Myeloma – Update on Treatment and Side Effects Management

November 7, 2013

Speaker: Asher A. Chanan-Khan, MD

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Slide 1 – Welcome & Introductions

OPERATOR:
Hello, everyone, welcome to *Myeloma – Update on Treatment and Side Effects Management*, a free telephone-web education program. It is my pleasure to introduce your moderator, Lauren Berger, of The Leukemia & Lymphoma Society.

LAUREN BERGER:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Our special thanks to Dr. Asher Chanan-Khan for sharing his time and expertise with us today. Following the presentation, we will take questions from the audience. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words.

JOHN WALTER:
Thank you, Lauren. I'd like to add my welcome to the patients, caregivers, and healthcare professionals on the program today.

All of us at The Leukemia & Lymphoma Society believe we are living at an extraordinary moment. Our mission is to cure blood cancers, including leukemia, lymphoma, myeloma, and to improve the quality of life for patients.

Since 1954 LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers. And we have awarded almost $1 billion to fund blood cancer research.

Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different forms of blood cancer.

An important part of our mission is bringing you the latest information about advancements in treatment for your blood cancer, so you can work with your healthcare team to determine the best options for the best outcomes.

Until there is a cure, LLS will continue to invest in research, patient support programs, and services that improve the quality of life for patients and their families.

We are fortunate to have as our presenter today Dr. Asher Chanan-Khan, one of the nation's leading experts in myeloma. We appreciate his dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and his care of patients living with blood cancers. I would like to thank him for providing us today important information on living with myeloma.

Thank you and I'll turn the program back over to Lauren.

Slide 2 – Myeloma Update on Treatment and Side Effects Management

LAUREN BERGER:
Thanks. I'm now pleased to introduce Dr. Asher Chanan-Khan, Professor of Medicine, Mayo School of Medicine, Chair, Division of Hematology/Oncology, and Vice-Chair of Research at Mayo Clinic Cancer Center in Jacksonville, Florida. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise today. I am now privileged to turn the program over to you.

DR. ASHER CHANAN-KHAN:
Thank you so much, Lauren. Thank you, John, for such a kind introduction. And thank you all for joining today at this very impressive venue that The Leukemia & Lymphoma Society has put together. It's always such a privilege and an honor for me to be able to participate in their effort and have seen their commitment firsthand in fighting blood cancers.

Today's talk will focus primarily on treatment and side effects or toxicities associated with them, in multiple myeloma. The talk is designed in four sections. The first part, I will talk to you about what multiple myeloma is, a brief introduction. This is for those patients who are recently diagnosed or those family members or caregivers who are just learning about this disease, so they can come along with us as we go forward and explore therapies. The second part of the talk, we'll talk about the existing therapeutics that are available, not necessarily requiring approval by the FDA or other regulatory agencies across the world. Meaning they are accessible to myeloma patients. The third part, we will discuss the promise of the future, which is therapeutics that are being developed by various pharmaceutical industries, investigators and academic centers across the country and across the world. That part of the talk brings a lot of hope and a flavor of where all the efforts are being directed, by various investigators and their collaborators. And the last part of the talk will focus on the side effects most commonly that are seen in this disease and associated with therapies. And this will give you a lot of opportunities to ask questions thereafter.

Slide 3 – Clinical Presentation
So let's talk a little bit of what myeloma is. Multiple myeloma is a B-cell cancer. There are different kinds of cells in the body and in the bone marrow and blood, and B- cells are one of the cells that results in production of humoral or protein-based immune system. Myeloma is a cancer that arises from plasma cells. Plasma cells are B-cell derivative cells. And therefore this is a B-cell cancer.

Typically most of the plasma cells that are normal plasma cells reside in the bone marrow. But plasma cells are scattered all over the body. The largest congregation being in the marrow. And therefore most of the time that when B-cells become cancerous, they result in infiltration and involvement of the bone marrow.

When plasma cells arise in other places of the body and develop a tumor, they're called plasmacytomas. And plasmacytomas in general are very sensitive to radiation therapy and almost in most of the cases, around 90% of the time, cured. So we won't talk much about them.

Myeloma is a disease when plasma cells become cancerous and reside in the bone marrow, at least in the initial phases of the presentation. As they grow inside the marrow, they secrete a lot of cytokines, change their environment, fool the cells that are supporting around them, and make – and all of this results in a lot of side effects or effects of this disease on the body.

For example, the growth in the bone marrow results in erosion of the bones themselves, resulting in lesions. In this particular slide, at the top you will see these large bluish color cells that are plasma cells and these are malignant plasma cells.

In the second picture you will see an unfortunate patient who has bone that is riddled with multiple lesions. Why we call them lesion is primarily because that part of the bone has eroded and the strength,

DR. ASHER CHANAN-KHAN:
the calcium-directed strength that is normally present in our bones, is diminished or absent. So osteolytic bone lesion is a characteristic of multiple myeloma.

Renal dysfunction or kidney malfunction is also a complication of this disease. And this results for various reasons. It is important for clinicians to know why renal function is going bad. It can be as a direct result of the disease or it could be side effects from other things happening within the body.

Typically the plasma cells are responsible for producing proteins and those proteins are responsible for an immune system that happens in our body. Think of it as in childhood we get tetanus and polio shots. What happens is these shots are proteins that are then fed to normal plasma cells and the normal plasma cells then develop an immune response, which is a protein in nature response. So when plasma cells become cancerous, they end up producing excessive amount of immunoglobulins or proteins. And this is one of the things that you will see in myeloma patients, as rising abnormal protein. And I'll show you a little bit later what it means.

Sometimes, rarely, myeloma cells also produce abnormal protein called amyloid. And amyloid is a protein which gets deposited in various parts of the body, such as the heart or lung, the brain, the blood vessel. And it is a very devastating disease called amyloidosis and that requires another talk on itself. But this is also one of the complications of multiple myeloma.

And lastly, as I discussed earlier, the myeloma cells are – plasma cells are supposed to be part of the immune system. When they go bad, the immune system goes down. And immune dysfunction or increased susceptibility to infection is also a complication of this disease.

Now patients often present with anemia, bone fractures, or they will present with excessive amount of fatigue. These are typical symptoms that are seen.

Slide 4 – Pathogenesis
In this particular slide, you will see that multiple myeloma can present in a various form of disease. There's a spectrum of disorders. So at the very left hand corner you will see MGUS, which means the cell just became cancerous, but did not develop into symptoms. And somehow it just stalled there and numerically while it was there, and it started producing the abnormal protein, but it did not have the bite or the sting of the disease itself.

Many patients with MGUS will remain like this throughout their life and will not need treatment. But increasingly with age, they will develop increasing susceptibility to transition into something called multiple myeloma, which is the gray color bar in the center of the slide, noted as intramedullary myeloma.

Most of the time myeloma stays in the bone marrow. But very recently, over the last few years, we have started to appreciate that as time goes by and new treatments come onboard, myeloma has developed a tendency to leave the bone marrow at some point and develop what is known as the extramedullary – medullary basically means marrow – extramedullary myeloma. And these extramedullary myeloma presents as tumor anywhere in the body, but most commonly around the spine and in the base of the skull. And these tend to have a very aggressive course and therapy seems to be less effective. But with the new treatments coming onboard, there's a lot of encouraging results already being seen.

