be also be interpreted that half of the patients will respond or more than half will respond without the third ingredient.

So all of this is important information and I would like to think that there's no one shoe that fits everyone.

Slide 29: Know your tools
The second important class of drugs that we rely on are called IMiDs and these are immunomodulatory drugs. These include two important drugs, thalidomide and lenalidomide. Both drugs work in some mysterious ways, but there are things that we know about these drugs.

Slide 30: Stromal Cell/Tumor Cell/T-Cell/NK Cell Drawing
One of the most important things that these drugs work is by stimulating the immune system. While if you give either of these drugs, thalidomide or lenalidomide, also known as Revlimid®, to myeloma cells, it causes changes internally in the cancer cell itself. But more importantly, concurrently, it stimulates cells called T cells or NK cells.

Activation of immune system, while at the same time weakening the tumor cells, is a very potent way of treating cancer in general. And myeloma has been very sensitive to both thalidomide and lenalidomide. Several trials have shown that if you combine these drugs with other therapies, that patients, up to 90%, will go into remission.

Slide 31: IMiD – Directed Therapies in Transplantation
If you look at this particular slide, thalidomide and dexamethasone combined today, reported many years ago, give 60% chance of response. While if you add lenalidomide to steroids you get about 90% chance of patients benefitting from this.

There are concerns and there are some intellectual ideas that are now being investigated, do we really need steroids and do we really need higher doses of steroids? And the current practice is to use low doses of steroids and Revlimid at the standard dose to induce remission and that will result in about 80% or so of patients responding. And the reason, I think personally, that low doses of steroids are better, because the steroids actually suppress the immune system. So if you are using a drug that is supposed to activate the immune system against tumor cells while you are mixing it with a drug that is supposed to suppress the

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immune system, that doesn't necessarily make sense. But if you use it at a lower dose, then the optimal responses may be achieved. In fact, several of my patients have taken Revlimid by itself in the first cycle and seeing that they would go into remission very fast, and many will not go, and then you will add steroids. But as I mentioned, the current standard of care, tested by various clinical trials, is to use Revlimid and steroids together, but steroids at a lower dose.

Slide 32: Controversial Decisions
So this leads us to controversies that exist in the treatment of myeloma. And these controversies are good. Although from a patient's perspective, it can be puzzling and it can be mind-boggling, why everybody does not agree. But when we talk about an incurable cancer it is better for us that we disagree because then we will investigate different ideas to tackle the problem.

There is a disease called hairy cell leukemia. Hairy cell leukemia is a leukemia or a blood cancer where every single person agrees in the world that you give five days of chemotherapy only and 95 plus percent of the patients are cured forever. You don't have to do it every month, you don't have to do it every six months, nothing. Five straight days of treatment, one chemical, and these patients are cured. Now that's what we would love to have for myeloma. But unless we get to that kind of a gold standard where we just give one treatment or one regimen for a few times or few times and it cures, we're obligated to test different strategies and therefore controversies exist.

The choice of first treatment, some people will use Revlimid and dexamethasone as full doses or low doses of steroids, some people will use thalidomide and dexamethasone. Others will rely on three drug combinations. Some would even test one drug. There are several combinations being tested. Do not feel that there is an anarchy and nobody knows what's happening.

From a patient perspective, if you are assured over 70 to 80% remission rate with a particular therapy, especially if your disease is aggressive and is expected to have end-organ damage, then this is – any of those regimens will be fine.

Most importantly, enroll in a clinical trial. Read about what the science in that clinical trial is. And see if you feel comfortable with that.

The duration of therapy, transplant one or two, sequence of transplant, early transplant versus late transplant, how many transplants should be done, role of maintenance therapy, should we be giving patients something endlessly forever, and these are all questions that do not have a correct answer, a right answer. There are answers, there are some answers, but they have generated more questions.

There are several clinical trials addressing these issues.

Slide 33: New Treatment Options Have Improved OS in MM
But at the end of the treatment section you will see this particular slide, which is what brings me hope. New treatments have clearly made an impact. The top graph is the latest graph over the last ten years or so. And it has shown for the first time that patients have started to have a better survival. And this is for younger patients only. Older patients tend to have less favorable outcome, even at this time where we have lots of treatment to offer.

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DR. ASHER CHANAN-KHAN:

Slide 34: Step 2: Stem Cell Harvest
Now the step two part is stem cell harvest. We talked about induction therapy. And the step two was if you are a stem cell transplant candidate, then you need to get a stem cell collected. After patients have gotten into a remission, stem cell collection is a very simple procedure. For those who want to know, there's a lot of literature on the LLS website to read about it. And it's not a cumbersome or a tough process.

