Living With Myeloma–Treatment and Side Effects Management

Speaker: S. Vincent Rajkumar, MD | June 3, 2013

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Slide 1: Welcome & Introductions

OPERATOR:
Hello, everyone, and welcome to *Living With Myeloma–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. Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Vincent Rajkumar for sharing his time and expertise with us today.

We have over 1,300 individuals participating from across the United States and from Australia, Barbados, Canada, China, Jamaica, Singapore and the United Kingdom.

We'd like to acknowledge and thank Celgene Corporation, Millennium: The Takeda Oncology Company, and Onyx Pharmaceuticals for their support of this program.

Slide 2: S. Vincent Rajkumar, MD
I am now pleased to introduce Dr. Vincent Rajkumar, Professor of Medicine, Chair, Mayo Clinic Myeloma, Amyloidosis, Dysproteinemia Group at Mayo Clinic in Rochester, Minnesota. On behalf of The Leukemia & Lymphoma Society, thank you, Dr. Rajkumar, for volunteering your time and expertise today.

The volunteer professionals who present our patient education programs receive no financial compensation for their time.

Dr. Rajkumar, I am now so privileged to turn the program over to you.

Slide 3: Multiple Myeloma–Treatment and Side Effects Management

DR. S. VINCENT RAJKUMAR:
Thank you so much, Lauren, and thanks for everybody who's on the call.

I am going to go through the treatment of multiple myeloma and management of side effects and supportive care with you in the next 40 minutes or so. After that I would be happy to answer any questions you have.

Slide 4: Myeloma
Multiple myeloma is a devastating malignancy. It is a cancer of the plasma cells. Plasma cells help us fight infections, by making antibodies. Approximately 20,000 people each year are diagnosed with multiple myeloma in the United States.

Slide 5: Bone Disease
In the last ten years we have made dramatic advances in the treatment of myeloma. When I see a new patient today, I am able to say that unlike, say, ten years ago, we have numerous options for therapy and these treatments are highly effective, as you see on this slide, where you can start with extensive bone disease and within a month or so, have almost all of these regress.

Similarly, in the last ten years, we have managed to treat complications and side effects much better. We've also improved significantly the overall survival for multiple myeloma patients.

DR. S. VINCENT RAJKUMAR:

Slide 6: Survival

Prior to the arrival of thalidomide, that was in 1999, the three-year survival rate of myeloma patients was only 42%. Now it is more than 80%, probably more than 90% in patients who are less than 65 years of age, eligible for a transplant. The average survival is in excess of seven to ten years.

Still, the survival of myeloma patients varies considerably, so that a particular patient may have an outcome that is much, much better or less better than what I've just given you.

Slide 7: Prognosis in Myeloma

How long a patient with multiple myeloma lives depends on many factors, just like in any other cancer. We have to ask the question, how healthy the patient is, that's the host factor. Whether there's kidney failure or not, how active they are. The second question is, how much myeloma are we dealing with, that is the tumor burden. We measure that by staging systems, International Staging System or the Durie-Salmon staging system.

All things being equal, though, the survival of multiple myeloma depends on many different cytogenetic abnormalities. And that is a marker of disease aggressiveness, which is how aggressive is the multiple myeloma.

Slide 8: Myeloma Risk-Stratification

If you look at the various genetic markers you could stratify multiple myeloma into three different groups. Most patients with myeloma, I would say probably 75% or more, have standard-risk multiple myeloma, where the FISH report or the cytogenetic report says the number of trisomies or hyperdiploidy, or it shows the presence of translocations 11;14 or 6;14.

These patients generally do extraordinarily well, particularly with new treatments. I think for patients less than 65 years of age, the average survival may be in excess of ten years.

There are about 15% of myeloma patients who will be in the intermediate-risk category, which is the t(4;14) subset. This group of patients did not have a good outcome until the arrival of bortezomib and since then, by using bortezomib early on in the disease course, the outcome has improved to match almost that of the standard-risk patients.

And then we have about 10, 15% of patients with multiple myeloma who have high-risk features at the time of diagnosis. This includes patients who have deletion 17p, 14;16 or 14;20 translocation and abnormal gene expression profiles. This is the group of patients in which we still need to make more advances and there are specific trials that are going to be designed just for the high-risk subset of multiple myeloma.

Slide 9: Myeloma Risk-Stratification

In general, the standard-risk patients seem to have an excellent outcome regardless of how you treat. And by that I mean it's like a marathon. There are many, many options we have. It doesn't matter which option is chosen first, as long as all the options are tried one after the other in sequence as needed, the outcome is great.

In the intermediate-risk group, bortezomib or Velcade® needs to be given early in the disease course, probably from the time of diagnosis. And if the patient is eligible, a transplant should also be considered.

DR. S. VINCENT RAJKUMAR:
In the high-risk patients we don't have a specific strategy that can overcome and these are patients who are candidates for clinical trials. What we know so far about this group is that achieving and maintaining a complete response is critical, particularly in this group. And in selected patients we are even considering allogeneic stem cell transplant, which is taking stem cells from a sibling or a matched donor.

Slide 10: Myeloma Drugs
There are numerous drugs that are available for the treatment of multiple myeloma. I have classified them into these three boxes here on this slide.

Until thalidomide came along, we just had steroids, alkylators. Alkylators are like melphalan and cyclophosphamide. And anthracycline, Adriamycin®.

Now since then, of course, we have had many new drugs. There is bortezomib, thalidomide and lenalidomide, which were approved a few years ago. And these three are independently active in myeloma alone or in combination with other drugs.

Now in the last years we've had two new drug approvals, carfilzomib and pomalidomide. And these are able to overcome resistance that occurs with the previous drugs. So a patient may have already failed bortezomib, Velcade, or Revlimid®, and carfilzomib or pomalidomide can still overcome that resistance. Carfilzomib is manufactured under the trade name of Kyprolis® and pomalidomide under the trade name of Pomalyst®.

Now there are other drugs which are active, which I'm hoping will get approved soon, and those are also Velcade-like drugs, MLN9708 and marizomib.

On the right-hand box you have drugs that are in Phase III trials or heading to Phase III trials, which have shown activity alone or in combination. And that includes panobinostat, elotuzumab, ARRY-520, anti-CD38 monoclonal antibodies such as daratumumab, and cyclin D inhibitors. This is the class, the five drugs that I've listed on the right side, these are the drugs that we are really looking forward to because we want to expand the number of classes of drugs that we have for use in multiple myeloma.

Slide 11: Myeloma Treatment Strategies
When a new patient is seen, or even during the course of the disease, there is a philosophical divide between two approaches and this is not just a philosophical divide that physicians have where certain physicians want to cure myeloma and certain physicians are more content with controlling it, but patients also come into camps. There are some patients who are willing to take on any number of side effects and any hits on the quality of life in order to pursue a cure. And at the same time I see patients regularly who tell me that how long they live is not as important as maintaining a good quality of life.

And based on these philosophical differences, you have various strategies that can differ. As you can see here, initial treatment for patients interested in a curative strategy may involve two or three or four drug induction, followed by one or two transplants, followed by maintenance therapy; the whole treatment going on for three, four years. On the other hand, patients interested in mainly a control approach or physicians philosophically predisposed to a control approach, may use sequential, two drugs, when that stops working another two drugs and so on. And they would also be willing to delay the transplant until it's needed, say, at the time of the first relapse. And then the maintenance therapy is given only when patients are not responding to the transplant adequately or they have high-risk features.

DR. S. VINCENT RAJKUMAR:
Unfortunately, nobody has done randomized controlled trials to compare these two approaches, to tell us which approach is better and which one would be wiser to use.