DR. ASHER CHANAN-KHAN:

Slide 5 – Diagnosis & Staging: Initial Diagnostic Evaluation
Now diagnosis and staging requires all these tests. We look at the blood, we look at electrolytes, we look at protein in the blood, we look at the kidney function, we look at skeleton or X-ray the bones. We do PET scans and FISH and MRI. All of these tests listed here, which is for your reference, are necessary to completely assess a myeloma patient. And this also involves a urine analysis over a 24 period to assess how the kidneys are doing.
If there's one thing you'll remember in this particular part of the disease, is that I'm very, very keen of always knowing how the kidneys are doing. Because kidney dysfunction can lead to compromised results in myeloma patients.

Slide 6 – Diagnosis & Staging: Serum Protein Electrophoresis
So let's discuss the most important test that actually is necessary almost always to define myeloma. On the left hand column you will see a wave-like graph which shows how the protein move on a gel. Gel is what we do, this is out of a blood. We take blood samples and we look at how the proteins are present. In the middle graph you will see there's an abnormal protein spiking right up, which is at the region known as the gamma region. And this second spike is what is called the M spike. A lot of myeloma patients have these, over 90% of these patients will have some kind of an M spike. And this M spike is very, very characteristic of multiple myeloma patient, or in general, B-cell or plasma cell cancer.

And we always want to know what this M spike is. And that defines what type of myeloma you may have.

So there are several kinds of immunoglobulin. They include IgA, IgG, IgD and M. And sometimes IgE. But IgG is the most common and that's what's noted over here. The third panel shows you something called immunofixation. And it can be a kappa light chain or a lambda light chain receptor. This particular patient is a kappa one.

So this is a test that we do a lot. M spike is also used to monitor how patients are responding to treatment.

Slide 7 – PET-Scan to Identify Focal Lesions
Now going to PET scans. PET scans are a way to assess how the disease is scattered all over. You will see this particular patient, where the PET scan was initially positive. And one of my colleagues, Dr. Sher, gave this patient just one pill, called lenalidomide, and in three months or so this whole disease disappeared. What a powerful statement this picture shows you, and highlights what the importance of this test is in managing patients with multiple myeloma.

Slide 8 – Criteria for Diagnosis of Myeloma
Last piece in this particular section is what is the diagnostic criteria for multiple myeloma. I showed you the spectrum of this particular disease, which arise from plasma cells. It can be a very benign and pre-malignant condition, such as the MGUS, and in which case the criteria is defined here of less than 3 grams, M spike. M spike is we just discussed. And if you do the bone marrow biopsy of these patients, the amount of plasma cells in their bone marrow should be less than 10%.

On the other hand, the red font over here on the right side, shows active myeloma, where you do the bone marrow biopsy, these patients are expected to have plasma cell concentration of more than 10%.

DR. ASHER CHANAN-KHAN:
And the M spike could be any number. But it's usually higher. But as you can see, the most important criteria, in this red right panel, is the fact that these patients have symptoms. They may have anemia, they may have bone lesions, they may have high calcium or abnormal kidney function. These factors define that the malignant plasma cells is actually having an impact, an adverse impact, on the body, by virtue of affecting the bones or the marrow or the electrolytes or the kidney. And this is what diagnose or defines the definition of multiple myeloma.

Once multiple myeloma is identified and there are lesions that are associated or there are effects that the disease is causing, treatment is needed. So this leads us to the second part of our talk, which will focus on what are the treatments.

Now I'll pause here for a few seconds and share with you that multiple myeloma unfortunately is incurable. Which also means that there are different kinds of treatment approaches. We don't necessarily know that there is one particular approach that is curative because the disease is not curable. There are folks who believe that allogeneic transplant or other modalities may result in cure of some patients. But by and large most myeloma experts believe that this is a disease that cannot be eradicated, but very effectively managed in the present time.

Slide 9 – Treatment Approach
So we'll talk about treatment approaches. There are treatment philosophies of various investigators across the globe. Some myeloma experts are very, very keen and very much convinced about a very aggressive approach from the very beginning. Others are more focused on quality of life and slowly escalating the intensity of treatment as required by the disease. So all of these approaches do exist among myeloma folks. And while it may sound very confusing, the fact is that all of us focus on trying to manage the disease in different ways and try to find out what the best approach is.

Slide 10 – Introduction
The last ten years or so have been very, very promising for myeloma. Numerous medicines have been approved and tons of them have already gone into clinical trials, as you will see in the later part of the talk.

Slide 11 – Improving Survival Over Time
What has been more impressive and rewarding is to see that these treatments that have been approved have made an impact in patient survival, ability to live longer with a good quality of life, and manage side effects very nicely.

So no longer is the time that I dread when I started in this field, I used to dread seeing patients because the survival was usually two or three years, no matter what you did. And once the disease came as relapsed or resistant, there was not much you could do about it. But no longer is that fear in me as a clinician and there's just so many tools as I will share with you, that can be used to control disease.

And during the question-answer session, I encourage you to think about what tools you are aware of and tools means drugs, and what are your questions regarding that.

The time has also come that it is important for each person and each patient to be analyzed based on their disease. Some patients, unfortunately, have very aggressive disease. They may have plasma cell

DR. ASHER CHANAN-KHAN:
leukemia, they may have plasmacytomas all over the body, or they may just not respond to any treatment. Those patients are high-risk patients. Some genetic tests can be done to find those patients out. And then there are people who have low risk or less aggressive disease. It is important now in present time to know these differences because it impacts long-term planning, which is critical for myeloma patients now.

Slide 12 – Initial Approach to Treatment of MM
Now I'll share with you a general pathway, a general philosophy, which is acceptable by most clinicians and myeloma experts. Typically, in the present day, patients with multiple myeloma, our first thought on, in context with whether they can go on to stem cell transplant or not. While it is not necessary, it doesn't imply that you have to have a transplant, basically it allows us to think that if we need to go that aggressive route and use stem cells and higher doses of chemotherapy, is this particular patient a candidate or not. If that patient is not considered to be a candidate, whether it's the age issue, comorbid or other conditions, such as heart dysfunction, lung dysfunction, other reasons, or kidney dysfunction, that may not allow them to go to transplant, then they go on a different route and that route basically allows them to be exposed to certain drugs called alkylating agents, more earlier than usual.

If the patient is younger, good performance status, and young could be as young as 70, transplants have been done up to the age of 70 or 80 years old. It's not a matter of age. It's a matter of how good the body's function and ability to tolerate chemotherapy at a higher dose exist.

If that is the case, then these patients tend to go through an induction phase of the treatment, which is the first treatment. And induction results in remission after the first treatment or second treatment. And then the stem cells from the same patients are collected. This is called autologous stem cell transplant. And thereafter those stem cells can be used for transplantation.

And the there is an issue of whether we should continue patient on maintenance therapy after transplantation or induction, or not. And there are studies that support it and there are studies and investigators who may say well, maybe not.

Slide 13 – Risk Stratification of Active MM
How do we stratify patients who are aggressive and who are not? Most common universally, so to say, available test, is the FISH analysis. There are new techniques such as genome testing, gene expression profiling, but I think the most validated across the globe that all of you can really rely and relate to is the FISH analysis, known as the fluorescence in situ hybridization. And those patients on the left hand corner, which shows deletion of chromosome 17, or part of 17 actually, are the most aggressive patients. And similarly, those who have translocation of 14 and that is part of the chromosome is broken from one part to the other chromosome. And so those who have involvement of chromosome 14 or 4 tend to have a high risk disease.