Slide 35: Step 3: Stem Cell Transplant
Step three is the stem cell transplant process that patient goes through. For those patients who choose or those physicians who rely on this particular strategy, basically it entails patients getting admitted and some centers also do it completely outpatient. The chance of a successful outcome in terms of completing the process, procedure, is over 95%. The chance of death is very, very low and 3 or 4% overall. And in experienced centers this is even lower.

The important thing is not the procedure itself. The important question that people have to ask is how good it is and did it do the trick for you or not.

Slide 36: Autologous Stem Cell Transplantation
But what is the procedure? Patients get admitted, they get a very high dose of chemotherapy called melphalan, and they wait for a few days and then they get their stem cells back. And the stem cells will take a few days to grow on your bone marrow and repopulate and reform a new bone marrow in your system. This particular approach – so the critical thing in this particular transplant approach is melphalan. That's what's going to kill myeloma, not the stem cells. So that's the critical thing that one relies on. And research has shown again and again that given patients going through autologous stem cell transplant – we're talking about autologous, your own – has resulted in survival advantage and that can range, in various studies, from ten months to a little over a year in the prior studies, and newer studies last – some of the data, because of the way the trials are designed in terms of maintenance and so forth, the questions asked are different. But the original trials that looked at transplant and no transplant clearly showed a survival benefit for patients up to a year if they were given chemotherapy or if they were given transplant. Now granted, at that time the chemotherapy that were used to address this question are the chemotherapy that we no longer use. And the therapies are far more effective now that we are using.

Slide 37: Stem Cell Transplantation
So there are investigators now that are trying to answer this question again.

Slide 38: Transplantation vs Conventional Chemotherapy
Is transplant important still with such progress in new therapies or should we just stop doing it or should we just hold it for patients who are really aggressive? And when should we do it? Do we need to do it right away or can we do it at a later time?

So these questions remain unanswered.

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Slide 39: The Importance of CR in Treatment of Multiple Myeloma
There is importance given to complete remission. CR is complete remission. What does it mean? Do you need to achieve complete remission, should you be dejected after induction therapy or transplant therapy, there is no complete remission? What is complete remission?

Complete remission, that if I do a test on a patient, then everything that I will – that will pick up the myeloma, is no longer there. And everything is absent, everything is normal. No M protein in the urine or blood and plasma cells in the bone marrow are in the normal range of around 4% and so forth. And there are no new lesions and so forth.

There are three different kinds of complete remissions talked about by myeloma experts. And we won't go into those details. Primarily there are categories of how good a remission is. Think of it as silver card, gold card and platinum card. So complete IFE (immunofixation) negative remission with normal light chain balance is considered to be the best approach that your immune system has also come back.

Now various people have reported that if complete remission is achieved, these patients tend to do better in overall outcome versus other patients that never achieve, and that's intuitive.

Slide 40: Meta-Analysis: Max Response to HDT and OS
If you go through vigorous treatment and you do not achieve a complete remission, there is clearly some cells that are very tough to deal with and what are the best approaches. And since they're already sitting there, their chances of relapses early and they will progress – those patients are expected to progress faster. So this isn't a sign that you can rely.

On the other hand, there is data to suggest that some people will reach a smoldering phase again and their disease will remain more or less stable for a long period of time.

Slide 41: Novel Agents in MM: Response Rates/Long-Term Outcomes
I suggest to my patients once you have completed a particular treatment and you're not benefitting any more, stop, hold and wait. And see how your disease responds. Sometimes the disease will remain quiescent or stable for a very long period of time. Other times it will take off.

Slide 42: Pase III: Apex Trial: OS
Since we have so many tools we know that we can always hit it with another regimen and get into a remission.

Slide 43: Step 4: Role of Maintenance Therapy
Now in the interest of time I'm going to go a little faster.

Step four is maintenance therapy. This is not a new concept. What is maintenance therapy?

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Slide 44: Again, Know Your Tools
Maintenance therapy is basically what happens after transplant or induction therapy. Step one. And whether it be transplant or non-transplant approaches, should these patients be given long-term treatment indefinitely until the disease starts to grow back. And this is an old concept. In the past steroids were used.

Slide 45: Post-ASCT Maintenance
An ideal agent that causes, that can be used for maintenance therapy in my mind is that which causes lower incidence of toxicity, has a low cost, is least cumbersome to the patient, requires least monitoring, and a drug that is effective and can actually improve survival.