At this point I think both approaches are reasonable, both approaches need to be investigated in clinical trials and a lot of it will depend on patient characteristics, as I'll show later on.

Now I'm sure that many of you have already started your treatment and are at various stages of multiple myeloma, so bear with me as I go through the treatment of newly diagnosed patients. However, much of what I have to say about newly diagnosed patients applies at various stages of the disease, during relapse as well.

Slide 12: Approach for New Patients
In general, when we see a patient with multiple myeloma, we wonder whether the patient really needs therapy, because there are some patients who have just MGUS or smoldering myeloma, who are better off watched. Once we clear that hurdle and we say yes, the patient does have myeloma and they need therapy, the next question we ask is, is the patient eligible for a stem cell transplant. And the reason we ask this question is because if patients are eligible for stem cell transplant, we want to avoid melphalan until stem cells are collected and stored for future use. So that's the first step that we go through.

If patients are not eligible for transplant by age or performance status, then melphalan-containing regimens are excellent options, in addition to the other regimens that don't have melphalan as well.

Slide 13: Induction Therapy: Transplant Candidates
For patients who are candidates for transplant, we generally give about four months of therapy with a variety of different regimens that we have, any one of those. And then we collect stem cells. And at that point most physicians would proceed to an autologous stem cell transplant, where the stem cells are used from your own body.

In some centers, such as the Mayo Clinic, patients may also be given the option of storing the stem cells in the freezer for future use and continue on that therapy. In that case it's called delayed transplant. We are not doing the transplant at the time of diagnosis, but we are delaying it maybe by three or four years.

Slide 14: Major Treatment Regimens
What treatment options are available? These are all drugs that I've listed here, which are very active. You have the doublets like thalidomide-dex, Revlimid-dex, Velcade-dex. They work well. And then there are the triplets where three or more drugs are combined. You have VTD, VRD, carfilzomib-Rd, PAD, CyBorD and so on.

I don't want you to think or remember the details of each of these regimens. Suffice to say that any one of these is going to give an extraordinarily good response in the newly diagnosed setting. And if a patient uses one regimen, say somebody starts on CyBorD and then three years later the myeloma comes back, then any of the other ones can be used. And in general the sequence of which regimen is used first, second or third, probably does not matter. It varies according to the center, it varies according to access to these drugs, it varies according to the country, and there's no real data that one novel agent-based regimen is going to provide improved survival compared to another. There are physicians

DR. S. VINCENT RAJKUMAR:
who prefer one or the other based on their own preferences and their own experiences, but I think as far as data goes, there's very little to choose one from the other. A lot depends on the patient's characteristics, host characteristics, risk features and so on.

Slide 15: Additional Options in Transplant Ineligible Patients
In patients who are not stem cell transplant candidates, in addition to the options that I listed on the previous slide, patients can also use melphalan-based regimens for initial therapy such melphalan-prednisone or Velcade-melphalan-prednisone or melphalan-prednisone-thalidomide, MP, VMP and MPT respectively.

Slide 16: Evolution Randomized Trial
Now we did have a good study that was conducted by Dr. Shaji Kumar, a colleague of mine at the Mayo Clinic, published last year, which showed that when we compared three different regimens, these three modern regimens, CyBorD, which is called VCD, VRD, Velcade-Revlimid-dex, or all four drugs put together, the VDCR regimen, you can see that the overall response rate is high in all the regimens. The complete response rates are similar in all three regimens. And so we think that three drug regimens are probably sufficient and you probably don't need to increase to four. And then three drug regimens in general are comparable to each other.

Slide 17: Transplant Eligible
This is the approach we take at the Mayo Clinic for newly diagnosed patients. We also look, in order to make the choice of which regimens to use, so if there are 20 regimens, how do I decide which one to use for a particular patient? So we go through the biologic risk characteristics, the cytogenetic differences that I mentioned to you, and then look at the patient's characteristics and pick regimens.

Our approach at this point, which is always posted and updated on msmart.org, is that for standard-risk patients, the vast majority of patients, we are content to give either Revlimid-dex or CyBorD as initial therapy. And then the transplant is given either early or delayed. If patients have the 4;14 translocation and they have intermediate-risk disease, we certainly need to give Velcade early in the treatment course and any of the Velcade-based regimens are reasonable. We prefer the CyBorD or the VCD regimen, which is Velcade-Cytoxan®-dexamethasone. And then if patients are eligible, we do pursue early transplantation for the intermediate-risk patients. For the high-risk patients we use the VRD regimens, which is quite an expensive regimen and it combines two novel drugs, Velcade and Revlimid together. And this regimen has given some of the higher CR rates in trials so far. And we use that regimen and follow that up with a transplant if the patients are eligible.

Slide 18: Transplant Ineligible
In patients who are not eligible for transplantation, we pretty much use the same approach. For standard-risk patients either we use Revlimid-dex or CyBorD. But the main thing is that, since we are not doing the transplant, we give the treatment for at least a year or a year and a half. I've seen people who have taken Revlimid-dex or Velcade-Cytoxan-dex for five months, six months, and then they stop therapy because everything is going on well. That is not adequate. Treatment for newly diagnosed myeloma in the absence of transplant should be for at least 12 to 18 months.

DR. S. VINCENT RAJKUMAR:
For the intermediate-risk disease, we prefer the CyBorD regimen and we give it for about two years. For the high-risk patients, we generally start with VRD and then we continue with some form of maintenance.

Slide 19: Lenalidomide Maintenance
Generally after a transplant we just watch patients without giving any further treatment. But in the last year there have been three trials that were published in the *New England Journal of Medicine*, looking at whether we can delay the time to progression and whether we can improve survival, by using Revlimid right after a transplant. So these three trials, two of them in the transplant population, one in the non-transplant population, they showed that you can delay when the myeloma becomes active again. That is defined by the term progression-free survival. That means how long does it take for the myeloma to become active again. And that changes significantly if you add Revlimid as maintenance. Instead of the myeloma coming back about two years after the transplant, now it comes three and a half years after the transplant or four years after the transplant, if Revlimid is used as maintenance.

So why do we not recommend Revlimid maintenance for everyone? At least at Mayo and myself, we don't recommend it for all patients because how long a patient lives has been shown to be prolonged only in one of these three trials. And we are waiting for results of the other two. Primarily because there is an increased risk of second cancers with the use of Revlimid. So if you look at the column "second cancers", you will see there's 7 to 8% risk of second cancers in patients who are taking Revlimid, compared to 2 to 3% if patients did not take Revlimid. Now these second cancers can be serious and therefore we are being cautious until we get more data on the survival of these patients.

Slide 20: Newly Diagnosed Myeloma With Special Circumstances
A number of myeloma patients, either at the time of initial diagnosis or somewhere during the treatment course, develop some special circumstances. One is plasma cell leukemia, when the plasma cells or the myeloma cells come out into the blood circulation and you can detect it on a regular blood test. Second one is extramedullary disease or extramedullary plasmacytomas. These are tumor-like outgrowths that grow in organs other than bone and can sometimes be seen even on the skin and the soft tissues. And a third is kidney failure, which occurs in about 10, 20% of myeloma patients at the time of diagnosis and in a lot more during the disease course. Now these patients need special attention.

Slide 21: Risk-Adapted Therapy
As I showed you before, for patients with high-risk, intermediate-risk and standard-risk disease, I've given you the regimens to use. If patients have plasma cell leukemia or extramedullary plasmacytomas, oftentimes we use a more aggressive regimen, which includes five or six or seven drugs to control the disease. A regimen that we commonly use is called VDT-PACE, developed by the Myeloma Institute at Arkansas.