And then there are other, on the left hand, which are more standard risk, or those who are considered to be less aggressive compared to the first group. And the approaches can be different.

So why are these groups segregated and does that matter? The answer is yes.

DR. ASHER CHANAN-KHAN:

Slide 14 – Incidence and Median OS by Risk Group
The high risk group tends to occur in about 20% of myeloma patients. As you can see in the right hand corner, most patients, 60%, will have a standard risk. And these tend to be the patients who live around eight to ten years median survival. Those who are high risk, unfortunately, have a very low survival of about three years or so.

Now if I take you back ten years ago, this was less than half what it is now. So clearly while we have improved the outcome of patients in this particular group, we certainly have a long way to go.

Slide 15 – Anti-Myeloma Therapuetics
These are the tools, in general. And I won't go through all therapies because of constraints in time, but you have these, about five known classes of drug, and then there are others, the sixth class, which are all investigational and other agents.

Alkylating agents have been around for a long time. Anthracyclines have been around for a while. Corticosteroids or steroids are very commonly used and have been around for a long time. In the last decade or so, immunomodulatory drugs, three of them are now approved and available to myeloma patients, are now making a major impact. They have already demonstrated how important they are in myeloma therapy. And then proteasome inhibitors, one of the most important, most critical target in multiple myeloma, is the proteasome. This target, when engaged and mitigated, results in very high response rates. In fact, proteasome inhibitors are by themselves, alone, have the ability to induce complete remission in a percentage of patients. And when combined with other drugs, even with IMiDs, they tend to be very, very potent combinations.

Slide 16 – Therapeutic "Tools" to Treat Myeloma
Now when you look at these classes of drugs, and on the right side you'll see just alphabet soup, it is intended to be that because there are many, many regimens. And these alphabets represent various chemicals that we mix together. It is only for you to see and appreciate that we have the ability to combine various classes of drug, whether it be steroids or alkylating agents or IMiDs or proteasome or anthracycline, we can combine them in various forms and come up with regimens. And so if you have received, let's say, IMiD therapy or thalidomide therapy and steroid, it is not unthinkable that your investigator or your physician may combine the same drug with another drug and give it back to you for a continued response to therapy. And so this ability to combine therapy and develop combination regimens is very, very important.

Slide 17 -- Selection of Best Therapeutic Options Based on Patient Risk Category
What are the potential strategies for risk-based treatment? So I'll touch a little bit and you're welcome to ask. As I mentioned earlier on, the selection of best therapeutic options now should be based on risk. The time fortunately has come that we don't need to fit one shoe on every single patient. Treatment can be tailored and should be tailored. And therefore it is imperative that part of your team taking care of you should involve a myeloma expert, whether you remain – whether you have to stay in that system or that physician or not, is not necessary. At least as part of your planning team, you should engage a myeloma expert who can help design a long-term plan for you, based on your risk.

DR. ASHER CHANAN-KHAN:

Slide 18 – Standard Risk
Now 60% of the patients, as I said, would have standard risk. That means they don't have aggressive – very aggressive disease. They have an aggressive disease, but not a very aggressive disease, and their expectation of having a survival in the ballpark of eight to ten years is high. And that's a sizable amount. I mean we were not talking about this kind of number in the very near distant past. But now we are. And so what is to say that with all the therapies that are coming down the pipeline, we will be talking about in the next few years, we may be talking about 15 or 20 years for the same group of patients. Now that's very important.

This is a disease that happened in the late 60s and 70s and most of the patients, so if you're talking about ten years and plus, we are talking about a very good strategy, in the absence of a curative regimen.

There are several drug combinations listed here. The intent is again to show you that with combination you can have one drug treatment or you can have a two drug treatment, or you can have a three drug treatment. And there's incremental benefit to that. Usually if you use any of the drugs, for one drug, you'll have anywhere a chance of about 30 or 40% chance of response. When you combine two drugs, the response rates jump up to 80%. And then when you get three, there are regimens that start to report anywhere from 90 to 100% of the patients responding.

Now it's important to mark my words. They are responding, they go into remission. They don't necessarily get cured. So many times I like to strategize, I like to see who are the low risk patients and where I can use one treatment, or at best two treatments, before I go on to giving them a combination regimen.

Slide 19 – High Risk
Now in the high risk group, you will see that the chance of this patient presenting is about 20%. And the survival is three years or so. And this particular group, most of us believe that a combination strategy is much more beneficial going forward with at least two or three drugs combined together, even though we will see response, chance of relapse is very, very high in these patients, and usually and often it's within a year or so.

I have highlighted here the first drug, which is bortezomib. Almost all of us believe now that in high risk patient group, a proteasome inhibitor, whether it be bortezomib or carfilzomib or maybe the newer agents, are very critical to make a difference in inducing remission and maintaining remission in these patients. And so it is important from this particular slide, I would like you all to have the message that one, that in high risk patients, first we need to identify them; two, we would prefer to use a combination strategy, so we can get them into remission faster; and three, that perhaps a proteasome inhibitor is almost a critical ingredient in trying to achieve our goals in this particular patient population.

Slide 20 – New Approved Drugs
Going to some of the new agents that came forward over the last two years or so, among these was pomalidomide and carfilzomib, and I'll spend just a little time to share with you what these drugs are doing. Because there's a lot of hype. Part of it is correct and part of it is a little bit over. And so recalibrating ourself and having the right impression about these agents is very, very important.

DR. ASHER CHANAN-KHAN:

Slide 21 – Phase 1 Trials
So let's talk about pomalidomide first. This is a third generation immunomodulatory drug. It's developed out of thalidomide. Similar concept as was with lenalidomide. There are some differences in the molecules and the activities. The side effects are different. But in preclinical testing, in the laboratory, it's one of the most potent drugs in suppressing and testing certain parameters about cytokines and so forth.

In the clinic you can see that in patients who are relapsed and refractory, approximately half of these patients, depending on what kind of patients we are talking about, will respond. In general you can say anywhere from 30 to 50% of the patients will respond to this drug in the relapsed or refractory setting. Important thing to remember is that one, it is almost always given in combination with steroids and that's how it is approved; number two, it does show activity, even in patients who have failed prior immuno-modulatory drugs or IMiDs, such as lenalidomide and thalidomide. Which is encouraging to know because - think about the same as a blood pressure medicine. You take one from the same class and if that is not working, you can use the other one or the third one. So this class of drug seems to have some degree of variability among its member, fortunately, so that it allows us to use different members at different times in the treatment of multiple myeloma.

Slide 22 – Responses
If you look at the response rates in some of the studies noted here, again, just to point out, there are two different doses being given, 2 milligrams and 4 milligrams, and most people believe that it doesn't necessarily had made a big difference in terms of dose response. You can use 2 or 4 milligrams in my opinion. A quarter of the patients will respond.

If you look at the bottom part, you'll see that the median time to response in various studies, was within two months or less. And that's very, very encouraging, especially in patients who are relapsing or whose disease is coming back fast.

Slide 23 – Patient Outcomes
One of the good things is its ability to induce response in a lot of patients, even despite prior failure of the same class. But on the other hand, if you look at this particular slide, you'll see that the median progression-free survival in some of these studies have been anywhere from four to six months, or in one particular study, eight months, if it was used in less resistant or refractory cases.

In most folks, this will be – to most patients this will be disappointing because hey, we go through all this therapy and the chance of me having average duration of remission is four or five months. But truly there are many, many patients who remain on it for many – for longer period of time and benefit.