So there are several trials ongoing and some reported – these are trials of thalidomide that were used in the past, and showed that there is a progression-free survival benefit. If you look at the right hand, and please go back and review these slides in detail so you are much more informed, that I am unable to cover in this talk, if you see progression-free survival, the numbers are 56 versus 44 months and clearly in the first-line, reported by Dr. Barlogie, seems to be that thalidomide maintenance seems to have a major impact in terms of progression-free survival benefit. Somebody taking thalidomide versus those who not.

Slide 46: Maintenance After Transplantation
On the other hand, overall survival, it has not changed. And this remains so in most of the cases except the last study, which was reported by Dr. Spencer.

Slide 47: CALGB 100104: Lenalidomide vs Placebo Maintenance Following ASCT
In the most recent time there are newer trials that are going on and I will go on to that particular trial. And these are two trials, one in Europe and one in United States. Have been completed and waiting maturity. But already reports are starting to show that if you give Revlimid at 10 milligrams, this is less than half the standard dose, that there seems to be an advantage in progression-free survival.

Slide 48: CALGB 100104: Efficacy Analysis
Overall survival still remains to be conclusively reported. And there's an important difference that people need to understand about this. Overall survival means at the end of the day that a person with myeloma live longer or not. Progression-free survival means that is how long the disease was controlled. And it seems like the CALBG trials, seems to have at least an inclination that there may be a survival advantage if Revlimid is given for a long term.

Slide 49: IFM 2005-02: Lenalidomide vs Placebo Maintenance after ASCT
The second trial was done by Germans in this format and I've included that for you to review, how it was given, and if you can relate to it. And this trial also showed a progression-free advantage for patients who were given – but no overall survival at this particular point. This is the bottom line at the end of this particular slide.

But all these information is very, very encouraging because it is showing trends of ability to control disease for a long period of time with just one drug.

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Slide 50: Lenalidomide Maintenance vs Placebo
Are there other drugs that can be used for maintenance therapy? And the answer to that is yes. Bortezomib has also been used for a prolonged period of time. Bortezomib in combination with thalidomide or steroids have also been used for a prolonged period of time. And that has also resulted in again control of disease for a prolonged period or progression-free advantage in patients.

Slide 51: Maintenance Therapy: Summary
And those patients who got the VT or bortezomib and thalidomide, seems to have done the best in this particular group.

Slide 52: VMP vs VTP, Followed by VP or VT
And in the United States that is available to you.

Slide 53: VMP vs VTP, Followed by VP or VT
Look at the blue graph, this is the best, on the right side, is the best overall advantage that patients have achieved with VT maintenance.

Now switch gears because I have about five or ten minutes left and I'll try to finish on time so I can take some questions.

Slide 54: Supportive Care
I'm talking a little bit about supportive care. This is important. And topics that I am unable to cover, please ask me and we can cover that in the question and answer session.

Slide 55: Supportive Therapies in Myeloma
Supportive care is important for obvious reasons. Patients are living longer, there are more treatments, as the bone marrow gets beat up or the disease has a longer duration to act on our bodies, there are tolls that the body suffers. Treatment itself as well as disease causes a lot of problems and therefore adequate control of these side effects of treatment or the disease itself need to be kept in mind.

Things that patients should ask. How are my bones? Things that you should ask. Am I anemic, can something be done about it, do I need blood transfusion or can I be given erythropoietic agent to stimulate my bone marrow to produce more red cells? Is my calcium normal? How are my kidneys doing? I know patients hate to do 24 hour urine. And believe me, I've done it, too. It's not easy to walk around with a jug. But 24 hour urine is the best way to check your kidneys and do that for yourself at least two or three times a year, a minimum. Any infections? It is important that you prevent yourself from infections. For those who are in the north of the country or in the colder areas, need to be more careful. Live vaccines are not a good thing to take and no safety data exists. But rather dead vaccines can be used. So talk with your primary doctor, or your cancer doctor, to find out if the flu vaccine this year is of use for you or not.

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DR. ASHER CHANAN-KHAN:

Slide 56: Impact of Bone Disease

Let's talk a little bit about the bone disease, if you look at the bone disease, we can do something about it. This disease likes to erode the bones and this particular slide shows a hole in the skull bone. And there are many ways we can tackle it.

Slide 57: Most Common Sites for Pathological Fracture in Myeloma

The most common site that it causes bones to be affected are in the vertebrae and this results in vertebral fractures, resulting in severe pain, shortening of the height of patients and so forth.

