

Mantle Cell Lymphoma: Update on Treatment

Brad S. Kahl, MD
April 3, 2014

Slide 1 – Welcome and Introductions

Operator

Good afternoon and welcome to Mantle Cell Lymphoma: Update on Treatment, a free telephone and Web education program. It is my pleasure to introduce your moderator, Lauren Berger.

Ms. Lauren Berger

Thank you and hello, everyone. On behalf of The Leukemia Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Brad Kahl for sharing his time and expertise with us today.

We would like to acknowledge and thank Celgene Corporation, Millennium: The Takeda Oncology Company, Pharmacyclics and Jassen Biotech for their support of this program.

You should have received or downloaded program materials, including a biography for Dr. Kahl and slides for his presentation.

If you have not already accessed the slides, you can view them or print them from our website at www.lls.org/programs. Following his presentation, we'll take questions from the audience.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's Interim President and CEO and Chief Mission Officer, Dr. Louis DeGennaro, who will share a few words. Dr. Lou?

Dr. Louis DeGennaro

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

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients.

To date, we have invested nearly one billion dollars in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

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In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients in their communities through our 61 chapters across the U.S. and Canada.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We're fortunate to have as our presenter today, Dr. Brad Kahl, one of the nation's leading experts in mantle cell lymphoma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on mantle cell lymphoma. Thank you all. And now, I'll turn the program back to Lauren.

Slide 2 – Brad S. Kahl, MD

Ms. Lauren Berger

Thank you. I am now pleased to introduce Dr. Brad Kahl, Associate Professor of Medicine and Director Lymphoma Service at the University of Wisconsin Carbone Cancer Center in Madison, Wisconsin. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise today. Dr. Kahl, I am now privileged to turn the program over to you.

Dr. Brad Kahl

Thank you, Lauren, and thank you, Lou, for those words and the kind introduction. It's really a pleasure to be speaking to everybody today. Hopefully, I can provide some useful information. I'll try to get through the planned talk in about 25 or 30 minutes and leave plenty of time for questions at the end.

And before I forget, I really want to take a moment to thank The Leukemia & Lymphoma Society for everything that they do for patients, for patient services and for research for patients with blood cancers.

Slide 3 – Disclosures

So today we're going to talk about mantle cell lymphoma. And as you can see on the slide, these are my disclosures. I do periodic consulting work for the companies listed there and receive research funding from the companies listed below.

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Slide 4 - Mantle Cell Lymphoma: 6% of NHL Cases

Dr. Brad Kahl

Mantle cell lymphoma is not a particularly common type of non-Hodgkin's lymphoma. It makes up about 6 percent of new cases each year, and the relative frequency of mantle cell lymphoma makes it relatively more difficult to study compared to some other cancers. As a result, we don't always know with certainty what is the best approach for patients.

Usually, to determine the very best approach for patients, it requires fairly large studies, so-called randomized clinical trials, where you compare one treatment against another head-to-head. And because of mantle cell lymphoma's relative infrequency, conducting large randomized trials proves to be very difficult. And as a result, the literature, or the data to guide physicians on how to best treat mantle cell lymphoma, is somewhat imperfect. And I think that will come out in my talk today, and it's something that I'm sure the patients and families on the call are aware of when they speak with their treating physicians.

Slide 5 - Mantle Cell Lymphoma

So, mantle cell lymphoma was first recognized as a unique entity just about 20 years ago. Before that it was confused as other types of lymphomas, like diffuse large B-cell lymphoma or follicular lymphoma or other types of lymphoma. And for many years even after it was first recognized, it was often misdiagnosed, but in the last 10 to 15 years misdiagnosis has become quite uncommon, and the tools to accurately recognize mantle cell lymphoma are readily available to any center. And as a result of our improved ability to recognize mantle cell lymphoma accurately, we now have better data on outcomes. We have more confidence in our treatment data.

There are a variety of effective treatments for mantle cell lymphoma. I'll talk about some of those today. And there have been several exciting breakthroughs in the past few years, and I will talk about those today as well.

Slide 6 – Presentation

So, the presentation of a patient with a new diagnosis of mantle cell can vary quite a bit. Some patients might come in feeling quite ill with so-called B-symptoms, which include fevers, soaking night sweats and unintentional weight loss. Some patients might come to the physician because of fatigue and found to be anemic. Other patients might come in with pain that could be the result of an enlarging spleen or enlarging lymph node masses. I've seen mantle cell patients come in with their initial presentation as just a change in their bowel habits. Mantle cell lymphoma has an unusual tendency to involve the colon and that can result in a change in bowel habits.

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Some patients might actually feel perfectly well and just notice a lump, which is found to be an enlarging lymph node, or a patient might feel perfectly well and just have routine blood work that shows some abnormality, like a high white blood cell count, and the excessive white blood cells are found to be mantle cell lymphoma. So, the way patients come to medical attention varies tremendously.

Slide 7 - Clinical Features

Now, the average age of a newly diagnosed mantle cell lymphoma patient is 64, but there's a huge range. We can see mantle cell lymphoma patients in their 40s and 30s. We see mantle cell patients with a new diagnosis in their 80s and 90s.