These are the results from clinical trials where lots of different kinds of patients were involved. But certainly it's not a drug that has demonstrated years and years of benefit yet. Currently it's only available for patients who have relapsed disease.

Slide 24 – Carfilzomib
The second drug I wanted to talk to you about was carfilzomib, which is also a new drug approved very recently and has been a very, very important drug to the myeloma therapeutics.

DR. ASHER CHANAN-KHAN:
Now carfilzomib is not necessarily going after a new target. It's going after proteasome, which is what Velcade® goes after. But it certainly has other effects also on the myeloma cells that are not necessarily well defined. But at the end of the day, it does induce remission.

The green figures on the top shows you data from one of our colleagues, showing that this particular drug doesn't necessarily hurt the nerves as badly as bortezomib did. And thus the incidence of neuropathy seems to be somewhat lesser or significantly less with carfilzomib than with bortezomib, which is an important thing to remember.

Efficacy in my personal opinion has been more or less the same, but the tolerability certainly better.

The challenge with this is because this drug is given more frequently and given IV versus bortezomib now being given mostly subcutaneously. So there is a little bit of a convenience issue with carfilzomib at present. But that may go away in the future as oral formulations are being developed on this drug.

As you can see in this particular study, the response rates for single agent in relapse are around again a third. And I mentioned earlier on that when you give one drug, the chances of anywhere from 30% – 30 to 40% chance of response rate. But when you start combining these drugs, the response rate goes up. And that's true for carfilzomib. There are many, many combinations of carfilzomib that have been investigated. Both with lenalidomide and dexamethasone. And if you give these three drugs, you get 100% response rate. If you give with pomalidomide and that has been done in relapsed setting, there is over 70 to 80% response rate.

Slide 25 – Promising New Agents
While these are very, very promising number, one of the things that I think the audience and patients want to know is not just focus on response. Do not only focus on what – how high the number should go. Keep in mind the side effect profiles of the combination. Keep in mind that are you the aggressive patient or are you the less aggressive patient, who doesn't need to exhaust all options up front, and can you be treated with least, so that drugs can be maintained later on for you when the disease relapses. That's a very, very important strategy.

Slide 26 – 31 Therapeutic Agents Currently in Phase 2/3 Development for MM
For most of you, you may not be able to read this slide as portrayed right now. This is just a message of hope. Over 30 new products, new drugs, independent drugs, are in clinical trials. When I say in clinical trials, meaning they are now being given to patients. They have reached that mark of preclinical and animal testing, where we feel as a community that it is safe to now test them in humans. And these are myeloma-focused drugs.

So you can see there are 30 new drugs. When I shared with you seven or eight drugs and I showed you how the survival is almost double, you can imagine if even half of these drugs get approved over the next couple of years, how much great it would be for patients with multiple myeloma.

When you'll download these slides, you'll be able to read individually which phase these drugs are and what category they belong to.

DR. ASHER CHANAN-KHAN:

Slide 27 – Myeloma Cell
This is how the myeloma cell in the landscape would look. There are all these new drugs at the bottom. There are all these new combinations at the top. And on the side, left hand side, you have the developed combinations that we can use now without any qualms and know the toxicity, know the response rate.

So this is a sequence, starting from the bottom, going all the way around, up and out. And that's how I think happen – new drugs come in, and then they go through various clinical trials, and then they will go through combination clinical trials, and some of those make it to the bonafide combination, that are then become standard in our use in the clinic.

Slide 28 – Select Phase 2/3 Clinical Trials in Myeloma
The three that are already in Phase III, which is the most advanced clinical testing, are ixazomib, which is again a proteasome inhibitor, that is a third one that's being looked at. Actually there are three more proteasome inhibitors being looked at. So there are others, but this is the third one that's gone into Phase III testing, so very promising.

Elotuzumab is a very, very promising antibody, which is a non-chemotherapeutic approach. More immune-based approach, and has already shown very promising results in Phase II testing. And this drug should also be available, God willing, in the very near future.

And panobinostat is an HDAC inhibitor. I won't go into the science of that, but it modulates the DNA, the cancer cell DNA, and allows other treatments to be more effective.

Slide 29 – Select Phase 2/3 Clinical Trials in Myeloma
There are several studies that have been done and there are more that are ongoing, but by and large, while there have been a lot of promise associated with that, personally I've not been very impressed by this particular drug or this class of drug yet. So time will tell how these drug studies will – or these drugs will make an impact.

Slide 30 – A Phase 2 Study of Elotuzumab
Elotuzumab, I really wanted you to learn about this, as you may have opportunities to participate in it or seek it out. You can see in the Phase II study, in combination with lenalidomide and low dose dexamethasone, over 84% of the patients demonstrated a response in relapsed-refractory setting. And that's pretty impressive. In relapsed-refractory setting, if you give len or len plus dexamethasone, the chance of response is roughly 60%. So you're clearly making an important impact with addition of a non-chemotherapeutic agent.

Slide 31 – Side Effect Management
Now let's move towards the last part of my talk, which will take a few more minutes, and then we will have time to ask questions as we go forward.

These drugs, while they have been very promising, they themselves, as well as the disease itself, can impact and do impact our body. Several side effects are noted. And it's important to know these side effects. Some of these side effects will be perceived by patients. Others will be picked up by the treating physician. And I'll share all of these with you and you'll have these slides as your handouts as well.

DR. ASHER CHANAN-KHAN:

Slide 32 – Anemia
So anemia is one of the most common presentations of multiple myeloma itself. And it could be mild, moderate or severe anemia. And while it can happen as a result of disease itself and filtrate in the bone marrow, it can also happen based on some of the treatments you get, such as alkylating agents or melphalan or bendamustine. These drugs can also – or cyclophosphamide– can cause also anemia. Lenalidomide can cause anemia as well. And so does pomalidomide. Radiation therapy can do that and bone marrow transplant procedures can do that.

Typically patients will feel excessive amount of fatigue, they'll feel breathlessness if they walk around the house. Or exercise or do play or something. And sometimes it interferes with sleep pattern of patients as well.

And the management of anemia is dependent on if it's because of the disease, then you have to treat the disease, of course. But if it's because of treatment, then we have to figure out whether we need to decrease the dose of the treatment in that patient, continue treatment. In severe anemia, which is usually defined as hemoglobin under 8 grams, we end up giving sometimes transfusion, depending on what symptoms it has.

A lot of times we use erythropoietin injections. These are growth hormones, specifically for red cells. And when you give them, it boosts your red cells and boosts your hemoglobin. So you can ask your physician about these injections and most of them, or all of them, should be aware of that, who's prescribing these drugs. You can ask about that and they can improve patients' anemia.

Slide 33 – Thrombocytopenia – Low Platelets
Thrombocytopenia, or low platelets. Platelets are cells that prevent patients and people and individuals from bleeding. Again, this side effect can be disease-related, that myeloma itself can suppress the bone marrow to a level that there is the production of – the production of these cells are significantly impaired. Or it could be drug-related. And it if's mild, it's around 100,000 or so. Moderate, is under 100,000, to about 50,000. And severe is under 20,000 platelet count.

Normally if patients have 20,000 platelet counts, they're fine, they will not spontaneously bleed. Their susceptibility to bleeding is not there. Under 10,000, it becomes critical.

Patients who have low platelets tend to have these skin spots, small dark red spots on their skin. They may have nose bleeds or gum bleeding. They may bruise easily or if they cut themselves, they may bleed longer, even with minor cuts. And you know the typical drug that does that is proteasome inhibitor or Velcade or carfilzomib would do that. But chemotherapy, such as bendamustine, cyclophosphamide, melphalan, these drugs also cause significant degree of thrombocytopenia.