Slide 58: Vertebral Body Fracture

And some pathological fracture could be really, really painful and nothing can be done about them, such as the rib fractures.

But the spinal fracture, especially in the thoracic or the lumbar region where the disease hits the most, can be tackled with something called vertebroplasty or kyphoplasty.

Slide 59: Kyphoplasty for Vertebral Compression Fracture

The better procedure in my mind is kyphoplasty. The doctor will insert a needle, which has a balloon, it will inflate the balloon inside the bone, and as it inflates, put a cement there. This cement will then make the bone solid and will cause the pain to be relieved. In most patients this procedure results in good success and ability to control disease very effectively.

Slide 60: Bisphosphonates

On the other hand a vertebroplasty can also be done, but usually not as effective.

These procedures should be thought of and the spine be checked, if you're having back pain, please contact your physicians and suggest that you may be evaluated. Not every person may get a vertebroplasty because the bones are broken too far, then this procedure may not be safe.

Slide 61: Renal Impairment in MM

The second important thing to focus on is renal impairment or kidney function. As I mentioned, 24 hour urine is very, very important to do.

Slide 62: Renal Failure Adversely Affects Survival

Make sure you keep an eye on your kidneys with your physician because as the kidney function deteriorates, so are the choices for some of the drugs that we give. And these drugs have to be curtailed in their dosing and therefore may compromise efficacy.

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DR. ASHER CHANAN-KHAN:

Slide 63: Bortezomib Use in MM Patients with Advanced Renal Failure
My favorite drug to use in renal dysfunction is bortezomib because it effectively reverses renal failure by stopping the protein production, especially the light chain results in resolution. Some of my patients who were on hemodialysis got bortezomib and combination therapy resulted in remission, that reversed their renal function completely.

Slide 64: Toxicities Related to Treatment of Myeloma
What are the side effects of some of the treatments? Most common that people ask me are neuropathy.

Slide 65: Peripheral Neuropathy Observed in Clinical Trials With Bortezomib
Neuropathy can happen for both thalidomide and bortezomib and rarely happens with Revlimid. But as you can see in this particular slide, over half the patients will have some kind of neuropathy with bortezomib. Simple thing to remember, if it's only numbing, you may not need to do anything. But if it becomes painful, then you need to inform your physician right away, hold treatment or dose reduce, and that will result in over 60% of the patients to get back to their normal stage or one stage better than before.

And neuropathy, if watched carefully, can certainly be avoided. There are new drugs in the same class as bortezomib, again acting on the proteasome itself, that have no neuropathy or very little neuropathy and those will be a very effective tool for us in future to avoid neuropathy.

Now some people will get it and others will not. And that's just the way it is.

Slide 66: Herpes Zoster or Shingles with Bortezomin
The important side effect of bortezomib, another important, is shingles. Simple measures to avoid shingles is to, whenever you're taking a prescribed bortezomib, make sure that you're taking acyclovir prophylaxis. I usually give it for four weeks after the last dose of bortezomib. And many times I have found that patients who start it before or forget to take it or it's not prescribed by somebody – now these patients will end up developing shingles and it's really painful. Bortezomib should always be given with acyclovir or Zoster prevention. Zoster vaccine has not been tested in the situation, so not recommended.

Slide 67: Marrow Suppression
Bone marrow suppression. Chemotherapy, Doxil®, cyclophosphamide, melphalan, and even lenalidomide or Revlimid and other drugs such as thalidomide and bortezomib have been reported to have effects on bone marrow in suppressing it.

Slide 68: Low Platelet Counts
Remember these are drugs designed to act on blood cells and blood cancer, so it's no surprise that they can actually cause a suppression of bone marrow. And as such, they should be monitored and cared for.

And there are many measures that we can stimulate the bone marrow, by using erythropoietic agents or Neulasta® or Neuopogen® to stimulate white cells.

Thalidomide and Revlimid are two drugs that are associated with blood clots and deep vein thrombosis.

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Slide 69: Deep Vein Thrombosis (DVT)
There are no consensus on what should be given to prevent that, but we know that if you use either heparin or aspirin, most commonly used is aspirin, or warfarin, or also known as Coumadin®, either of these measures can prevent deep vein thrombosis and decrease the chance of happening, significantly low level.