For reasons we don't understand, it's much more common in men than in women. It's typically advanced stage at presentation. And by that, I mean it typically involves lots of places in the body. We usually will find it in the bone marrow and in the blood. So, we think of mantle cell lymphoma really as a blood cancer. Because it traffics in the blood, by definition, it's everywhere.

So, a lot of patients get concerned when they hear they have Stage 4 disease, but I would urge people not to put too much emphasis on that term, Stage 4. That's a bigger deal if you're talking about breast cancer or lung cancer, but in mantle cell lymphoma most patients are Stage 4 or at least Stage 3. So, that's really quite typical for mantle cell lymphoma and is not really the most important feature.

Extranodal involvement is very common. By that we mean involvement outside of lymph nodes. So, that would be places like the bone marrow or the blood and, as I mentioned, the colon. And when we see it in the colon, some patients will present with a colon that's full of little polyps, and that's called lymphomatous polyposis.

I put a question mark by the word "curable with conventional therapy." We generally think of mantle cell as not curable with conventional therapy. By that, I mean with drugs, with chemotherapy, although it's becoming apparent that we can achieve very long remissions for some patients. And we all have patients now who have been in remission for over 10 years, and we're just not sure whether we can apply a cure label to such patients because of the natural history. So, I put a question mark by that because it's just not clear.

And I consider mantle cell lymphoma to be a moderately aggressive form of lymphoma. There's certainly other lymphomas that grow faster and are more aggressive than mantle cell, and then there are lymphomas that are more slowly growing than mantle cell lymphoma.

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Slide 8 - Proposed Model of MCL Pathogenesis

Dr. Brad Kahl

This next slide, the proposed model of mantle cell pathogenesis, is for the experts on the call. There's usually a wide range of expertise on calls like this. And I won't spend much time on this. But, virtually all cases of mantle cell lymphoma have what's called a translocation. And what that means is two little pieces of DNA have broken off from their normal place on the chromosome and swapped with another little piece of DNA on another chromosome.

So, the translocation is between chromosome 11 and chromosome 14. And when that happens there's a gene called cyclin D1 that makes a protein called cyclin D1, and the cells, these lymphocytes, end up making too much of the cyclin D1 protein, and that sends an abnormal signal to the cell to proliferate or to grow abnormally.

Normally our cells have very tight regulation that tells them when to divide and when not to divide, and when cyclin D1 is over expressed, that sends a divide signal to the cells. So, one becomes two and two becomes four and four becomes eight, and so on and so on, and the cells grow in this out-of-control fashion.

So, just about everybody with mantle cell lymphoma has this 11;14 translocation. We consider this an early event. And then, what can happen later is that the cell develops additional genetic abnormalities. In other words, other abnormalities within the DNA and within the chromosomes, and we call that a complex karyotype. And sometimes those abnormalities will result in a fundamental change in the mantle cell, so that it starts to grow much faster and much more aggressively, and we call that blastoid mantle cell. Fortunately, blastoid mantle cell is relatively uncommon and probably is less than 5 percent of new mantle cell diagnoses.

Slide 9 - Diagnosis of Mantle Cell Lymphoma

So, the diagnosis is not hard to make anymore. The cells have a pretty characteristic appearance under the microscope, and they have what we call a characteristic immunophenotype. We can apply special stains to the biopsy and look for the expression of these things called CD5 and CD20, which are proteins that are sticking outside the cell, and then the cyclin D1, which is a protein that will be expressed in the nucleus of the cell. So, it's pretty easy nowadays to make a diagnosis of mantle cell lymphoma with modern technology.

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Slide 10 - Improvement of OS in MCL During the Last Decade: GLSG Cohort (1996-2004) vs KLG Cohort (1975-1986)

Dr. Brad Kahl

Now, I'm happy to report that the prognosis for mantle cell lymphoma appears to have improved considerably over the past 20 to 30 years. On the slide depicted here, this is called a Kaplan-Meier Curve, the red curve shows a typical survival curve for mantle cell patients diagnosed in the late '70s and early '80s. And the curve above it, that's the darker curve, shows the average survival for patients diagnosed in the late '90s and early 2000s, and we fully expect that for patients diagnosed more recently, the outcomes are even better. And probably the most gratifying thing that I have witnessed in mantle cell lymphoma during my career is the improvement in outcomes. And what we're able to tell patients and how we're able to talk to patients is markedly different than how we did it 15 years ago.

Now, one of the things that makes talking about mantle cell lymphoma a little difficult is there is what we call heterogeneity from patient to patient. Some patients come in with a very aggressive case. Some patients come in with a more typical case. And some patients come in with so-called indolent mantle cell or a slower moving kind.

Slide 11 - Prognostic Factors: Molecular Signature

And we're starting to get a little bit of a handle on how one might identify such patients by looking at the expression of certain genes. This is not something we can do routinely, but we hope to be able to do it someday, where somebody walks in the door with a new diagnosis of mantle cell and we could apply a series of tests that could help us figure out if a patient has a more aggressive type, a more typical type, or a more indolent type. We don't have that ability right now but that is a major goal in mantle cell research.