Does IMiDs cause thrombocytopenia? Yes, some of them do and others don't. For example, thalidomide doesn't do that, but lenalidomide does cause thrombocytopenia. And so does pomalidomide.

Again, the management and treatment of this particular side effect will depend on what is happening. If it's critical and patients are already starting to have skin spots or bleeding in their gum when they're brushing their teeth, if that is already happening, perhaps platelet transfusion may be needed.

DR. ASHER CHANAN-KHAN:
In most cases, we go by without needing any transfusion. And many times, even though platelet come down, if patients are being treated with bortezomib, which is known as Velcade, we continue to treat those patients, because eventually the platelets will come up.

So there are various measures and it all depends upon how – what the exact cause of thrombocythemia is in patients.

Slide 34 – Renal Failure Adversely Affects Survival
Now renal failure is another important side effect of disease itself, as well as a side effect of various treatments that we use.

So one of the important things I wanted to bring to everybody's note is the fact that anemia – renal failure compromises survivability. In this particular graph we can see the median overall survival of patients diminished significantly if their serum creatinine goes above a certain level. Serum creatinine is a measure of renal function. As the creatinine goes up high, the survivability of patients goes lower and lower. And that primarily is because of the disease aggressiveness itself, but also because of the fact that certain drugs cannot be given to these patients, or if they are given to these patients, then their dose has to be adjusted accordingly.

Slide 35 – Kidney Damage
What are the causes of kidney damage or renal damage? As I mentioned, the disease itself is a big problem. Proteins produced by myeloma cells can actually cause the renal function to deteriorate. Sometimes dehydration, which is a very important factor in myeloma patients, can worsen it. Amyloidosis is another cause. And hyperviscosity basically means that because of excessive protein production by these myeloma cells, the blood becomes so thick that it doesn't necessarily flow well to the kidney, causing renal damage and deterioration of kidney function.

A very important point here is the dye associated with CT scans. Every now and then I see patients who are not diagnosed with multiple myeloma, were having back pain, went to an emergency room, got a CT scan and got a dye injected and found out that they have all these lesions and then referred to me. And by the time they come here, because of the dye that was given to them, the kidneys were damaged. CT scans with dye are not to be given to myeloma patients. CT scans by themselves without a dye can be done and that would not be a problem.

The best treatment when patients are coming in with kidney damage from the disease is, whatever regimen you use, one of the most important things to include is a proteasome inhibitor, such as Velcade or carfilzomib. There's extensive amount of data with bortezomib or Velcade in patients with renal failure, that these patients, if started earlier on, can be salvaged and their kidney can be reversed to normal functioning. I have had patients who had dialysis, needing dialysis, and started on treatment, came off the dialysis and absolutely normal kidney.

Painkillers such as ibuprofen, Motrin, non-steroidals class of drugs, is very detrimental. Last month I had a patient who was a known myeloma patient, has been for years, had started developing pain, took a lot of painkillers over the weekend just because he was hurting. Ended up being in the emergency room with complete renal failure. Very important. It is better to use morphine or certain drugs that don't hurt the kidney, than these particular agents.

DR. ASHER CHANAN-KHAN:

Slide 36 – Herpes Zoster or Shingles with Bortezomib
Herpes zoster is another important side effect of treatment. This is very important and very under-appreciated by many a clinician. Anybody who's getting a proteasome inhibitor, bortezomib or subsequent class of drug such as carfilzomib, should be on zoster prophylaxis or shingles prophylaxis. Shingles happens as a rash, it can be very painful, it can disseminate and sometimes it can be lethal. And it can be easily prevented by a drug which is orally given, an antiviral drug called acyclovir. Studies have shown that if people are maintained on this drug while through the treatment, and approximately about four weeks or 30 days after they stop treatment with bortezomib or other agents of the same class, that they will not develop shingles. And this is very important. Shingles vaccine, by the way, has not been considered safe in myeloma patients at this point, so I would not recommend patients taking that in order to prevent this side effect of bortezomib or same class of drug. It's important to use prophylactic acyclovir in these particular patients.

Slide 37 – Neuropathy
A lot of times I've gotten questions about neuropathy. And this has been a case because of three important reasons. Neuropathy can happen in myeloma patients themselves. Myeloma, there are some kind of myeloma cells that produce abnormal proteins and antibodies that can actually go and infiltrate nerves and can damage them. Sometimes I've seen myeloma actually infiltrating the nerves or developing tumors around the nerves, causing nerve damage. So myeloma itself can do that. But then the drugs that we use, such as thalidomide or bortezomib, can also cause nerve damage. Part of it I alluded earlier on, that carfilzomib may have less of this.

Then the third or fourth cause is the direct damage of the spine, where all the pain nerves and other nerves come out of. And myeloma being a disease that likes to affect the spine and the spinal bones, they can crush those bones or fracture them, and that can result in pain as well.

Treatment of this particular side effect or symptom of the disease, again dependent what is happening. If it is disease-related, then we need to treat the disease, radiate the disease, control the disease faster, such as those patients who may have cord compression, where immediate disease control is imperative, to prevent permanent nerve damage to critical organs such as bladder or rectum and so forth. And that has happened. Every now and then we will see patients who would have so much disease and such a fast-growing disease, that critical organ nerves will be affected and that can be detrimental.

If it's related to drugs, then dose titration down, using a lower dose, increasing the frequency. In case of bortezomib, but by changing from IV administration to a subcutaneous administration, has helped tremendously, patients' decreased incidence of neuropathy.

And as you can see, even after drugs are approved, we continue to learn for years and years to go by. There are certain treatments you can use, such as Neurontin, Lyrica, vitamin supplements have been used, such as B6. And various cocktails have been talked about, that can help patients control neuropathy.

Not everybody benefits from every measure. There's a whole spectrum of response. Some people do very well with Neurontin or Lyrica, these drugs that are nerve protective drugs. Others don't do very well. And these drug trials should be done and if there's no benefit, then perhaps going off these drugs is reasonable.

DR. ASHER CHANAN-KHAN:
Dose modification is very important.

So one of the things that you can do as patients or caregivers, is to communicate very effectively to your provider, to your physician and clinician or nurse practitioner, that you're starting to have neuropathy. It can be just numbing and tingling or it can be burning sensation or it can be as debilitating as severe pain that can be really, really affective. Some patients may have gait or motor problems. They may not be able to walk properly. I have seen patients who have lost their eyesight or their hearing completely as a result of neuropathy from drugs. Those cases are very rare, so it's not for you to be alarmed about. But clearly these side effects tend to happen and it's worth remembering them.

Slide 38 – Deep Vein Thrombosis
The next side effect that we're talking about is the deep vein thrombosis or blood clot. It is important to know that some of the drugs, such as lenalidomide, thalidomide and pomalidomide, this particular group of drugs tend to have a side effect, which is for some reason, predisposed, certain patients to develop blood clots. And they can happen anywhere in the body, but most commonly in the calves. Symptoms typically are pain in the calf or swelling of the calf muscle area, redness over it. It can happen very spontaneously. You may be sitting or sleeping and it'll come about. And sometimes this clot can travel to the lung, in which case the symptoms are usually just shortness of breath or breathlessness, even at sitting and patients are doing nothing. This is one of the reasons that anybody who's getting these drugs are required to be on some kind of anticoagulant drug. It can be as simple as aspirin, a baby aspirin, or warfarin, or in some cases we've used heparin as well, depending on each case individually. But some sort of anticoagulation should be given when using these drugs.