Slide 70: Osteonecrosis of the Jaw – ONJ
The last side effect that I would like to discuss with you is osteonecrosis of the jaw. Now this is a side effect that came about in the last few years as a result of exposure to patients for a prolonged period with a drug called zoledronic acid. Now I didn't discuss much about zoledronic acid because zoledronic acid is given to prevent bone lesion or progression of bone lesion. And when zoledronic acid or pamidronate is given, the ability of bone lesions to grow and ability of myeloma cell to manipulate bone cells to cause these lesions is controlled. But when that happens, usually patients were given this drug in the past for about two years or so, and the reason is we found that as patients are living longer and this drug is given for a prolonged period of time, a thing called osteonecrosis of the jaw happens. And what happens is that the jaw bone starts to necrose or die and the teeth become loose. If any of the patients are on this particular therapy called bisphosphonates or zoledronic acid or pamidronate and have loosening of the teeth or pain in the jaw, they should consult. And for those who are care providers, should know to ask this question of loosening of the teeth. Remember, most of the patients will think problem in their teeth are to be dealt with through the dentist. But this is a problem that comes from the treatment that we prescribe.

Slide 71: Risk Factors of ONJ
There are certain risk factors. Dental extractions and so forth, you know, things that drill into your bones should not be done while you are on this particular therapy. If you must take certain measures in terms of doing your dental work before you start pamidronate, and there's never a rush to start a bisphosphonate. Very rarely would I use bisphosphonate on the first visit or so forth.

Slide 72: Management of ONJ
Usually there's enough time to first get a dental evaluation done and then start this therapy and that is the wise way to go. If you are in a situation where you need the therapy right away or where it was prescribed, that is absolutely fine. Sometimes it requires that kind of urgent treatment, especially if you have high calcium. But nevertheless, dental evaluation is important. All dental work should be done before that. And if osteonecrosis does happen, stop the bisphosphonate therapy and there are certain treatment options that can be done to prevent this or resolve this. There's no definitive treatment that we have been able to identify at this point that would cure this or prevent this completely, except for certain measures that would be done. People may be given antibiotics for this and so forth, that has resulted in some patients getting better.

Slide 73: Conclusion
I will hold now and switch back to the moderator and just so that we can have some time to answer questions.

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Slide 74: Question and Answer Session

LAUREN BERGER:
Thank you so much, Dr. Asher Chanan-Khan, for a very clear and a very informative presentation.

It is now time for the live question and answer portion of our program. So for everyone's benefit, please keep your questions general in nature and Dr. Chanan-Khan will answer them with a general answer.

LAUREN BERGER:
Thank you. We'll take the first question from the web audience, please, and Mike asks, "What are the latest thoughts on treating high risk patients, for example p17 deletion, in a maintenance and relapse or refractory setting?"

DR. ASHER CHANAN-KHAN:
Certainly. And thank you, Mike for asking.

So the concept is that when patients have aggressive disease, a certain 17p deletion or any other chromosome abnormality that makes them a higher risk, and if they are in relapse and refractory setting already, their disease is clearly identified as a B status, very, very powerful and difficult to tame.

These are the patients that I highly recommend first and foremost to go onto clinical trials. Seek out trials with new therapies that have effect in 17p deletion and so forth. This has been a very challenging group of patients, especially 17p, because it results in very aggressive disease and there's not no known bonafide treatment that works in these settings.

Now if you don't have access to clinical trials or there are no clinical trials that you can seek that would address this issue, then it needs to be looked in context with what are the available choices that the patient has not been exposed. So if you have been treated or a patient has been treated with IMiDs or bortezomib before, you may consider the reverse combination. Multi-drug combination is usually the way in my mind to go with this kind of disease.

We are hoping that there will be drugs that will be developed for 17p deletion patients, but these are drugs that may target p53 mutation and so forth, and those are the drugs that are readily not available, but they are on the horizon and at some point we will see them.

But my answer to your question would be if you have high risk disease, first you need to be in a myeloma center for sure. Or at least have them plugged into your care some way. And then look out for the latest therapies that may challenge the myeloma cell in ways different than conventional therapies that we are using.

LAUREN BERGER:
Thank you for your question, Mike. We'll take the next question from the telephone audience, please.

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OPERATOR:
Our first caller is Henry from Missouri.

HENRY:
Good afternoon, Doctor, thank you very much for a very inspiring presentation. My question is in regard to are you familiar with osteosclerotic myeloma without POEMS syndrome and could four and a half years of treatment with Zometa® in any way contribute to that?

DR. ASHER CHANAN-KHAN:
Thank you, Henry, for asking that question. My personal experience with osteosclerotic disease has been limited. I have not seen as many cases as others may have reported. But osteosclerotic myeloma represents a disease where the bone does not typically have punched out holes or osteoclastic activity and, and this is for the rest of the audience, usually when myeloma bone disease happens, the minerals go away and there's a lot of holes there and there's no connective tissue there to hold it, and so these will be looked at on an X-ray as punched out or depleted bones and so forth, as I showed you in the picture. Osteosclerotic disease is usually where there's a lot of sclerosis, a lot of fibrosis happening in the diseased bone.