Slide 12 - Clinical Prognostic Features: MIPI

There are some things we can do to estimate prognosis just based on clinical features. There's a clinical prognostic index called the MIPI, Mantle Cell International Prognostic Index. And four factors have been associated with survival in mantle cell lymphoma, and these are age, performance status, LDH and the white blood cell count.

So, the older the age, the worse the performance status, the higher the LDH or the higher the white blood cell count; these are all associated with worse outcomes relative to better parameters for those things. And that's something that we can calculate in every newly diagnosed mantle cell patient.

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Slide 13 – Treatment

Dr. Brad Kahl

Shifting gears to talk about treatment, there's not a standard single way to treat mantle cell lymphoma. It really varies quite a bit from country to country, from center to center and from doctor to doctor. And I'll give you the way I think about it.

So, if I have a new patient who comes in with a diagnosis of mantle cell lymphoma, one of the things I will ask myself, "Is this patient a candidate for an intensive treatment?" And I'll talk a little bit more about intensive treatment, but generally that means more aggressive treatment, either more chemotherapy, higher doses of chemotherapy, or possibility of a stem cell transplant.

These intensive approaches, which are generally reserved for younger mantle cell patients, tend to produce longer first remissions than less intensive approaches. And so, it's definitely a conversation that I'll have with a younger mantle cell patient and offer them the option of an intensive strategy, which results in more short-term toxicities and more short-term side effects, but then has a payoff later, hopefully that the remission that we establish with that more intensive treatment will last longer than a non-intensive strategy.

The other question that I will ask is, "Could this patient be considered for the so-called watch and wait strategy?" And occasionally, not often, but occasionally, maybe one out of every 10 or two out of every 10 mantle cell patients who come in, their mantle cell was picked up just incidentally and they actually feel perfect. And you stage that patient, and you see that they have a very, very low burden of disease. There's not much mantle cell there.

And the group from Cornell University in New York City has studied this approach. And they have shown pretty convincingly, in my opinion, that there's no harm that is inflicted upon patients if they do start out on a strategy of watch and wait. If you guess wrong and their disease moves relatively quickly, well, the treatment can be started a month later or two months later or three months later when it becomes obvious that treatment needs to be initiated. On the other hand, you will find occasional patients who can do this watch and wait strategy for several years. And I have personally had several patients who have been under watch and wait programs for many years before we eventually had to get to treating their mantle cell lymphoma.

Slide 14 - Intensive Treatments

So, I mentioned the intensive treatments. These are generally reserved for patients 65 and under. That number 65, I should have put in quotes. I don't mean to sound dogmatic about that. Many centers will take patients up to age 70 or even a little older

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through intensive treatments. I have not been very satisfied or impressed with the results in older patients going through intensive strategies.

So, my own personal cutoff is more like 65 and often 60. And I find for older patients the intensive strategies have a lot more toxicity, a lot more side effects and the outcomes are not as good with the intensive strategies.

I'm more likely to take a 63-year-old patient or a 62-year-old patient and offer a non-intensive strategy than a lot of physicians. But, I definitely will have a long conversation with the patient about the pros and cons of the different approaches.

So, examples of intensive strategies: a commonly used approach is a regimen called R-CHOP with alternating R-DHAP. These are different chemotherapy recipes. You do three cycles of each in an alternating fashion. And then, the patient, once they're in a remission, you collect their stem cells and you do something called an autologous stem cell transplant, which generally produces a deeper quality remission. That's a very common strategy. Some centers will just use the R-CHOP and not do the R-DHAP, followed by stem cell transplant.

A regimen that was pioneered at the MD Anderson Cancer Center is called HyperCVAD. It's a very aggressive, intensive regimen, which uses alternating regimens that include a high-dose methotrexate and high-dose cytarabine. There's a regimen called the Nordic regimen, which is very similar to the two regimens I just mentioned, and that's a regimen that I am particularly fond of as an option for younger patients.

And, with these intensive approaches, most of the literature suggests the average length of the first remission is over five years, which is tremendous considering that data just 15 years ago suggested that the average survival for mantle cell lymphoma was only three years. And so, we're incredibly gratified that these intensive approaches are producing first remissions that are much more durable than things we saw in the past.

Slide 15 - Non-intensive Treatments

As far as non-intensive treatments, I think there are a couple of very reasonable options that can be considered. These again are generally reserved for patients who are somewhat older, who are going to have more difficulty with an intensive regimen, or for younger patients who have comorbidities, other health problems that would make an intensive regimen difficult for them.

And so, typical non-intensive treatments--and these are still hard. I don't mean to make it sound like these are easy. There's nothing easy about them. But, the R-CHOP regimen for usually six cycles, or more commonly nowadays, we're using a regimen

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called rituximab-bendamustine for six cycles, which in a couple of studies looks like it might be slightly better than R-CHOP for establishing remission.

And then, for these older patients who cannot take an intensive regimen, we usually will follow this with a strategy of what's called maintenance rituximab. Most of the people on the call probably know about rituximab.