The incidence of this side effect to happen is approximately about 15% in patients. And when you give this prophylaxis, the chances of that comes down to about 3 to 5% at best. So there's a significant benefit to using prophylaxis.

And this is a second indication, this is a second side effect that I'm mentioning to all of you, where prophylaxis mattered. The first was shingles. And shingles prophylaxis, almost 100%, if you use the prophylaxis, 100% of the patients will benefit. In deep vein thrombosis also, when you're using these medications, if you use prophylaxis, you can decrease this particular side effect significantly in patients.

Slide 39 – Vertebral Body Fracture
Now vertebral body fracture or fractures of the spinal bone, is very, very common side effect of the disease itself. Sometimes it also is a side effect of treatment. And when does that happen? Sometimes the disease has taken so much hold in the spinal bones, if you look at the left hand corner, you can see the fracture, sometimes the disease has grown so much that the architecture of the bone is very weak. And when you treat the disease, as it dies, it was actually supporting the architecture from inside while it was eating it. And when the disease dies inside with treatment, these bodies will collapse. So every now and then I see patients who have advanced disease and I will treat them. And after second cycle or so, they'll start complaining of pain in their back. If you witness this kind of a symptom, you will know that happens in patients who have advanced spinal involvement.

Most of the time this can be fixed. The most common symptom is pain.

DR. ASHER CHANAN-KHAN:
But other nerve dysfunction such as numbing and tingling can also happen in hands and feet. This can be fixed by a procedure called kyphoplasty. It's an outpatient procedure. They put a balloon, they inflate the different ends of the bone, up and down, the roof and the floor of the bone, and put cement there and fix it. And by restoring the height and the architecture of the bone, the pain, the pressure on the nerves underneath that bone is relieved. And a lot of patients can have symptomatic relief from this particular side effect.

There are side effects of this procedure. Sometimes chronic pain can happen. Sometimes cement can leak. But by and large this is a very safe procedure and should be done.

Slide 40 – Biophsphonates
Because we all know that bone is an area that this particular disease likes to affect, we tend to use bisphosphonate therapy in these patients. Now bisphosphonates are agents that work in a very interesting manner. Nature has put two kinds of important cells in the bones. One cell produces bones. It lays down new bone. So you know, those who were young, like myself, I fell when I was about 10 years old, fractured my bone in the arm, was in a cast and six weeks later everything was healed and nothing could be detected ever again and I never had problems with my arm. So those cells that have the ability to put down new bones are called osteoblasts. These cells, nature put them to lay down new cement, new calcium, new foundation. And when the cells and the body tries to heal this way, like any other scar, bone scars also happen from osteoblasts, and nature has put them, very smart carpenters in there, who work as a refining cell, and these are called osteoclasts. Osteoclasts dissolve excess rough bone surfaces and smoothen them and dissolve the bone, excess bone away, that osteoblasts have put down.

What myeloma does is excite these bone-eating or bone-dissolving cells, called the clasts, and as a result, you start seeing all those lesions that I showed you earlier on in the talk. Bisphosphonate therapy, such as zoledronic acid or pamidronate, are drugs that have been used in myeloma, and they have been used in other disorders also, such as osteoporosis and osteopenia, patients with breast cancer and prostate cancer. These drugs basically stop the osteoclasts from further dissolving the bone and prevent the lesions that happen in the bone from growing further. These are very important drugs and they're used frequently in patients who have bone disease with multiple myeloma.

But they also have side effects. One important side effect is kidney damage. So zoledronic acid, which is the newer version, not necessarily more potent version, a lot of times folks erroneously impart a message that perhaps zoledronic acid is much more potent than pamidronate, which is an older drug, by the same company, same mechanism of action. But truly studies have shown that in terms of effects in preventing skeletal lesions and so forth, both drugs are equally effective. Zoledronic acid is usually given over 15 minutes and that's what the package insert and the company proposes, but I still like to take my time, over half an hour to 45 minutes to give this drug to patients, because it does have a renal toxicity, kidney damage, and that kidney damage is usually linked with the speed of how this drug is given to patients. So it's always safe if you take another 15 or 20 minutes to get this drug, it's not a big deal, because it does prevent kidney damage. Pamidronate, on the other hand, takes two hours and is much more safer in terms of the incidence of kidney damage. And a lot of time I rely on just that drug to help patients.

DR. ASHER CHANAN-KHAN:

Slide 41 – Osteonecrosis of the Jaw

The other important side effect of this drug, which is the last piece of this talk, last section, slide, is the osteonecrosis of the jaw. And this is a debilitating side effect. And I put it at the last because unfortunately there's not much that can be done when it's happened. These drugs, both pamidronate and more so zoledronic acid, and that's one of the other reasons that I tend to shy away from this drug, if I can, since there's no advantage of using, except time, so this particular drug, for some bizarre reason, affects the jawbones. And it causes necrosis of the jawbone. And once that happens, the tooth that is on top of that necrosis or teeth, maybe more than one, can actually break and fall. They basically just loosen and fall. And on the right hand corner you will see that ulcers and bone loss happen. I've had patients who actually had pieces of their jawbone fell out while they were trying to eat a meal and they brought it to me and said this is what happened. And this is an important side effect, well recognized by oncology community as a result of this.

While there's no cure once this happens, people unfortunately have to live with this disorder, they lose their teeth, they may have a very foul-smelling mouth or breath, and they may have pain and they may not be able to eat appropriately. And it's really a big challenge to manage these patients.

But there are now recognized measures that can be done to prevent. So for example, if you are on bisphosphonate therapy or you are prescribing bisphosphonate therapy in a patient who needed dental work-up, should be off the therapy for at least four to six weeks before you can do dental procedure. Now let's back up again. What dental procedure? Any dental procedure that requires going into the jawbone, pulling teeth out, drilling in the jawbone, is what is important here. Cleaning teeth, whitening, or scaling, none of that impacts this disease, so it's not necessary.

The other thing is that I like to do, dental work-up and dental evaluation, prior to even starting therapy. I have said to patients, hey, whatever dental work-up you need to do, let's do it right now.

Now this is important to remember. Myeloma therapy can be started and bone therapy may not need to be started immediately. You can start with myeloma therapy so that the disease can be targeted, but the bone therapy can be delayed until the patient has completed a dental evaluation. And that's an ideal and the smartest way to address this particular side effect of the drug.

I also tend to believe that once patients have gone into complete remission, that the myeloma is no longer at a substantial level in their marrow and it's not affecting the bones as such, that there's no need to continue bisphosphonate therapy to prevent bone lesions. Especially if they're in a well-monitored setting.

However, there is an important caveat here. There are recent studies that show that zoledronic acid, if used in a prolonged fashion, on a monthly basis for a long-term maintenance therapy, may provide some progression-free survival or more control of disease itself in some patients. And for many investigators and folks, they tend to believe that that is important enough for them to put patients on these drugs for a longer period of time than previously done. So I for one person don't necessarily do that because I think that right now there are so many other tools that can be used to control disease, that perhaps that is not necessarily important in my mind.