Again the treatment for these is to treat myeloma itself, the plasma cell that is underneath. These are rare conditions and specifically controlling the – and this goes for all the rare kinds of myeloma, when you're talking about IgD myeloma or we're talking about myelomas that are non-secretory myeloma. Any myeloma that is causing end-organ damage and osteosclerosis will also fall into that category, is causing symptoms and is causing end-organ damage, should be treated as a myeloma. Because of the rarity of these diseases or these entities, it's hard to do clinical trials and answer specifically.

LAUREN BERGER:
Thank you for your question, Henry. We'll take the next question from the web audience and this question is from Jack and he asks, "I'm an 81 year old patient with multiple myeloma, diagnosed in 2009. I had successful treatment with thalidomide, dexamethasone and also prednisone. I've recently relapsed and I'm considering a trial with lenalidomide, dexamethasone and alemtuzumab." "What's your assessment of the outlook for success of this combination of drugs and what length of time will I obliged to be on it?

DR. ASHER CHANAN-KHAN:
So very, very important question, thank you so much for asking this. Thank you also for highlighting the point that you are participating or considering to participate in a clinical trial. It's only by participating together with your physicians and researchers in myeloma can we make a difference in curing this cancer.

What you have asked is a very important question and this is for the rest of the audience. Alemtuzumab is a monoclonal antibody and you know, monoclonal antibodies, what I've not talked about, are new therapies in ways of acting. Monoclonal antibodies are – the mechanism of this particular way of treatment is to develop a protein or a drug that mimics your own immune system. And use that to target specifically the cancer cell. So these are very targeted therapies.

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DR. ASHER CHANAN-KHAN:

The concept of combining lenalidomide, steroids and elotuzumab or any other monoclonal antibodies, there are several out there now that you should look at, is to boost the immune system by developing monoclonal antibodies that will go and target the cancer cell and the lenalidomide will then stimulate the immune system against the cancer. Very elegant design, very elegant science behind it. And it is already demonstrating very high efficacy in clinical results.

So when you look at the clinical trial, a good thing to remember is that you're going to get lenalidomide and steroids, which we know already work in about 70% of cases in relapse setting. And at best – so at worst you will be expected to have that kind of a response. On the other hand, if the new drug works, then the chances of you responding are very high.

But I think it's a very good study to participate in. The results are very, very promising. Monoclonal antibodies are non-chemotherapeutic approaches, working with your immune system to work in. For patients who are in that situation, please do consider that as they will be very important tools for us in the future.

In terms of how long the duration is, that is the answer that the clinical trial that you are going into, they will be able to provide you what is the expected duration of therapy that they would like you to be on.

LAUREN BERGER:
Thank you for your question, Jack. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question is from Wanda from Michigan.

WANDA:
Hi, Doctor, thank you very much. I have a lesion and a PET scan just showed that I still have a lesion in the right sacrum and sacroiliac joint. I had an MRI in 12/09, went from a 6.3 by 4.7 down to a 5 by 2.2. And I've had extensive treatment and I had a stem cell transplant a year ago. But this is causing a lot of problems by pushing into nerves going down my right leg. And I've had 20 doses of radiation. They say I can have no more radiation. And they can't cut it because of the way the nerves are going to my leg. So did you have a suggestion what would be the next method of treatment? I'm on no follow-up treatments since stem cell transplant. But the PET scan is still showing that to be malignancy.

DR. ASHER CHANAN-KHAN:
Certainly. And thank you for asking the question, Wanda. Again, looking at the whole big picture for the rest of the audience, what can we do for bone lesions and what are the strategies that can be dealt with? And as you can hear from Wanda's voice, and Wanda's concern is that there is still pain and the disease is causing problems by various maneuvers.

Now the step one of treatment of bone disease is to treat the myeloma cells. Stop the myeloma from hurting that part of the bone and the rest of the bones that exist. Step two is to start bisphosphonate therapy, so that also stops the bone cells from eating their own bone.

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DR. ASHER CHANAN-KHAN:

Step three is once patients are in remission, look at the bone structure again. If it's in the spine, can you fix it? If it's in the rib, can they heal, do some maneuvers that will allow various bones of the body to heal or repair them? And lastly, if none of these things work, we use radiation therapy to try to sterilize that area from cancer cells, so that it can benefit. Sometimes, unfortunately, Wanda, as you are going through this particular process, there is only limited amount of stuff that can be done.