Slide 16 - Rituximab: Anti-CD20 mAb

Rituximab is a so-called monoclonal antibody. It's not a chemotherapy drug. It's a protein. We all make antibodies that help us fight infections. And this is an antibody that's made in the lab that we can infuse intravenously into patients. And the antibody will coat the patient's B-cells, including their mantle cells. And when it does that, it tries to trick the patient's immune system into fighting the cancer. And there was a very nice study done by the European Mantle Cell Consortium that was published in the New England Journal of Medicine just about a year and a half ago that showed a very nice benefit for older patients who received maintenance rituximab as part of their standard regimen. So, I offer that to all my patients who do not receive an intensive strategy.

Slide 17 - Watch and Wait

I think I talked about the watch and wait probably adequately and probably don't need to say anymore about that. It's an appropriate option for a small minority of patients.

Slide 18 - Novel Treatments for Mantle Cell Lymphoma

I want to end up the talk today just by talking about some new treatments for mantle cell lymphoma. The last couple of years have really been incredibly exciting to see the new developments and new options that our mantle cell lymphoma patients have.

Slide 19 - Targeting Intracellular Pathways

So, really the future of cancer treatment is to try to figure out what makes a cancer cell tick. What's going on inside that cell that gives it a growth advantage? And it turns out that there are intracellular pathways. These are biochemical pathways that are very active inside these cancer cells. And we're getting a better understanding of which pathways are active in mantle cell lymphoma.

And based on this knowledge we now have drugs like bortezomib, which target a molecule called the proteasome. There's a drug called temsirolimus, which targets a target called mTOR. We have a drug called lenalidomide whose target is a little less well defined but is looking to be a promising agent in mantle cell lymphoma. We have

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an agent called idelalisib, which targets a protein called a PI3 kinase. We have an agent called ibrutinib, which targets an enzyme called Bruton's tyrosine kinase or BTK.

An even newer is a drug called ABT-199, which targets a protein called BCL-2. And all of these things have shown or are showing promise in mantle cell lymphoma.

Slide 20 – Bortezomib

So, bortezomib is FDA approved for relapsed mantle cell lymphoma. It's given either intravenously or subcutaneously. It was approved several years ago based on the results from a study called the Pinnacle trial. And this is really the first new novel agent that we had in mantle cell lymphoma. And the overall response rate, if one uses bortezomib by itself, is about 33 percent. And it's a good drug for mantle cell lymphoma. The main toxicity is peripheral neuropathy, and one has to be very careful to monitor for that toxicity and side effect when giving bortezomib.

Slide 21 – Temsirolimus

Temsirolimus is a drug that has approval in the European Union for relapsed mantle cell. It is not been approved in the United States. The efficacy was pretty modest. And I think it just was not as impressive as the FDA was hoping. And for that reason it did not get an approval in mantle cell lymphoma in the United States, but it is approved in Europe, and it is an option for some patients.

Slide 22 – Lenalidomide

Lenalidomide is a very exciting new agent. Lenalidomide received its approval in relapsed mantle cell lymphoma just last summer. It's approved for patients who've had two prior therapies, one of which includes bortezomib.

This is a pill. It's given 25 milligrams orally, daily for 21 consecutive days. And then, the patients take a week off. And then they start it over again. Its approval was based on data from the so-called Emerge study, which had 134 patients. And just about 30 percent of the patients responded to the lenalidomide, which is not a great number but it's an okay number. But, if a patient was a responder, the median duration of response was an impressive 16 months. And so, to have a new option for our mantle cell patients that they could take this pill and get good control over their disease was an exciting new option.

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It's a pretty well tolerated medication. Some patients have problems with fatigue and diarrhea and rash and will require some dose adjustments on that basis.

Slide 23 - Lenalidomide and Rituximab (R²)

What I'm even more excited about is the combination of lenalidomide and rituximab. When you put these two together there seems to be synergy. They work better than either one alone. And investigators have now published on this combination of lenalidomide and rituximab.

The other name for lenalidomide is Revlimid. So, sometimes you might hear this regimen called R-squared. And the response rate for this particular combination was almost 60 percent. And so, the majority of patients were responding to this particular combination. So, I think this is an excellent new option for relapsed mantle cell lymphoma.

Slide 24 - Targets of B-Cell Receptor Signaling

So, this kind of complicated cartoon here is something called the B-cell receptor signaling pathway. And there are a variety of new agents now that are targeting enzymes that are downstream from the so-called B-cell receptor.

Every B-cell in our bodies has a B-cell receptor on its surface, and that's the part of the cell that helps it recognize an infection or a germ. And it turns out that if we have a cancer that comes from a B-cell there's some sort of a signaling through this pathway that we don't totally understand, but if we can disrupt that signaling, we can get these cells to die.

And so, the first drug that showed some activity was one called fostamatinib, and we learned about this at the ASH meeting a couple of years ago. It was very exciting. Fostamatinib hasn't been developed much in lymphoma, but is being developed in rheumatoid arthritis. But, not long after that came another drug. It was first called CAL-101, and now it has the name idelalisib. That targets this enzyme called PI3 kinase, and this is proving to be a really good target in B-cell malignancies. And then, more recently than that, along came a drug called ibrutinib, which targets this enzyme called BTK. And ibrutinib is probably the most exciting agent of all.