For patients who are in kidney failure, one of the main concerns is to use drugs that are not cleared by the kidney, so that there's no extra side effects. Velcade, thalidomide, steroids are all safe to use in kidney failure and you can give the same dose as patients who don't have kidney failure. And so we prefer those drugs to control the kidney failure and then we can use other treatments when needed.

In general, and I will cover this later, with any of these regimens we use low doses of dexamethasone and once-weekly Velcade.

DR. S. VINCENT RAJKUMAR:

Slide 22: Treatment of Relapse

As I mentioned, many of the treatments that I discussed can be used in patients with relapse as well. When a patient relapses the first question I ask is, what was the response to the first regimen that they received? If a patient has had, say, VRD as their front-line therapy, and then one year later the treatment was stopped, and three years later the myeloma is back, we usually go back to the first regimen because we know it works and it works well.

The second consideration is whether the relapse is only paraproteins. So many of you may have had just the protein going up with no other side effects, in which case oftentimes we just need to hit it back with a milder regimen and it will get the myeloma back into remission. Versus an aggressive relapse where the myeloma is back and this time there's either kidney failure or bone lesions or high calcium, where the treatment now has to be more intense. So we look at what regimen was first used, we look at how aggressive the relapse is, indolent versus aggressive, and then decide on the treatment regimen.

We also look at whether stem cells are available. If a patient has had collection of stem cells for two or three transplants and the first transplant works really well, then the myeloma comes back, that would be a good time to use another transplant because we can get them back into remission for some more years.

Slide 23: Myeloma Treatment

This is probably one of the most important slides, which is that we really need to look at the patient in the middle. And those various triangles represent the host characteristics, the aggressiveness of the disease, how much tumor burden we have, and the patient's preference, in order to decide which kind of approach to use, whether it be in the newly diagnosed setting or in the relapsed setting.

I would prefer that most of you investigate the availability of clinical trials because a lot of the progress has been made by patients willing to participate in clinical trials and by many, many clinical trials that have been done in the last ten years. So even though I have presented rough algorithms on how to approach multiple myeloma treatment, we generally tell people that we prefer, if they are eligible, to participate in clinical trials.

Slide 24: Randomized Trials

These are some examples of newly diagnosed trials that you or a newly diagnosed patient could consider. And these are listed on this slide. There are new trials that are coming up. The ECOG trial is going to look at carfilzomib or Kyprolis-Revlimid-dex versus Velcade-Revlimid-dex. There is a SWOG trial for high-risk patients, looking at elotuzumab combined with Velcade-Revlimid-dex. It's not so important to remember the trials, but the concept that participation in clinical trials and asking your physician about participating in clinical trials is important, because there are many innovative trials that are now available.

Slide 25: Thalidomide, Lenalidomide, Pomalidomide

Now let me shift gears and go through some of the treatments we have currently in use and the side effects associated with these treatments, and how to manage these side effects and some supportive care issues.

DR. S. VINCENT RAJKUMAR:
Now the drugs that we call iMiDs, or immunomodulatory drugs, there are three of them: Thalomid®, Revlimid, Pomalyst. The generic names are thalidomide, lenalidomide and pomalidomide. As you can see, they look the same in terms of chemical structure, with just minor differences. However, when you give these drugs to the patient, their behavior is quite different, one from each other.

Thalidomide is a drug notorious for causing sleepiness because it was developed as a sleeping pill. It also is one of the most constipating drugs around. It can cause nerve damage like numbness, tingling. And these are all things to remember.

Revlimid, on the other hand, generally doesn't cause that much sleepiness, constipation or neuropathy, but low blood counts and predisposition to infection is a consideration. Similarly, rash is a problem with thalidomide and Revlimid.

Pomalidomide is the new drug that was approved in the last year and it's more potent. I think it is probably a little more well tolerated than even Revlimid. Low blood counts seem to be the main problem.

All three of these drugs may cause blood clots and so all patients need to be on some kind of blood thinners.

Slide 26: Bortezomib, Carfilzomib
Now the other class of drugs that we use are the proteasome inhibitors. These block a protein enzyme that we all have in cells called the proteasome, and thereby cause cells to die. The first one that was approved is Velcade, also called bortezomib. And the new one approved is Kyprolis or carfilzomib.

Now Velcade, when it was first developed, the main side effect was nerve damage or neuropathy, numbness, tingling, often painful. It has some GI side effects like nausea. Some patients may have vomiting or diarrhea. Low blood counts are also a problem. Infections, particularly herpes zoster or shingles activation, is a problem and we routinely give something to prevent that.

Kyprolis generally in the studies done so far does not seem to have that much neuropathy as bortezomib does. However, there is some concern with people getting infusion reactions, particularly with shortness of breath and lung symptoms, that we are carefully watching and studying.

Slide 27: Side Effect Management
How do we manage many of these side effects that patients may experience with these drugs as well as the old ones like melphalan and dexamethasone steroids? I want to make sure that everyone talks to the physician. You need to probably make a list of the symptoms that are occurring from the last time you saw the physician, so that you can mention the side effects. Never hesitate to point out to a physician what kind of side effects you're experiencing. Because many of these can be managed and many modifications can be made.

Some side effects can become quite permanent and problematic and so it's better to bring it to the notice of the physician. Oftentimes patients worry that if they tell something maybe the physician might stop that drug, which is controlling the myeloma quite well and you don't want them to do that. But please have a good communication.

DR. S. VINCENT RAJKUMAR:
My teaching has always been that it's better to prevent side effects than to deal with them after they happen. And this is something that not all physicians are using and so it's probably something worthwhile exploring with your physician, if you feel like you're not getting some of the strategies that I'm recommending.

Slide 28: Dexamethasone (Decadron®) Dosing
Number one. Steroids are part of almost all myeloma regimens. This can be either in the form of prednisone or dexamethasone or Decadron®. One of the first things to make sure is that nobody gets high-dose dexamethasone. That is the 40 milligrams given four days on, four days off, four days on, four days off. That regimen is associated with inferior survival. Increased risk of almost everything from blood clots to pneumonia, to rash, and cardiac side effects. There are a few select patients who may need the high-dose dexamethasone, and in those patients the physician will tell you why they particularly need it. But as a default, in general, we don't use the high-dose dexamethasone with any of the modern regimens. The one that we use is just 40 milligrams once a week and sometimes we even reduce that dose to 20 milligrams once a week, once the patient has responded well.

Slide 29: Bortezomib (Velcade®) Dosing and Prevention of Neuropathy
The second drug that one needs to be very careful about is Velcade. Now Velcade as I mentioned to you, when it first came out, nerve damage was one of the big problems and I was not a big fan of Velcade at that time because some patients could get very severe neuropathy, even within two, three months. And sometimes it came on unannounced. Patients were doing extremely well, three months, and then the fourth month they have an intolerable neuropathy with severe pain. Again bortezomib or Velcade neuropathy is better prevented than treated. And the best way to prevent it is from the beginning use once a week Velcade, not the twice a week, and to give the drug subcutaneously, under the skin, not intravenously. The risk of severe neuropathy drops from like 25% down to less than 5% with these two strategies, each one, and together, by giving it once a week and subcutaneously, you can probably lower it to very, very low numbers. In fact, there are many patients of mine who are able to take Velcade for years on end after starting and maintaining with the once-weekly subcutaneous. It has become a regimen that you can actually give very long term.

Now there are times when Velcade has to be given twice weekly and there are times when it has to be given intravenously, but I think the default is generally once weekly subcu. And we also start giving breaks, by giving it three weeks on, one week off, after the myeloma is fairly well controlled.