If your disease is relapsing and your PET scan is showing relapsed disease, the most important thing that I can think about is that your disease needs to be first controlled and you have to go back to step one instead of just doing radiation. Because every time you'll radiate and you'll try to go back and the disease is growing, it's not going to work.

Surgical maneuvers in the site that you have described, which is a sacrum and so forth, are usually not helpful and actually results in significant problems. So that would not be advised.

Most importantly I would advise you to contact a myeloma center of excellence, where you know that they are myeloma experts who have dealt with these problems before and maybe they will be able to help you better.

LAUREN BERGER:

Thanks for your question, Wanda. And after the call if you would like to call our Information Resource Center to get resource information on a cancer center of excellence, that would be a good suggestion, and their telephone number is 1-800-955-4572.

We'll take the next question from the web audience and this one is from Michael and he asks, "What is the best treatment for amyloidosis caused by multiple myeloma? I have it in both my heart and my kidneys."

DR. ASHER CHANAN-KHAN:

So, Michael, this is again a tough situation, as I mentioned very briefly. Amyloid is something that worries me a lot when I see. I'm always scared of it, have lost a lot of patients and there are a couple of people in the country who are specifically world expert in amyloid. Almost every time when I see a patient who is amyloid, I try to make an effort for them to go and see the amyloid experts. There's one in Boston, Dr. Ray Comenzo, and the Boston University has also several experts. But Mayo Clinic also in Rochester has several experts in amyloid area.

To answer your question, what is a usual approach, is to treat myeloma. So who's producing the amyloid? Is the cancer cell that is producing. If you shut off the cancer cell, you limit the progress of the amyloid deposition.

Unfortunately, once it's deposited, it is very hard to get rid of it. It takes a long time, which means a patient has to be in remission for a prolonged period of time, for slowly the organs to come back. There is known to have a point of no return, where there's enough amyloid deposited that despite treatment things will not get better.

DR. ASHER CHANAN-KHAN:

This is an area of aggressive, ongoing research, and the best thing that you can do is seek out expert help and try to get into clinical trials where new drugs are given to patients who have amyloid. There's no other way to treat amyloid but to treat the disease itself.

LAUREN BERGER:
Thank you for your question, Michael, and we wish you the best. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question is Barney from Pennsylvania.

BARNEY:
Doctor, I want to thank you very much for a very informative lecture. I'm smoldering. I was diagnosed five years ago with multiple myeloma. After my second bout with bacterial meningitis and two comas, and I get an infusion every four weeks of Gammagard®, and my oncologist feels that quite possibly this might be helping to level off my counts, my blood counts. Could he be correct?

DR. ASHER CHANAN-KHAN:
So, Michael, you raise another important issue that I touched earlier on, infection. Plasma cell cancers are prone to immune suppression. They cause immune suppression. And patients with immune deficiency as a result of these particular cancers tend to have unusual infection, life-threatening infection. And if you have had infections like meningitis, which are usually not seen in common population, but if you have it – so if you had it twice, that clearly suggests that your immune system is down.

Now a typical myeloma patient would have bone lesions or kidney failure, anemia, something like that, or high plasma cell levels in the bone marrow, making the physician say ha, this is myeloma, let's treat it, it's going that way, that's a typical approach. However, smoldering myeloma and myelomas that are stage 1 may just present with immune suppression, like yourself. This is a situation where you may not see a lot of disease, but a disease that has specifically targeted your immune system. In this case, if there's no other identified causes of your infection and the relationship between your meningeal or brain infection with immune suppression is made on certain tests, then I think immunoglobulin is a Band-Aid situation that would not be a good way to proceed in future.

But even if you're artificially supporting yourself by other people's immune protein, what you then need to do is consider whether you have reached a point where treatment is necessary.

For those of you who are online and are – or have smoldering myeloma, this is a disease which sits between a pre-malignant MGUS and an overt multiple myeloma. So numerically you haven't reached that point, where people would say oh, let's treat myeloma. On the other hand it's not even benign, it's not so comfortable that you should just sit on it forever.

DR. ASHER CHANAN-KHAN:

So a very careful monitoring plan, a very careful history, sharing the information of your infectious complications and other complications, watching kidney function, and all of these have to be done very carefully and diligently on smoldering myeloma.