Slide 25 – Idelalisib

So, just to go through these quickly, idelalisib is not FDA approved for mantle cell lymphoma. It may be someday. It's a PI3 kinase inhibitor, and there's now a Phase I experience, which means it was a dose finding study in relapsed mantle cell lymphoma.

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It had 40 mantle cell patients. And in that study we worked out the recommended dose of idelalisib, and we showed an overall response rate of 40 percent and an even better response rate for patients who received the dose above 150 milligrams orally twice a day. It was generally a very well-tolerated medication. You do have to be careful for some liver irritation. So, that has to be monitored with blood work.

Slide 26 – Ibrutinib

A lot of people on the call have probably heard about the drug ibrutinib. And ibrutinib was approved by the FDA for relapsed mantle cell lymphoma in November of 2013. The recommended dose of ibrutinib is 560 milligrams orally each day. And it was based on the results of a Phase II trial that was published in the New England Journal of Medicine and there were 111 patients with relapsed mantle cell lymphoma.

The overall response rate to ibrutinib was almost 70 percent with a median duration of response of almost 18 months. The drug was very well-tolerated. It had very little effect on blood counts. There were some issues with diarrhea and fatigue and fluid retention, although in my experience these issues have been relatively minor for patients and quite manageable.

Slide 27 - BCL-2 Inhibitors

And I just want to finish up by talking about the BCL-2 inhibitors. These are not as far developed, but BCL-2 is a protein that gets over expressed in mantle cell lymphoma. And when it does, it sends a signal to the cell that tells it not to die. And if you can knock down the level of BCL-2 inside a cancer cell, you can make the cell more willing to die.

And so, we really sort of envision these BCL-2 inhibitors being used in combinations, where you might give a patient a BCL-2 inhibitor, knock down the BCL-2 levels, and then you would come in with perhaps chemotherapy or another active agent, like ibrutinib, and you would get even more cell kill with the combination.

Slide 28 - ABT-199

Well, it turns out that ABT-199 is showing some early activity just as a single agent in mantle cell lymphoma. And in an ongoing Phase I study, nine of the first 11 patients had partial responses to ABT-199. And it's a very well-tolerated medicine without major problems with toxicities.

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It's too soon to say whether ABT-199 will be a breakthrough as a stand alone treatment in mantle cell lymphoma. It might be. But, I'm very hopeful that even if it's not a stand alone therapy, it might turn out to be a very useful agent in combination.

Slide 29 - How to sequence in R/R MCL

So, when I have a patient with mantle cell lymphoma that's come back after first-line therapy, these are the strategies that I think are most attractive at this time. I would first consider ibrutinib. It's the most active agent that we have for relapsed mantle cell lymphoma and it's the best tolerated. And so, that would be my first choice for a patient with recurrent mantle cell lymphoma.

If I had a patient who ibrutinib did not work for or couldn't take ibrutinib for some reason, my second choice would be the R-squared combination, which is rituximab and lenalidomide. And then, my third choice would be bortezomib, which is still a useful agent in relapsed mantle cell lymphoma but has some issues with neuropathy, and that's why it would be my third choice. But, there are three good options right there for relapsed mantle cell lymphoma.

Slide 30 - The Future

So, I really think the future for mantle cell is going to be rational combination of these targeted agents. Agents that hit the B-cell receptor pathway are looking very active in mantle cell lymphoma. And so, I think over the next few years we're going to see a whole lot of studies looking at combinations of ibrutinib, which is the best new agent, plus some of these other exciting promising agents, like ABT-199 or bortezomib or other new proteasome inhibitors or lenalidomide. And there is even a trial going on now around the world which is looking at ibrutinib plus standard front-line chemotherapy, like bendamustine-rituximab.

I think honestly in the next few years we're going to have a whole different perspective on how to manage mantle cell lymphoma with these new agents significantly improving outcomes.

Slide 31 – Conclusions

So, my conclusions are that the prognosis is improving for mantle cell lymphoma patients, and I think this is due to a combination of new therapies and new stem cell transplant strategies, which I didn't talk about a lot today. Clinical trials are essential for gaining new knowledge about how to improve the field and move the field forward in mantle cell lymphoma. And I gave examples of several recent exciting breakthroughs that have me personally very optimistic for mantle cell lymphoma patients.

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Slide 32 – Questions?

Dr. Brad Kahl

And with that, I'll stop at this point, and we can move on to the question-and-answer portion.

Ms. Lauren Berger

Thank you, Dr. Kahl, for a very clear and informative presentation.

Slide 33 - Question & Answer Session

It is now time for the question-and-answer portion of our program. We'll take the first question from the Web audience. And this one's from Cheryl Lynn.

"I am newly diagnosed with mantle cell lymphoma found in my breast. My oncologist is surprised and said she has never seen this kind of lymphoma in the breast. Is it really uncommon? Also, I don't want to do chemo again at this age. Can I start with less toxic treatments since the doctor said there were new drugs?"