Slide 30: Blood Clots
Blood clots. These are problems, in general, myeloma patients probably have a slightly higher risk of blood clots than patients who don't have myeloma. But it's made worse by drugs like thalidomide, Revlimid and possibly pomalidomide or Pomalyst. Again, better to prevent than to treat. All patients getting iMiDs, all patients getting thalidomide, Revlimid or pomalidomide should be on some blood thinner. If they have no other complications, no other risk factor for blood clots, an aspirin a day should be enough. If they have other risk factors for blood clots like a history of a blood clot in the past or they have other cardiac problems, are not moving around too much, then a more potent blood thinner like Coumadin® or warfarin or low-molecular-weight heparin is needed. If a blood clot does occur, then patients should go on Coumadin or low-molecular-weight heparin, but they can still continue the treatment.

DR. S. VINCENT RAJKUMAR:
Blood clots in myeloma with these drugs are generally, even when they occur, not very serious in most patients, but there are 3, 5% of patients who can get blood clots in the lungs, which could become life-threatening.

Slide 31: Stomach Ulcers and Bleeding
When we give steroids, another big problem that happens frequently is stomach ulcers and bleeding, particularly with the steroid dose. High-dose dexamethasone can irritate the stomach and cause significant stomach pain and even stomach bleeding. And therefore we use the lower dose of dexamethasone, that helps, but in general we use some kind of antacid like Prilosec® or Zantac® or something like that, routinely, in all patients when taking dexamethasone in order to prevent these side effects.

Slide 32: Other General Tips
As I mentioned to you earlier, there are other tips that people can use. Dexamethasone patients get anxiety and inability to sleep in the night. Some patients have told us that when they take the dexamethasone at bedtime they are able to sleep and then the next morning they're able to be awake and alert when the dex actually kicks in. So if you take it in the morning and you find you're not able to sleep in the night, then try the dexamethasone in the night and see if that will help.

Giving breaks with the Velcade, giving it weekly for three weeks and then giving one week off, and that one week off makes a lot of difference in quality of life. So once the myeloma is controlled, then giving those weeks off or treatment holiday often helps.

In patients who are older, Revlimid at the 25 milligrams may cause excessive fatigue and so ask your doctor to see if you're doing well, to reduce the dose to 15 or even 10 milligrams, to control these side effects.

Long-term use of Revlimid, like very long-term, two, three years later, there is a subset of patients will get pretty bad diarrhea and some patients can get thyroid problems and those also have to be kept in mind then, you should inform your physician.

Slide 33: Infection Prophylaxis
Myeloma itself increases the risk of infection and this is made worse by our treatments. We recommend that newly diagnosed myeloma patients, for the first three or four months, should be on some kind of antibiotic such as Levaquin®. Patients taking Velcade should get always some prophylaxis for shingles, such as acyclovir or valacyclovir or Valtrex®. Patients taking steroids for a long time should take prophylaxis against pneumocystis, which is a parasite that can cause lung infection. And usually one Bactrim™ a day, like single strength, or inhalation with pentamidine can take care of that.

Slide 34: Supportive Care: Bisphosphonates
Let's just do a little bit of supportive care. We have made a lot of progress in myeloma because bone disease, the incidence and frequency, has been lowered by the use of drugs called bisphosphonates. This includes Aredia® or pamidronate or Zometa®, also called zoledronic acid. These drugs are generally used in almost all patients with myeloma, especially if they have bone disease. Recent studies show that the use of these drugs may even prolong life. However, they do have side effects and therefore we usually recommend them monthly for a year or so and then lower the frequency to every three months and after two years or so, stop it.

DR. S. VINCENT RAJKUMAR:

Slide 35: Osteonecrosis of the Jaw
You should get your dental hygiene checked and teeth extracted before these drugs are started because there's a complication called osteonecrosis of the jaw where, as you can see on this slide, the jawbone is exposed inside the mouth, and that can be painful and cause problems. So we generally recommend having teeth work done before starting on these medications. And to not take it indefinitely, but for, say, a year or two and then watch.

Slide 36: Supportive Care
There are other supportive care measures that have also helped patients. Pain control is very important. Kyphoplasty or vertebroplasty can be done to decrease pain due to compression fractures in the back.

Occasional patients, we generally avoid radiation in myeloma, but occasional patients, where they have a very large single painful lesion that's causing a lot of pain, radiation helps quite well.

Slide 37: Redefining Myeloma
Before I close I just want to tell you about new things that are developing in the field. So far for patients who are asymptomatic with myeloma, called smoldering myeloma, we generally watch these patients without starting therapy, until bone lesions or renal failure occur. Now there is a move to redefine multiple myeloma because we have started to look at the question, now that we have so many good drugs for myeloma, is it possible to cure this disease by using these effective treatments early in the disease course, rather than waiting for the bone lesions to happen, when it may be too late.

Slide 38: Biomarkers of High Predictive Value in "SMM"
And so a group of us are working on redefining multiple myeloma and there are some high-risk smoldering myeloma patients that we can identify, who might benefit from early therapy, such as patients who have lots of bone marrow plasma cells, more than 60%, or when the light chain ratio is 100 or more. So smoldering myeloma patients with these kind of numbers, we are starting to look at treating early, and there are more biomarkers that we are looking at.

Slide 39: High-Risk Smoldering Multiple Myeloma
We think that there is a group of smoldering myeloma patients, called the ultra-high-risk smoldering myeloma patients, who might benefit from treatment. There is a group of smoldering myeloma patients called high-risk smoldering myeloma, who may be candidates for a trial that is ongoing across the U.S. looking at early therapy with Revlimid. And then the vast majority of smoldering myeloma patients who may not need any therapy. And so there are centers in the U.S. who can differentiate these three groups and try and predict which patients with smoldering myeloma may need early therapy. There is probably going to be a publication coming out soon showing that early therapy of smoldering myeloma may prove to be beneficial and prolong life, and so I wanted to share this information with you.

Slide 40: Contact
Now I know I've covered a lot of aspects of myeloma treatment and supportive care and it's very hard to keep these things in mind. I do not mind getting emails from patients as long as it's like a few lines with a

DR. S. VINCENT RAJKUMAR:
general question, I usually reply. If you have a more specific question about yourself, send me a note anyway and if I can help I will. Otherwise you may need to go and see one of the myeloma specialists and I can help give you names of people who might be helpful.

I've also given you Twitter accounts that I operate, where if you ask a general question and I reply, it will go to not just you, but to others as well.

I will close here and I will be happy to answer any questions for the remainder of the time. Thank you very much.

Slide 41: Question and Answer Session

LAUREN BERGER:
Thank you so much, Dr. Rajkumar, for a very clear and informative presentation.

We'll take the first question from the web audience, please, and this question was asked by three different people, Dan, Pamela and Tracy. "What is the connection between myeloma and amyloidosis, and are there difficulties in treating a patient who has myeloma and amyloidosis, and what kinds of treatments do you use that might be different than if you just had myeloma?"

DR. S. VINCENT RAJKUMAR:
Thank you. That is an excellent question. Amyloidosis is a protein problem. Approximately 10% of patients with multiple myeloma may have amyloid on top of the myeloma. And conversely, approximately 10% of patients with amyloid may have multiple myeloma in addition to the amyloid. What is amyloid? As you know, myeloma patients know very well that there is an M protein or a monoclonal protein that is measured to follow the multiple myeloma. This M protein is actually the antibody that is made by the myeloma cells. Pieces of this antibody can go and deposit themselves if they're abnormal, and to misfold, they don't fold properly, and these misfolded proteins can get deposited in various organs in the body such as the heart, liver, tongue, kidney, and cause heart failure, liver failure, enlargement of the tongue, kidney failure and so on. This process is called amyloidosis. It requires certain specific tests to diagnose.