DR. ASHER CHANAN-KHAN:

Slide 42 – Thank You
In the last slide I would like to acknowledge all my colleagues at Mayo Clinic, who are at three different campuses. Mayo Clinic represents one of the largest multiple myeloma disease-focused groups and perhaps – and definitely in the country, but perhaps in the world. There are so many myeloma experts in this organization and we are divided in three different campuses, so we are in Rochester, Minnesota, which is north mid – well, Midwest, so to say. Arizona, towards Pacific. And Florida, which covers the Southeast. And it's just been an impressive opportunity to be with such world class myeloma experts in one organization, that work so seamlessly and have contributed so much to this field, starting from Dr. Kyle, who has dedicated his life, over 50 years or so, to myeloma therapy, and all the way down to the new generation myeloma experts that are joining the group.
So I'll stop here and hand it back to Ms. Berger.

Slide 43 – Question and Answer Session

LAUREN BERGER:
Thank you so much, Dr. Chanan-Khan, for a very clear and informative presentation. You've given us so much information. It is now time for the question and answer portion of our program. We'll take the first question from the web audience please, and this is from Kate. Kate asks, "What are the benefits and risks of a chemo holiday after 16 months of Revlimid® therapy, 12 months of Velcade plus Revlimid, prior to the Revlimid alone?"

DR. ASHER CHANAN-KHAN:
What a fantastic question and thank you for asking. This highlights exactly what countless myeloma patients are going through. So the question, let me rephrase it for you, the question pertains to maintenance therapy. A lot of investigators believe that controlling the disease long-term by continuous therapy may be an important way to do that. And there are several trials that have done. Patients post-transplant or post-induction have been maintained on Revlimid for a long period of time, as yourself. The premise is that it may impact their survival. The studies have shown that clearly you're able to control disease longer than somebody who is not getting it. But what has never been proved before, or has not been investigated and is not being investigated even now, is if one if you were to stop after you achieve the best response? And when the disease came back, you were started back on treatment right away. And does retreatment or maintenance equal better or different?

Why is this important, is exactly the reason you have. Continuous treatment, for long period of time, limits patients' ability to go around, be independent, forget the disease for a while. Cumulative side effects happen. Bone marrow continuously being bombarded by an agent. Studies that were recently done and published over the last year or two showed that continuous treatment with lenalidomide has resulted in a portion of patients developing different kind of cancers. The exact etiology or the reason for that is not known, but continuous treatment has resulted in these side effects. If you're also on steroids, that doesn't help you either. Your immune system almost always remains compromised when you're on steroids. If you are taking blood thinners, depending on what you are taking, is another added disadvantage. And then the cost of it is also an issue as you go forward.

DR. ASHER CHANAN-KHAN:
In the absence of cure or in the absence of big survival advantage, this remains a challenge. So what do I do? We at myeloma group at Mayo Clinic believe that again we have to come back to what the patient's risk is. If you are among those 20% of the patients who have high risk disease, then continuous treatment, maintenance therapy, is important for you. Because unfortunately those are the patients whose disease comes back fast, comes back rapidly, and it becomes a challenge controlling it.

If you are among the group that has low risk disease, then perhaps it is important to see that how much continuous therapy should be given. Although we don't know the exact amount or duration of treatment for these patients, new clinical trials that are coming forward, again, from various centers, led by my colleague at Mayo Clinic, will be looking at why not just do two years of maintenance therapy and then stop after that. You get the maximum benefit, thereafter don't do more.

Drug holidays are important. They're important for your body as much as they're important for your psychological well-being, they're also important for your body to recover. These are not innocuous drugs. They're not – even though they're reported or shared as non-chemotherapy drugs, good drugs, immune-mediating drugs and so forth, they have side effects, and continuous treatment is not necessarily always the best thing.

I always found that patient need a drug holiday, they enjoy a drug holiday, it is good for them mentally and it – this is a marathon, fighting this disease is a marathon, and so you do have to pace yourself.

I hope that I was able to answer your question.

LAUREN BERGER:
Thank you and thanks for that question, Kate. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Henry in Missouri. Your line is now open.

HENRY:
Yes, Doctor, you just touched on my question here in your previous answer. But my question was in regard to secondary cancers associated with taking Revlimid. I recently heard that the Mayo Clinic was recommending a maximum of two years on Revlimid, after someone has had melphalan previously. What is your position on that? Is that Mayo Clinic-wide or is that doctor?

DR. ASHER CHANAN-KHAN:
Thank you, Henry, for asking this question. So again this question is about maintenance and how do we best use it, what are the best agents to use it, and so forth.

First, to answer your question directly, for those who are not aware of this issue, the issue is that patients who have received autologous stem cell transplant after melphalan therapy were randomized to either receive Revlimid maintenance or nothing, which was the standard of care, was to do nothing after transplant. And two different studies were done. And both studies showed that patients who received Revlimid as a maintenance or lenalidomide, tend to have a higher incidence of different kind of cancer,

DR. ASHER CHANAN-KHAN:
second cancers they are called. These cancers could be bone marrow cancers other than myeloma, or they could be solid organ or skin cancers or other types of cancers, or AML, which is a kind of a leukemia.

So clearly both the studies were able to demonstrate this particular side effect of lenalidomide chronic therapy. Whether two years of therapy is better than indefinite therapy, we don't know the answer to that. Nobody at Mayo Clinic knows the answer to that. Those studies have not necessarily been done. This is what I mentioned, that Mayo is leading in partnership with other organizations that forms the ECOG, looking at a defined maintenance period of about two period. We believe as a group that limited amount of treatment, a defined period of treatment, may be much more important than indefinite. And in that context that study's going to go.

However, this particular side effect seems to be unique to patients who have received autologous transplant. Whether it is the autologous transplant that just makes the right environment for this particular side effect of second cancers to happen, would that happen with other patients who have not received melphalan, are questions that are tangentially answered, but not conclusively through studies.

One of the encouraging things, Henry, that you will see, is that these monoclonal antibodies that are being developed, may have a very important role in maintenance therapy. And they may be the way to go in future, or at least worth trying in future as they become available.

So answering your question more directly, we don't know, but I certainly, for one, among the myeloma group at Mayo, don't necessarily prescribe lenalidomide maintenance indefinitely.

LAUREN BERGER:
Thank you for your question, Henry. We'll take the next question from the web audience and this is from Alan. Alan asks, "Can you compare the effectiveness of chemotherapy with a transplant? Does one approach lead to a better survival rate or is it patient-dependent?"

DR. ASHER CHANAN-KHAN:
So, Alan, thank you for asking this question. I will try to understand what's in your mind. Chemotherapy, I would imagine you are relating to all the new drugs, pomalidomide, lenalidomide, and carfilzomib. All of these drugs versus – the novel agents, which are often referred to, versus the transplant.

The reason I think that that's what you're asking is most often nowadays, we don't use chemotherapy up front or induction – in induction any more, unless they are part of a regimen such as cyclophosphamide being part of some regimen and so forth.

So the answer to your question is that, as I showed you earlier on, patients who are diagnosed with multiple myeloma need to go through an induction treatment. And that induction treatment can be anything. It can be one to four drugs, combination. And most of the time people make that decision, physicians make that decision, based on their experience, what they are comfortable with, based on what they've heard some experts say, based on their fear of how aggressive the disease is or how much it is, or how soon they want to get a response out of a patient.

DR. ASHER CHANAN-KHAN:
Now as I mentioned during the talk, it is imperative now I think that individualized approach be applied to myeloma patient. Myeloma is a marathon now. It is a long-term planning. Especially for those who are not high risk, standard risk patient. So if you are a standard risk patient, as I mentioned again and again during the talk, the chances of your survival are significant, in eight to ten years. And eight to ten years I say significant because that also gives a lot more time for new drug development.