Dr. Brad Kahl

So, mantle cell lymphoma presenting in the breast is unusual. I don't think I have seen that before. But mantle cell can easily present anywhere in the body. So, I can't say that I'm surprised. Mantle cell is just kind of funny that way where it can show up anywhere. I don't think the presentation in the breast makes us think it's going to be a different kind of case. It's just a little bit unusual.

It's hard to say what the best treatment for that presentation. A patient with mantle cell lymphoma presenting that way needs a full staging evaluation. You need to look at the bone marrow. You need a whole body scan of some sort, either a CAT scan or a PET scan to determine the tumor burden. You need to know the blood count, need to know the MIPI score, and you need to know the patient's age in determining what's the most appropriate initial strategy.

And the question about whether the person could receive something other than chemotherapy, well that depends. And these new agents that I just showed you all have specific labels that were given to them by the Food and Drug Administration. And they all say, "Okay to use after one line of therapy." None of these agents are approved by the FDA to be used as a first-line treatment. And they're expensive. They're quite expensive. And the reality is most third party payers, meaning private insurance, would be unwilling to pay for these new agents used as a front-line therapy because they're unproven in front-line and because they're very expensive.

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Ms. Lauren Berger

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

Operator

Our question comes from Edith calling from California. Please state your question.

Edith

Yes, I was diagnosed five years ago with mantle cell lymphoma. I started out with R-CHOP, which did not put it in remission at all. And then, I started three months later with Rituxan and Velcade and have been on it, a regimen of Rituxan and Velcade one week, followed by Velcade for two weeks and one week off. And I am still on that. It still seems to be keeping the cancer cells at bay.

So, my question is, at what point do you think I should maybe start a program of ibrutinib? I see that it has a 70 percent rate. Would it be wise to wait, as long as this is working for me, until it stops working and then maybe go to ibrutinib? So, I don't know. I'm 87-years-old.

Dr. Brad Kahl

Okay, so that's a really good question. We have a patient who's on a prolonged therapy that is still working and now there's this new exciting treatment. And the question is, should someone stop a treatment that's working to move on to a new potentially more promising treatment?

My generic answer to that would be, if someone's on a treatment and it's working well and the toxicity is acceptable, I would keep using that treatment as long as possible, and I would always try to have something in your back pocket for later.

So, in a case like that, or similar to that, I would not stop a treatment that's working unless the toxicity was becoming a big problem. I would keep doing that until it stops, and only then would I move on to the next thing. That would be my personal strategy in a situation like that.

Ms. Lauren Berger

Thank you for your question, Edith. We'll take the next question from the Web audience. And this is from Miriam.

"What is your opinion on the appropriateness of yearly PET/CT scans for mantle cell lymphoma? I'm in remission for three plus years post-bone marrow transplant. And what might be the treatment of choice if this year I relapse after my bone marrow transplant from several years ago and post-R-CHOP, which I took in 2005?"

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Dr. Brad Kahl

Okay, really good questions. So, let's take the imaging question first. That's a really hard one to know how to answer. Personally, I would keep doing the imaging once a year. If I had a patient who, maybe, let's say, they got out five years from their stem cell transplant and everything was looking good, then perhaps you could maybe cut back the imaging to every other year for a few years.

Now, I will admit that you'll get a wide variety of opinions on that question. And there are some really smart doctors who take care of mantle cell lymphoma who would say you need to be imaged more than that, and I know some really smart doctors who take care of mantle cell lymphoma who say you should be imaged less than that, which just proves nobody really knows the right answer. But, the fact is, mantle cell lymphoma does come back in most, if not everybody, at some point. And so, I think to do some kind of imaging with some degree of regularity is appropriate.

Now, personally I don't do PET imaging as a surveillance tool. It's very, very, very sensitive, and I think you're more likely to get so-called false positives. So, I'm more likely just to use a CAT scan as a surveillance tool, but that's just a personal strategy. I see too many fake-out results with a PET scan that then you're obligated to go get more tests, and it can be very anxiety provoking for patients, but that's just a personal thing.

The second question was if the mantle cell comes back three, four, five, six years after a stem cell transplant, what therapy would be most appropriate? And I would say ibrutinib would be the most appropriate therapy to consider in a situation like that in 2014.

Ms. Lauren Berger

Thank you and thanks to Miriam for her question. We'll take the next question from the telephone audience, please.

Operator

Our next question comes from Gevone calling from Virginia. Please state your question.

Gevone

Doctor, I was diagnosed to have indolent MCL, and my chromosome carrier type was normal. I did not have any translocation of T-11 and T-14, but I was positive in cyclin D1.

So, what I'm trying to find out is, since it has been diagnosed as slow growing, plus I do not have any other symptoms as far as lymph nodes or any other fever or any other symptoms, so my question is, is there anything I can do with diet, as I have read about holistic approaches and juicing, or exercise or anything else that can keep the indolent MCL to stay indolent for a long time?

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Dr. Brad Kahl

Right. So, the question is, can a patient with a mantle cell lymphoma that's behaving itself pretty well, if the patient does some lifestyle modification, such as certain diets or a certain exercise, can that make the cancer behave in a different way?