Myeloma itself doesn't usually go to the liver and the heart. It just stays with the bones. It may cause kidney failure by precipitating in the tubules, but in amyloid the proteins actually deposit and infiltrate these organs.

Amyloid patients, because they have organ dysfunction in addition to the myeloma, need to be treated with more care. The risk of side effects is greater. The risk of mortality from a stem cell transplant is also higher. With myeloma there's 0 to 2% mortality with a transplant versus in amyloid, it's higher.

So we just approach amyloid patients with more care because the heart may be involved or the liver or the kidney may be involved.

The symptoms of amyloid are fairly straightforward, so if you have these symptoms, your physician should be able to pick it out. The diagnosis is made on biopsy.

LAUREN BERGER:
Thank you for your question and for that very comprehensive answer. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Elizabeth in Massachusetts. Your line is now open.

ELIZABETH:
Hi. Thank you very much, Dr. Rajkumar. I'm wondering what your research has shown regarding how long a patient should be on bisphosphonates, infusion therapy, after stem cell transplant. Thank you.

DR. S. VINCENT RAJKUMAR:
Thank you for the question. The question is, how long should a patient be on bisphosphonates after the stem cell transplant. The specific randomized trial that looked at this question, there was a French trial led by Michel Attal, took patients after a transplant and divided them into three groups. One group got no treatment, one group got bisphosphonates and one group got thalidomide and bisphosphonates. They did not find any major benefit to the bisphosphonates after the transplant was done. Now remember these patients got two transplants in France, so they've already received probably about eight to nine months of bisphosphonate therapy. And then the question was, should they get additional therapy. That's the only trial available to answer this question and using that trial as our backup, the Mayo Clinic guidelines are that we use monthly bisphosphonates for about a year or so and then after that, reduce it to every three months, so that we keep the benefit, but reduce the risk of the osteonecrosis of the jaw and other side effects that can occur from bisphosphonates. And so if you're after a transplant, I'd probably give you every three months for a year and then stop it, so by two years from the initial diagnosis, patient would be off everything, for a while at least. If the myeloma comes back active, then we can resume it back at the once-a-month schedule.

LAUREN BERGER:
Thank you for your question, Elizabeth. We'll take the next question from the web audience and this question is from Peter. "I receive subcutaneous Velcade injections twice a month. What can be done about the reaction I have at the site of the injection? I have large red welts which sometimes last for two weeks."

DR. S. VINCENT RAJKUMAR:
Thank you for that question, Peter. It is not easy. The manufacturer does have some recommendations on diluting the Velcade a little bit more to avoid these local reactions. But if it's just red spots which are not itchy or not bothersome, then it's okay. But if they're itchy, they're irritating and painful, then we probably should switch back to the intravenous route. If the dilution doesn't work.

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

OPERATOR:
The next question comes from Nancy in New Jersey. Your line is now open.

NANCY:
I have osteonecrosis of the jaw from high-dose Zometa. And my Zometa was stopped and then my IgG is coming up to like 1,960. And I was curious if the Zometa would work well with my rising number to lower that. Or the osteonecrosis, would that eliminate me from getting it again?

DR. S. VINCENT RAJKUMAR:
The question is, if a patient already has osteonecrosis of the jaw from Zometa, can you give them Zometa again. And the answer is yes. Osteonecrosis of the jaw is a complication of the Zometa, which probably occurs during some dental intervention. The fact that it's occurred doesn't mean that it's going to happen again when you give the Zometa again. We usually don't like to give Zometa once this complication has occurred, so we give patients a break for a while. But if the myeloma comes back and it's causing bone disease, then we just go ahead and start it back when needed, but just pay close attention to the dental hygiene before starting it, and avoid any dental extractions or interventions while the patient is on that therapy. So yes, you can go ahead with it.

Now these drugs were used monthly because that's how the trials were done, but biologically they have very long half-life. If you give Zometa once, it probably stays in that place for a year or so or more. So we generally think we don't need to give these drugs monthly. And so if you were to restart I would say take it every three or four months and that way you'll reduce the risk of this complication happening again.

And then finally, I don't think this drug by itself is going to lower your IgG level. We have done studies, very rarely does Zometa or Aredia actually lower the M protein level. It always has to be done in conjunction with specific myeloma therapy, trying to kill the myeloma cells.

LAUREN BERGER:
Thank you for your question. We'll take the next question from the web audience and this is from Nat. "Are there any other crucial questions or things that a newly diagnosed patient needs to ask about or be aware of?"

DR. S. VINCENT RAJKUMAR:
That's very broad question. The things that a newly diagnosed patients should be aware of, number one, is, are they a transplant candidate, what are the cytogenetic abnormalities, which type of cytogenetic abnormalities do I have, and how does that influence the choice of therapy. They should talk to their physician about, are we going to do a transplant early or not. Patients less than 65 we recommend that they collect stem cells, enough for at least two transplants. Patients over the age of 65 are better off with an early transplant, if not, collect enough for one transplant and freeze. Maintenance therapy after the transplant is completed. Make sure you check off the main things. Prophylaxis against shingles with Valtrex or something like that. Bisphosphonates, should I take Aredia or not. Something for the stomach. Some antibiotic for the first four months. Be aware that blood clots can happen, so if one leg swells up and the other one has not swollen up, then you probably have a blood clot and should be seen quickly. Those are some of the things to keep in mind.

LAUREN BERGER:
Thank you and thank you for your question, Nat. And just for your information, if you'd like a list of questions or suggestions to speak with your physician or treating team about, please call the Information Resource Center and they can help you personalize these questions and I'll give you that information at the end of the program. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Robert in California. Your line is now open.

ROBERT:
My question is, I took Velcade and it was very effective, but troublesome with my body, so the physician cut the protocol short. In the meantime I have two side effects. One, diarrhea, that's been going on for about four months and it's getting better, but the treatment has been somewhat lacking I think. And then very severe neuropathy in the toes and the fingers. How do we accomplish curing those issues?

DR. S. VINCENT RAJKUMAR:
One question for you before you go off the call. Were you also taking Revlimid?

ROBERT:
I am on Revlimid now.

DR. S. VINCENT RAJKUMAR:
And is the diarrhea since you started the Revlimid or even before?

ROBERT:
Before. But the diarrhea is improving, I must admit, but it's been a long siege.

DR. S. VINCENT RAJKUMAR:
I will answer the question. So as I mentioned early on, many of these side effects, better to prevent than to treat because once they do occur, only time can help these things. Particularly neuropathy. What we can do is maybe mask the neuropathy with Neurontin® or antidepressants or some pain medications. Similarly for the diarrhea, use antidiarrheal medications to control the diarrhea. But both those side effects, when they happen, they tend to last for a while and only with stopping the treatment and waiting for some time to elapse will allow those side effects to go away. The good news is that we have so many options for myeloma, that hopefully your physician will be able to find a regimen that does not contain the offending agent. So with Velcade, if Velcade's the one that caused the problem, and you do need a Velcade-like drug, then Kyprolis can be used and it has very little neuropathy risk. One can also use other drugs like Revlimid and dexamethasone or melphalan or cyclophosphamide instead, to gain time. So after a year or two has gone by and all the neuropathy and everything else is resolved, if you really need, you could try Velcade again. But given the other options, you want to probably try all those and exhaust before you go back to Velcade. And if you do go back to Velcade, then you don't do the twice-weekly intravenous route, which is probably what caused these symptoms, and rather do once-weekly subcutaneous, three weeks on, one week off. Hopefully the side effects will be less.

LAUREN BERGER:
Thank you for your question, Robert. We'll take the next question from the web audience. "What is the longest length of time that a patient can remain on Revlimid after transplant, if the patient has no serious side effects?" And that's from Sandra.