There are now clinical trials available in patients with smoldering myeloma because of concern that these are patients that kind of sometimes slips through the crack because we think they're not that aggressive, they don't have that aggressive disease, but by the time you find out they've already suffered some major complications like infections that you have suffered.

LAUREN BERGER:

Thank you for your question, Barney. We'll take the next question from the web audience and Milo asks, "Do I have to combine Revlimid 25 milligrams with dexamethasone and Velcade® for my maintenance therapy? It seems too much."

DR. ASHER CHANAN-KHAN:

Milo, you asks, again, so my task today was to try to educate on tools and thought processes and why one would be combined and try to illustrate and demonstrate that there are different kinds of diseases within myeloma.

Maintenance therapy, to date the data, as I showed you, you can go back and look at the slide and look at the information very carefully, maintenance therapy has been done for a long time, starting from steroids and thalidomide, now Revlimid and bortezomib. And most trials have shown that you can control your disease longer than if you were not on therapy. This is number one. Most trials have shown, point number two, most trials have shown that there's no survival advantage, one or the other, or if it is, it's very few months. What people have not shown is if Milo was taking a maintenance therapy and Mark was not taking a maintenance therapy and Milo got progression-free survival or even six months benefit in controlling the disease or year benefit of controlling the disease longer, but when Mark's disease came back that same therapy was given to Mark and he ended up into in remission as well and benefitted at the time of relapse. So the question of maintenance was is retreatment at time of relapse, is also not answered. We don't know whether patients should be on maintenance or not. We know that it does help in progression-free survival. But a lot of people in myeloma will not necessarily just jump into maintenance therapy.

There is now, as of 2011, an increased awareness that maintenance therapy, with at least Revlimid, may be somewhat beneficial to patients. But again we have to really see conclusive data on survival and conclusive data on how much benefit it is. Because if you're tied – there are issues with maintenance therapy, you're tied up to a center forever, you're being monitored for a prolonged period of time, and your quality of life is hampered, these are not treatments that are very benign, they have side effects, so there are issues associated with it. The benefits should outweigh the side effects and all the other issues associated with chronic therapy.

DR. ASHER CHANAN-KHAN:

Having said that, we don't know the answer whether one drug is good for maintenance, we don't know the answer we should be giving two drugs. I showed you the B-T and B-P, which is bortezomib, thalidomide and bortezomib, prednisone data. B-T seems to be better, but not compared to one drug. One versus two drugs versus three drugs maintenance therapy has not been tested.

So first you're in a maintenance arena, then you are taking three drugs to control your disease. It all depends what your kind of disease is. I can tell you what I have done. Have I ever given RVD maintenance to anybody? No. If I have to, if they have that aggressive of disease, they will show me and I will retreat them. The reason is I would rather hold onto a therapy at the time of retreatment than hoping the three drug will benefit these patients, when I don't even know whether two drugs or one drug is better or not.

So there is a lot of unanswered question, but these questions are being tackled. If you're in a clinical trial, then that's a reasonable question to answer with your physician. If you're not in a clinical trial, this is certainly not standard.

LAUREN BERGER:
Thank you for your question, Milo. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question is Laura from Florida.

LAURA:
Hello. I want to thank the doctor for such informity. I have just had an autotransplant in July and I want to know what its long term maintenance of it and the side effects.

DR. ASHER CHANAN-KHAN:
Thank you for asking that question. The question in general is when you go through autotransplant, go after high dose melphalan, how long should a patient feel tired or fatigued and how long does it take. And it all depends on how bad the disease was to begin with, if you had a lot of disease to begin with, and individual patients vary in their response also. Once the disease is controlled, it takes in my mind, in my experience, at least six months for you to become better. But every month is supposed to be progressively better than before. And if things are not happening, if this is not happening, then there's something certainly wrong. But clearly if you expect to be absolutely where you were before all of this started to happen in your life, expect about a year or so or more before it gets better. And there is a percentage of people who would never achieve their normal level of performance, unfortunately. Remember this is a huge dose of chemotherapy given, it's very, very toxic to the body in principle, but fortunately our bodies are usually able to, in most cases able to recover very well. So anywhere from six months to a year is a usual period to be patient.

Slide 75: LLS Information

LAUREN BERGER:
Thank you for your question. And thank you for all of your questions. Our program has come to a close. Please help me thank Dr. Chanan-Khan. We hope that many of your questions were answered. If we were not able to get to your question or we can provide additional information or support in your next steps, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572.

On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us today. Good-bye and we wish you well.

OPERATOR:
Thank you. This does conclude today's presentation. We thank you for your participation. You may disconnect your line and have a great day.

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