At the moment there's no evidence that eating a certain diet, juicing or even exercising a certain amount makes the cancer grow differently. And so, I can't recommend that as a way to make the cancer behave a certain way.

Having said that, it definitely pays dividends to exercise and eat healthy because then the patient is generally more healthy. And, if someday a patient needs to go through treatment for mantle cell lymphoma, the healthier you are in all aspects, the better your heart, your lungs, your kidneys, your liver, everything. It's just a lot easier. It's way easier to go through treatment if your body is generally healthy.

And so, that should be reason enough to do those things, but I would be lying if I said if you ate some special diet or did some special program it would make the mantle cell grow in a different way. There's truly no evidence for that.

And I'll just make the point; I think everybody needs to be really careful about what they read on the Internet, which is not a quality controlled source of information. Unfortunately, there are a lot of people in the world who try to get rich off of sick people, which I think is a shame, people trying to sell their stuff at the expense of people with serious diagnoses. And I find that kind of infuriating.

I never give a patient anything that has not undergone rigorous testing and has been proven to be safe and effective. And so, you'll never hear me recommend anything for anybody that hasn't undergone that level of scientific rigor before I can recommend it.

Ms. Lauren Berger

Thank you for your question, Gevone. The next question is from the Web audience. Michelle asks, "How can I find out about clinical trials if my physician has just enough time with me to discuss my current treatment?"

Dr. Brad Kahl

That can be really frustrating and difficult. There is a website called clinicaltrials.gov, which can be a little cumbersome and clunky, I think, but is a decent place. I think this is probably a place where your societies can help you. The Leukemia & Lymphoma Society has patient services, and sometimes they can help with activities like that or they can reach out to physicians.

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Dr. Brad Kahl

But, finding available clinical trials can be a real challenge, and there's no perfect one stop shopping for that. But, clinicaltrials.gov is a reasonable starting place. Asking your physician to help is another reasonable starting place, and contacting your professional society is another reasonable place.

Ms. Lauren Berger

You can also call or e-mail The Leukemia & Lymphoma Society's Information Resource Center with questions about clinical trials and other questions about your treatment. The telephone number is 800-955-4572. Also, on our website at www.lls.org/clinicaltrials, there is more information about clinical trials, and there is a flyer in your participant packet which provides information on this.

So, thank you, Michelle, for your question. And we'll take the next question from the telephone audience.

Operator

Our next question comes from Christine calling from New York. Please state your question.

Ms. Christine

Hi. My name's Christine. I'm calling from Columbia. I just had a question about after a stem cell transplant. Are you giving these patients Rituxan maintenance?

Dr. Brad Kahl

I'm not. The question is rituximab maintenance after an intensive strategy. There's not any data that's out there that's convincing that would suggest that outcomes are substantially enhanced by rituximab after an intensive strategy.

Someday we might get that kind of data but to date there isn't. And usually people's immune systems are pretty weakened after a stem cell transplant and rituximab weakens it even further. And so, I've seen folks try rituximab after a stem cell transplant and run into some little problems here and there with low blood counts or an infection. So, I'm a little on the cautious side about recommending rituximab after a stem cell transplant until we get better data supporting it. Having said that, I will fully admit that there are plenty of docs out there who do employee that in their practice.

So, I don't want to make it sound like it's wrong to do. I guess I'm indicating that I have not seen enough evidence to make me feel comfortable doing it yet.

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Ms. Lauren Berger

Thank you for your question, Christine. We'll take the next question from the Web audience and this one's from Jeffrey. "I am not able to tolerate maintenance Rituxan. I am in remission but wonder if this will be an issue if I have a relapse."

Dr. Brad Kahl

That's a tough situation. Occasionally you get folks who have problems with maintenance rituximab or rituximab administrations. They have infusion reactions or blood pressure problems or other things.

So, if someone can't tolerate it, they can't tolerate it. And I would just say then, for a patient like that, I wouldn't try to substitute it with some other sort of maintenance, and I would just take all the options that you have for relapsed disease and you just kind of hold those in your back pocket: ibrutinib, Revlimid, bortezomib, and you use those when you need them.

It's true that some patients will experience exceedingly long remissions even without rituximab maintenance: four or five, six, seven, eight, nine, 10 years. And so, patients can have really prolonged remissions without maintenance therapy. If you can't take the rituximab, then so be it, and I would just save those other things for some other day in case you need them.

Ms. Lauren Berger

Thank you for your question, Jeffrey. We'll take the next question from the telephone audience, please.

Operator

Our next question comes from Laura calling from Texas. Please state your question.

Laura

Yes, my husband had HyperCVAD, four rounds of that, a stem cell transplant and maintenance Rituxan.

In January, he had three lumps on the back of his head, and surgery showed that those lumps were mantle cell; PET scan negative. Bone marrow biopsy was negative. He started ibrutinib and five days later the lumps were gone.

Does ibrutinib kill the mantle cells, because we were under the impression it just blocked them from spreading, the ibrutinib?

Dr. Brad Kahl

It kills them.

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Laura

So, it's possible that in five days it would have killed those cells on his head?