DR. S. VINCENT RAJKUMAR:
Thanks for that question, Sandra. There is no limit. On the trials that you saw, there were patients who stayed on Revlimid for four years or so. At Mayo we have patients who have stayed on Revlimid for seven, eight years even. I have patients who participated in the very, very first newly diagnosed trial of Revlimid ever conducted, who are still on the trial, and that's probably eight, nine years later. So there's no limit. What we don't know is whether the duration of therapy can increase the risk of second cancers or other complications and therefore some of us are recommending that if we do do maintenance, to restrict it to two years, and then watch closely and restart it, if the myeloma seems like it's coming back. That's just a judgment call. If you're doing well on four years, very hard for someone to say stop unless you are concerned enough to stop. There is a trial that ECOG, Eastern Cooperative Oncology Group, is going to conduct, where we are going to compare two years of maintenance versus indefinite, to try and determine what is the optimal duration to which Revlimid should be given.

LAUREN BERGER:
Thank you for your question, Sandra. We'll take the next question from the web audience from Perry, "I'm living in partial remission and continuing low-dose Revlimid. Other than lab tests, which are taken monthly, what are the signs I need to watch for, to tell me that my myeloma condition has deteriorated and that I might be refractory for Revlimid. How fast can deterioration occur? I visit with my doctor or nurse practitioner monthly."

DR. S. VINCENT RAJKUMAR:
Thank you, that's a very commonly asked question and patients want to know what can I do to make sure that we catch the relapse in time. I try to reassure patients that if you're getting followed regularly, particularly if you're getting followed monthly, we hope that 99% of the time we will catch the relapse on the blood test before you get any symptoms. We watch the serum M spike and the serum free light chain assay regularly. The urine should be checked at least once every three to four months because sometimes there's something called a light chain escape, where the myeloma relapse is occurring primarily in the urine and you can miss it if you don't check the urine. And occasionally initially the patient has had an M protein, but at the time of relapse there is no M protein and the relapse was mainly in the bone marrow. And so watching the hemoglobin and the blood counts give the clue as to whether something is going on. So nine out of ten times or more we should be able to catch the relapse before you get any symptoms, as long as you're followed regularly and they're checking the correct test. Serum M protein, free light chain assay. Every three, four months, urine test. Get a blood count every few months – monthly on treatment or every three, four months if not on treatment.

What are the symptoms that myeloma might be coming back? If you find yourself getting new pain that is unexplained in one particular area, you need to tell the physician and they need to image it. Even if the X-ray is negative, if the patient complains of persistent shoulder pain, I would get an MRI of that area. Any new fatigue, weakness, may suggest that the kidneys are failing or the calcium is high. And so you

DR. S. VINCENT RAJKUMAR:
want to again bring that to your physician's attention, if that happens. Any lumps or bumps. Most of the time myeloma doesn't cause any lumps or bumps, but as I mentioned to you, at the time of relapse, patients can get extramedullary plasmacytomas outside the bone. And those can be felt. So if you get a bump that is new, you may want to call the physician's office in between the visit and say something new has cropped up and I need you to look at it and maybe take a biopsy.

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

OPERATOR:
The next question comes from Bill in Indiana. Your line is now open.

BILL:
My question is that I was on Zometa for five years after I had my chemo and everything. And I went through the necrosis, the very beginning of it. International Multiple Myeloma Foundation sent me the mail on it, but it was too late. So they took me off of it. But I feel my bones are more strengthened with it. So when I've been going to all these teleconferences, and the doctor says some people have it every three months, and when I went back to my doctor he said he'd rather not me to do that. Isn't Zometa good for your bones as far as strengthening it? That's my question. Because if so, then I need to find another doctor.

DR. S. VINCENT RAJKUMAR:
I will answer that question. So if you had, like the other patient who stated the same question, if you had Zometa and it caused a complication like osteonecrosis of the jaw, restarting that treatment is not a decision that is made lightly because, you know, sometimes the osteonecrosis of the jaw can be quite bad. I've had a patient, for example, who has to have their whole lower jaw taken out. So this is not made very lightly. And what we look at is how bad is the myeloma, how much bone disease are we having, is that so much that Zometa can be given to manage that, even though I'm risking the jaw. And I'm sure your physician is making that call by saying that right now your myeloma seems to be reasonably well controlled, right now there are not that many active bone lesions, so why take the risk of Zometa. So they may be making that judgment call. And you want to ask your physician if that's the call that they are making. And if they say yes, I have considered it and I think it's probably wiser to hold off, then you respect the physician's judgment. If you do start it, the strategies to reduce the risk of the osteonecrosis are to try and give it every three or four months rather than monthly, or sometimes even once a year may be enough. For patients with osteoporosis who don't have myeloma, one dose of Zometa once a year is actually enough to help bone formation. So those are some tricks that can be tried. But the first call on whether or not to restart it is made with a lot of caution because of the risks.

LAUREN BERGER:
Thank you for your question, Bill. We'll take the next question from the web audience and this question is from Thomas. "If a patient has no chromosomal abnormalities and other genetic abnormalities, is it possible for this patient to develop such anomalies in the future?"

DR. S. VINCENT RAJKUMAR:
Excellent question. In newly diagnosed myeloma patients, if you do FISH with all the correct probes and if the FISH is negative, you do more sophisticated genetic testing, almost all patients with myeloma will have some abnormality. If you don't find it, it usually means that the myeloma is so low in tumor burden that they were not able to detect these abnormalities. It's a sensitivity question rather than whether it's there or not. It's because many of these abnormalities actually happen at the MGUS stage and so they're carried on at the time of myeloma. Having cytogenetic abnormalities doesn't mean that the myeloma is necessarily bad or anything like that. It just depends on what cytogenetic abnormality are we talking about. Like having trisomies or having 11;14 is a good thing. So just having them is, by definition, not immediately a bad thing.

Number two, if you don't have any cytogenetic abnormalities and they did a good FISH and a good cytogenetics, then congratulate yourself because it may be that your myeloma is too early and that there are too few plasma cells for them to actually detect these abnormalities, that might be the reason. And those patients generally do very, very well, better than even good-risk cytogenetics.

Number three would be that yes, even if you have nothing to start with, during the disease course patients will develop new cytogenetic abnormalities and that's because again these were there from the beginning and they are becoming manifest later on. Or new abnormalities are developing as the disease progresses.

There's a very, very interesting paper that was published from the Mayo Clinic's Scottsdale group, some of my colleagues, in *Blood*, which showed that when a patient is newly diagnosed with myeloma, they already have probably two or three different kinds of clones present and that one of the clones is dominant. And when you use treatment and kill those cells, then another one might show up years later, so that's another way a patient may start with nothing or start with one abnormality and show up with a different one later on.

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

OPERATOR:
The next question comes from Jerilynn in Ohio. Your line is now open.

JERILYNN:
Thank you. This is Jerilynn's husband, John, who is actually the patient. My question is this. I've been through chemo twice. The first time we did it I went through a transplant. This time I spoke with my doctor and decided to not go through a transplant. Went through six rounds of Velcade. Now we have to talk about maintenance medication. My doctor is kind of pushing for the Velcade. I'm kind of pushing for the Revlimid. The reason I'm pushing for the Revlimid is because the Velcade gave me very serious diarrhea to a point where I'm now on Lomotil® to take care of that. What is your opinion on the maintenance medication?