In that context it is imperative to pick what regimen you are going to do. A few years ago, it was imperative that everybody get a transplant and that was considered to be the only way that people would have a survival advantage, which usually lasted – measured approximately eight or ten months or twelve months at best, versus those who didn't get transplant. But nowadays we believe that various other regimens can deliver more or less the same benefit to patients as transplant does. And transplant can be deferred later on in the course of the disease. Such trials are ongoing and conclusive answer hopefully we will get in a few years. I'll stop.

LAUREN BERGER:
Thanks for your question, Alan. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Pat in Pennsylvania. Your line is now open.

PAT:
Thank you, Doctor, for your very good presentation, once again. I'd like to know if taking Revlimid and dex would cause a side effect of short-term memory loss. And also where can I send my body for myeloma research when my time ends?

DR. ASHER CHANAN-KHAN:
Pat, thank you so much for asking. What a wonderful question and a different topic that I had not addressed during my presentation.

Thank you for also thinking about the future generations and willing to donate your body at the appropriate time. There are various centers near you, U Penn and so forth are in your area, and in Mayo Clinic, a few times my patients have been kind and able to share that and we have learned a lot and developed a lot of therapies as a result of such contributions.

Revlimid and dexamethasone, as well as other chemotherapeutics, have been reported to have effect on memory. How they do that, we don't necessarily know that. And some people are affected a lot more than others. My patients have often complained about, that they may not necessarily be as sharp in doing mathematics, or they may not be as sharp remembering their notes if they are a pianist. Some people have complained that they just don't remember things and sometimes they think it's funny, sometimes it's a debilitating issue.

These drugs do penetrate the brain. That is a known fact. They have a CNS effect or the central nervous system, brain effect. And they do cause memory dysfunction.

DR. ASHER CHANAN-KHAN:
I don't know of any particular strategy that can prevent it. But if you are starting to see that, one would be to objectively get evaluated by your physician that that is happening. And then seek if there are other alternative treatment strategies that can be used. This is again another reason where I would not necessarily favor continuous treatment versus intermittent treatment, when needed by patients. Again, another reason that we should be cautious of writing these therapies forever and ever.

LAUREN BERGER:
Thank you for your question, Pat. We'll take the next question from the web audience and this is from John and John asks, "What can be done to reduce skin reaction to the injection site when using Velcade?"

DR. ASHER CHANAN-KHAN:
Good question. John, I don't necessarily have a good answer for you, which basically means I don't have an answer for you. There are times that you can use topical steroids, creams, to decrease the redness and the erythema that happens. You can use it a little bit ahead of time, the evening before at the site that you anticipate to get. You can use it afterwards also. But by and large I personally don't necessarily have a good answer to help you with that, that this could be completely relieved. And if it is extremely debilitating, then people have gone back to using intravenous use of bortezomib, which has been used in the past. Or switching to the newer version. And by the way, there's a new version of bortezomib coming as an oral formulation, which may be much more good in such situations. And for patients who have these reactions locally, more significantly so than others, maybe those oral drugs would be the best way to go.

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

OPERATOR:
Our next question comes from Mary in Florida. Your line is now open.

MARY:
Thank you. Doctor, I understood you say immunoglobulins over-produce in myeloma. I've been diagnosed six years ago, I was on Revlimid plus dex, Velcade plus dex, and now I'm on pomalist [sic] plus dex. But my immunoglobulins have always been very low.

DR. ASHER CHANAN-KHAN:
Mary, thank you for asking. And this completely highlights the reason, why the introduction was short, I just wanted to give a flavor, I couldn't go into the biology of the disease, but you brought a very important point.

So for the audience, what Mary is asking is what happens to the immunoglobulin. So all of us have different kinds of immunoglobulins. There are five different classes of immunoglobulins, as I mentioned earlier, A, G, D, E. Myeloma cell produces a particular kind. So in the example that I showed you, this particular patient's immunoglobulin was IgG kappa. And so this particular patient produces IgG levels.

DR. ASHER CHANAN-KHAN:
When you measure this particular patient's IgG levels, those will be high. As the disease will go more and more, I mentioned to you that the immune system goes down, which part of immune system goes down and that's the immunoglobulin. The normal immunoglobulin, so taking again this case, which would be IgD, IgA, IgM, in this particular patient will go down. And the abnormal will rise. So what happens is the bad guys go up and up and the normal immunoglobulins go down and down. This is what we call involvement or hypogammaglobulinemia. Hypogammaglobulinemia of the uninvolved immunoglobulin is a characteristic feature of multiple myeloma, happens very frequently in all patients, like yourself. And that's what you are experiencing, is hypogammaglobulinemia of the non-involved protein. But your involved protein will be anticipated to be high.

LAUREN BERGER:
Thank you for question, Mary. We'll take the next question from the web audience and this is from Kashika. "How often should a PET or CT scan be done to track the lesions of multiple myeloma? I have had three scans in the past 12 months. Is that too much?"

DR. ASHER CHANAN-KHAN:
Thank you, Kashika, thank you very much for asking this question. PET scan is a relatively newer technique incorporated into myeloma management. There is no magic number of why and how often PET scan should be done. There are some investigators who would say the disease should be investigated or managed or followed only by PET scan and that's the best way to do it. And others would say no. And then there's a group that will be in between.

Depending on what is the indication to do PET scan. So if you are a patient who does not have an M spike, whose disease cannot be measured by light chains or immunoglobulins that are high, and you are non-secretory myeloma, then perhaps PET scan is the most optimal way to follow your disease. And in that case, having it done three times, depending on how your risk of your disease was and what treatment you are getting, and what are the expected chances for your response, would be an appropriate thing.

On the other hand, if you have other parameters, whether they be in the urine or in the blood, that can be followed, to monitor your response to therapy, then those will be preferred and you can have a baseline PET scan done, and then after you've completed, concluded your treatment and all other parameters in the blood and urine have resolved, demonstrating remission, that a follow-up PET scan could be done.

So PET scan's utility varies by the scenario or the type of myeloma that exists and also where your physician thinks myeloma is popping up, especially if there is suspicion of extramedullary myeloma popping up, that's sometimes is a test that I love to use to find out.

LAUREN BERGER:
Thank you so much, Kashika, for your question, and thank you all for your questions. We hope this information will assist you and your family in your next steps.

Slide 44 – Myeloma and Caregiver Online Chats
The Leukemia & Lymphoma Society offers online chats for myeloma patients and for caregivers. Each of these chats is held weekly on Tuesday evening from 8:00 PM to 10:00 PM Eastern Time, and the chats provide forums for patients and caregivers to share experiences and support each other during this time. These are two separate chats. They are moderated by oncology social workers and they're free. So please consider participating. For information, go to **www.LLS.org/chat**. Or you can contact an Information Specialist at The Leukemia & Lymphoma Society.

I know there were a lot of questions today, so if we were not able to get to your question, please call an Information Specialist at LLS at **800-955-4572**, or you can reach us by email at **infocenter@LLS.org**. We would be happy to provide you with information about myeloma research, clinical trials, other questions about treatment, and also questions about financial assistance for treatment.

Thank you again for participating and thanks so much to Dr. Chanan-Khan for volunteering his time today.

On behalf of The Leukemia & Lymphoma Society, goodbye and we wish you well.

END