DR. S. VINCENT RAJKUMAR:
Thanks for that question. I hear you. If you have a drug that you know causes a particular type of side effect and it was very disturbing to you, and a physician recommends that you take that drug indefinitely as maintenance, you are naturally going to be alarmed. I cannot tell for sure whether Revlimid would be preferable for you because I have to go through your story to see what you had initially or not. Both drugs are good. If Revlimid has worked in the past for you or you've never had Revlimid, it's okay to try that instead. Remember, that also causes diarrhea long term. Some of the ways you can reduce this is just using a lower dosage. The group that did the Velcade maintenance trial, they gave Velcade only one dose every other week, so that's only two doses of Velcade in a month. Maybe at that dose the diarrhea will not be that bad. If you do decide that even that risk is too much and you want to try Revlimid, then use lower doses, like 10 milligrams a day, three weeks on, one week off, which is the maintenance dose used in the trial, rather than the full dose of Revlimid. Actually those are the two best maintenance drugs out there. All of the other drugs for myeloma, like thalidomide, melphalan, cyclophosphamide, they don't lend themselves so well to maintenance therapy because of more chronic side effects.

LAUREN BERGER:
Thank you for your question, John. We'll take the question from the web audience and Maureen asked, "Twenty-four hours after taking 20 milligrams of dexamethasone I get significant flushing and burning in my eyes. What can reduce this side effect? Is it an allergy type reaction, but not life-threatening? It lasts about 12 hours."

DR. S. VINCENT RAJKUMAR:
Thanks for the question. I have not encountered that, so I'm not really sure exactly what advice to give you, other than maybe to try and see if you can talk to an eye physician, an ophthalmologist. Steroids are funny. It may be that you're getting dry eyes. All kinds of eye ailments, people actually use steroids to try and mitigate that. So if the steroid itself is causing you problems, I'm at a loss for suggesting a treatment. And probably better off seeing an eye physician and seeing what exactly is the problem with the eye and dealing with that.

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

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

HILMA:
Hi, good morning, thank you everybody for this conference. I would like to know what can I do to increase my white blood count. I was on Velcade and Revlimid, but for the past two months I was changed to Pomalyst and dexamethasone. But my white count keeps going down, down. And apart from getting the Neupogen®, is there anything I can do to help increase the white count?

DR. S. VINCENT RAJKUMAR:
The answer is probably not. It really depends on why the white count is low. If the white count is low because the myeloma is occupying the bone marrow and it needs to be treated, then the best way to improve the white count is to treat the myeloma with whatever treatments are necessary, which means temporarily the white count could go even lower until all these myeloma cells are killed and the bone marrow recovers. On the other hand, if the myeloma has been controlled but the white count is still low, that's probably a drug effect. Revlimid, Velcade, pomalidomide, melphalan, Cytoxan, all these drugs cause low blood counts. And if we are clear that the low count is really a drug effect, then there are only two choices. If you really need to give the drug at the same dose to control the myeloma, then you have to add growth factors to see if that'll allow you to keep that dose. If you think you don't need to give that drug at that dose and you can try to see if you can get away with a lower dose, then we lower the dose, either by giving an extended break between the cycles, like instead of one week off, give two weeks off or three weeks off to allow the counts to recover, or just dropping the absolute dose, like instead of 2 milligrams of pomalidomide, try 1 milligram, see if that helps, etc.

LAUREN BERGER:
Thank you for your question, Hilma. We'll take the next question from the web audience and this is from Robert. "Can you please talk about the evolution of vaccines for the treatment of multiple myeloma, particularly things that are in trial now?"

DR. S. VINCENT RAJKUMAR:
So vaccines for myeloma, boy, we've been trying to do vaccines for myeloma for ages. Myeloma poses particular problems because the cancer is a cancer of the immune system itself and so you are trying to harness the immune system to attack something when the whole immune system is suppressed by a cancer of the immune system itself. That's one big problem. The other problem is, we need to identify the antigen that you would target the immune system against. And that's been a problem because, unlike other lymphoma cells, there are no particular targets on the myeloma that are unique to the myeloma cell. So if you're trying to target something, it'll cause more damage. And then, of course, because the immune system is suppressed, even if the antigens are out there, the body doesn't recognize them as foreign and just doesn't do anything, so we have to stimulate the immune system. Maybe just teach it to recognize these antigens and to mount an immune response, trying to kill these myeloma cells.

So all these problems and questions have remained and that has limited the vaccine field. We have numerous trials, Mayo, Hopkins, Philadelphia, a lot of centers are doing studies looking at vaccines, but these are the barriers to getting a successful vaccine approach. But it's improving. I think the dendritic cell approaches where you take a patient's myeloma cells and then incubate them with the dendritic cells, to teach the dendritic cells to press in the antigen, and then reintroduce the dendritic cells back into the patient to mount an immune response, those strategies seem promising.

A lot of it requires pretty intensive one-on-one, like you can't have a generic treatment for all patients, but the treatment is individualized patient by patient and that makes it more cumbersome to get it from the lab to the actual clinic, outside a trial setting. But lots of research is going on and in a general sense we are still very encouraged.

DR. S. VINCENT RAJKUMAR:
At Mayo we are also looking at virotherapy, which is like immunotherapy, where viruses naturally don't like the immune system, particularly viruses like the measles virus. So if you introduce a measles virus into the body, it goes straight to the plasma cells and kills that. And we are trying to see if we can use something like that to kill the plasma cells. Others are doing gene therapy protocols. And of course, Revlimid, pomalidomide, thalidomide, they are immunomodulatory drugs. They do stimulate the immune system. So there are studies going on with transplant, allogeneic transplant, which is an immunotherapy in itself, where you take stem cells from someone else, a closely related donor or a matched donor, and try and see if those cells will target and attack the myeloma cells, a graft-versus-myeloma effect. And to potentiate that people are trying to see if we can add on thalidomide or Revlimid to improve the efficacy of such approaches.

So a lot going on. Nothing is extremely ready for outside the trial setting, for a clinical use basis, but on trials, if you go to clinicaltrials.gov, you'd probably identify trials that are looking at these approaches. Thank you.

LAUREN BERGER:
Thank you for your question, Robert. And for more information on searching for a clinical trial for yourself, and something that might be in your area, call The Leukemia & Lymphoma Society Information Specialists and they can do a personal search for you.

We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Frank in Tennessee. Your line is now open.

FRANK:
Yes, hi. My question is regarding subcu Velcade for maintenance post-transplant, after a remission has been achieved. What is the dosage recommended, the frequency recommended, and the length of time that Velcade should be used for maintenance?

DR. S. VINCENT RAJKUMAR:
Excellent question. A lot of extrapolations and it's controversial because some of my colleagues disagree with me in the amount of extrapolations we are doing. The subcutaneous Velcade study was done in relapsed disease, using a twice-weekly schedule. The once-weekly regimens were used with an intravenous schedule in front-line setting. And now we are extrapolating all these studies into various different patient populations that have not been tried. I do justify that because we know Velcade given subcutaneously gives the same amount of drug, except it doesn't give you the very high level that you get with the IV dose, which is the cause of the neuropathy. But it does manage to give all of the Velcade that was given to the patient, so what we call the area under the curve, the amount of Velcade that's actually bioavailable, is the same whether you give it IV or subcu. So I'm willing to extrapolate.

So having said that, the best maintenance study with Velcade was the HOVON trial, which gave Velcade maintenance for two years, using an every other week schedule. So if you take Velcade 1.3 milligrams per meter squared, which is the standard dose, subcutaneously, every other week, you're talking two

DR. S. VINCENT RAJKUMAR:
doses a month. A very reasonable schedule that you can live a normal quality of life and the only change you'll be making from the HOVON would be they gave it IV and we're giving it subcu, but I think it's a reasonable extrapolation.

LAUREN BERGER:
Thank you for your question, Frank. We'll take the next question from the web audience and this is from Stuart. "After initial therapy, if remission is achieved, would you also suggest a stem cell transplant be done?"

DR. S. VINCENT RAJKUMAR:
Excellent question. People are asking that question in the clinical trial that the Dana-Farber and the IFM are doing. They are giving VRD, which will get a good response in almost all patients, and after four months they're dividing patients into a group where one-half of the patients will get a transplant and the other half will get the VRD. And the question is, can we delay the need for the transplant now that we've achieved a great remission with the initial treatment. The results of that trial will not be available for quite some time, probably a couple of years or more.

In the meanwhile we then have to make an answer to that question based on judgment as well as prior studies. Prior studies show that when patients respond well to initial therapy, the advantage of early transplant is not as pronounced. The PETHEMA Group, or the Spanish group, took patients with new myeloma, gave them treatment, and those who responded well were divided into two groups. Half of them got a transplant and half of them did not and the survival was the same.

The way we interpret all this literature at Mayo is that if the patient is young enough, less than 70, 72 years of age, we try to give them the benefit of the transplant. But if patients are responding very well to therapy, we don't insist that the transplant be done early. But the trick to doing the transplant late is that the center needs to be willing and able to store your stem cells early, because you don't want to give two years of treatment and then try and collect stem cells. You won't be able to collect stem cells. So four months, you collect stem cells now. You collect enough for two transplants if you are less than 65. If the center is able to freeze it for future use, these stem cells are good for five, ten, fifteen years. If they're able to freeze it, then the timing of the transplant, whether you do it now or later is really up to you. And we do offer that kind of a choice and many other centers also do the same thing. But not all. Sometimes the insurance companies balk at that and some institutions don't have the facilities to freeze the stem cells, in which case then you are limited by your choice and then you have to do the transplant early.

We think that transplant will benefit all patients, whether they are in good response or not. And if you are eligible we still continue to recommend it. The only thing that is optional is the timing. It's when to do the transplant, not whether to do the transplant.

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

OPERATOR:
Our next question comes from William in Tennessee. Your line is now open.

WILLIAM:
Thank you, Doctor, for the conference. I'm a two-year survivor and I'm on Revlimid at the present time. My question, I think a person touched on it a while ago, my white counts have fallen. They're still within limits, but like I had an 8 point something when I started the Revlimid, recently, and I have been on other drugs also. But anyway, on the Revlimid it's fallen to 4 point something. Is there a supplement or anything that can be taken to help that? And I think, like I said, the other person touched on that, but my question would be, is there a supplement or are supplements bad with the myeloma? That's my question, thank you.

DR. S. VINCENT RAJKUMAR:
I would say, first of all, when you take Revlimid the white count is going to drop some because that's one of the side effects. At 4,000 it's still fairly normal, so that you don't really need to do anything about it, it's safe. We don't recommend any general supplements. There's nothing you can do to improve the white count in a general supplement sense of the word, so we don't recommend those. Number two, there are some patients who get low on critical vitamins that are required for the white count, that is B12 and folate. A number of Americans have B12 deficiency. And so whenever somebody has low counts, I do check the B12 and folate to make sure that easily reversible things like giving them B12 shots or B12 capsules or folate is not overlooked. So B12 and folate can cause low white counts and you want to check that and make sure that that's not the problem because a number of people have those two deficient. If those two are okay, then you really don't need any supplements.

The only other thing to watch out is that all these drugs have long-term consequences. Revlimid long term can cause bone marrow damage and that may be the reason the white count is dropping. So if it's a new development, you should mention it to your physician, that it's a new development and is there a possibility that the Revlimid is damaging the bone marrow, such as causing what we call MDS or myelodysplastic syndrome. And a bone marrow check at the time of your myeloma check, or a bone marrow just to see how you're doing, may reveal if that's indeed going on. But specifically no particular supplements are recommended and they're probably not going to be of use.

LAUREN BERGER:
Thank you for your question. We'll take the next question from the web audience and this one's from Jill. "My husband's been on Velcade since October, 2012. He's starting to have emotional outbursts of crying. He was never an emotional person. Is this type of side effect possible from Velcade?"

DR. S. VINCENT RAJKUMAR:
I have not heard of that. It is most likely a dexamethasone thing, if the person's husband is also on steroids, that will explain that kind of a problem. You can get from anger to I cannot live with my spouse anymore to I cannot sleep to people getting violent to crying and depression. All of those are problems with dexamethasone or steroids. And the only way out is to reduce the dosage. It could be an unrelated depression. Depression manifests as weeping, crying, tearful, and it's something that patients with cancer can get very easily. And can be easily treated with antidepressants.

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

OPERATOR:
The next question comes from Ruth in Florida. Your line is now open.

RUTH:
Thank you so much. This is a wonderful conference. I guess I'm asking you to evaluate my therapy and am I on the right track or if I need to change anything. I was diagnosed with multiple myeloma four years ago. I never had bone lesions. I was in about the middle stage of multiple myeloma and they did not recommend me for stem cell transplant. I was put on Revlimid, 25 milligrams, and dexamethasone and Zometa. And I have worked my way through these years to where I am right now, my bone marrow biopsy had only traces of cancer and I'm on 5 milligrams of Revlimid right now. Should I proceed like I am or should there be some kind of change?

DR. S. VINCENT RAJKUMAR:
I wouldn't change anything. You're doing extremely well. I have many patients like you. So I would do the same thing and continue the same treatment.

LAUREN BERGER:
Very good. Thank you for your question, Ruth. We'll take the next question from the web audience and this one's from Victor. "Do you have any thoughts on taking curcumin together with Revlimid for maintenance?"

DR. S. VINCENT RAJKUMAR:
Yes, it doesn't work. Curcumin does not work in myeloma. The studies that were done in Australia, I wrote two editorials on those, I don't think it has any therapeutic effect. Whatever they saw is just well within the normal variation. There's no proof it works. If somebody shows proof that it works, then we'll revise our opinion.

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

OPERATOR:
Our next question comes from Patty in Wisconsin. Your line's now open.

PATTY:
Thank you for taking my call. I was diagnosed in late September of 2012 with multiple myeloma. And I had a good response. I guess there were no bad markers. And I was on Revlimid. I started with the Revlimid, Velcade and dexamethasone. And then that was just switched to the dex with Revlimid. A couple of months ago I started getting nausea and throwing up, so my oncologist took me off the Revlimid and has not substituted with another treatment. And I was really only in remission for at most two to three months. And I guess I'm concerned that now I'm not on anything. Could you address that?

DR. S. VINCENT RAJKUMAR:
How many months total have you had treatment so far?

PATTY:
I started treatment in October and I probably stopped in about late March.

DR. S. VINCENT RAJKUMAR:
Yeah, I think you probably should talk to them. You probably need at least six more months of myeloma therapy, just to make sure it doesn't come back quickly. It's very hard again to give an individual opinion for you. But generally if you just give four, five months of therapy, it comes back probably in the next few months. So please go back to your physician and say you talked to me and if they want they can email me.

Slide 42: LLS Resources

LAUREN BERGER:
Thank you for your question. And thank you all for all of your questions. We hope this information will assist you and your family in your next steps.

If we were not able to get to your question, please call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572 or reach us by email at infocenter@lls.org. Our specialists can provide you with information about myeloma research, clinical trials, other questions that you may have about treatment and also questions about financial assistance for treatment.

In addition, The Leukemia & Lymphoma Society offers online chats, which offer an opportunity to share experiences with other patients and to support each other. These chats are for myeloma survivors and they're moderated by an oncology social worker and you'll find information in your packet.

Please help me thank Dr. Rajkumar. We are so grateful that he has volunteered his time with us today.

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