Dr. Brad Kahl

Yes.

Laura

Oh, fabulous.

Ms. Lauren Berger

Thank you for your question, Laura. And we wish your husband the best.

We'll take the next question from the Web audience and this one's from Phil. "My latest clinical trial of ibrutinib-Rituxan has not shown any improvement in my disease. I am considering T-cell therapy. Is there any data available on using T-cell therapy with mantle cell lymphoma when drug therapies have failed?"

Dr. Brad Kahl

Really good question. I'm afraid I don't know off the top of my head what the data for the different T-cell therapies are in mantle cell specifically. There is an emerging story with T-cell therapies for B-cell malignancies. And so, my assumption is that T-cell therapy has the potential to work and work well in mantle cell lymphoma, and I'm sure there's a handful of patients across the country who have gotten T-cell therapy for mantle cell, but I'm not 100 percent sure about that, but there are several centers that are trying the strategy: University of Pennsylvania, Memorial Sloan Kettering, Fred Hutchinson in Seattle, City of Hope are all places that are working hard on this so-called adoptive T-cell strategy.

And to explain it sort of simply, they'll take a patient, and they'll take their T-cells out of their blood, and they will inject the T-cells with some DNA that'll make those T-cells express a new protein. And then, they grow the T-cells up in the lab. And then they infuse the T-cells back into the patient. And this new protein that the cells express will now help the T-cells target the patient's B-cells. And since mantle cell lymphoma is a B-cell lymphoma, these T-cells will knock down whatever B-cell lymphoma the patient has. And the treatments worked very well in chronic lymphocytic leukemia, which is kind of a cousin of mantle cell lymphoma. And I'm sure we'll start to see some data in mantle cell lymphoma.

So, I think it's a promising strategy for mantle cell. I just don't have any personal experience with it, and I don't know of any data that I can quote you in mantle cell lymphoma, but there's every reason to think the strategy could work in mantle cell.

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Ms. Lauren Berger

Thank you for your question, Phil. We'll take the next question from the telephone audience, please.

Operator

Our next question comes from Dorothy calling from Florida. Please state your question.

Dorothy

Yes, on ibrutinib, I just wondered if as a second round treatment, is approved by Medicare, and we were told it's extremely expensive. How expensive are we talking about range wise?

Dr. Brad Kahl

Ibrutinib is about \$13,000 a month. And my impression is that it will be covered, I think I heard by Medicare. Although, I've been telling all my patients on Medicare to make sure they have drug coverage supplements, because if you have one of these 80/20 deals where you have to pay 20 percent, 20 percent of \$13,000 every month is obviously incredibly expensive.

And so, people really need good prescription drug coverage. And then, hopefully, like in our state in Wisconsin, we just got an oral chemotherapy parity bill passed by our state legislature last week. I think the governor is signing it today, where oral chemotherapy will get the same kind of coverage as IV chemotherapy, but I know that varies from state to state.

So, this is a problem, the price of the oral chemotherapy drugs and the spotty drug coverage that some people's insurance has. So, if you have Medicare you definitely need a supplement. And if you have private insurance you can't have some crazy copay system or it'll add up to a lot of money in a hurry.

The company does have a patient assistance program. The whole thing is very new. And so, I don't have much experience with the patient assistance program yet. But, I believe that will help a lot of patients who have inadequate reimbursement from their insurance company.

Ms. Lauren Berger

Also, The Leukemia & Lymphoma Society has a Co-Pay assistance program, so I encourage you to contact us. There's a flyer in your program material, but also for information you can call 877-557-2672, and we'll be happy to provide any information and help you apply for that.

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Ms. Lauren Berger

We'll take the next question from the Web audience and this one's from Gerald. "I have mantle cell with blastoid variant. I have undergone a bone marrow transplant. Will this cure me or can the lymphoma still relapse?"

Dr. Brad Kahl

Unfortunately, the lymphoma can still relapse. There's no guarantee of cure with any strategy we have. We think the strategy that has the most potential to cure people would be stem cell transplant from a donor. That's called an allogeneic stem cell transplant, and that's certainly a highly appropriate strategy for many patients, but it's a risky strategy. Approximately 20 to 30 patients who have an allo-transplant will succumb in the first two years, just due to complications of the treatment. So, we don't recommend that strategy routinely, but usually for people with relapsed mantle cell or some other high-risk features.

So, it's just very hard to know when you can tell a mantle cell patient whether they're cured or not, and I'm reluctant to use that word because I don't want to say things that I'm not sure about. And I just try to talk to patients in terms of long remissions. Are some mantle cell patients probably cured? Probably are. I just don't know at what frequency, how often that happens. So, I'm just real careful about using that.

Ms. Lauren Berger

Okay, and thank you for your question Gerald, and thank you all for your questions.

Slide 34 – The Leukemia & Lymphoma Society Contact Information

If you have not had your question answered, please feel free to call The Leukemia & Lymphoma Society's Information Specialists at 800-955-4572. Information Specialists are available to speak with you and to answer your questions from 9 a.m. to 9 p.m. Eastern time. We can provide information about clinical trials, financial assistance or other questions you may have about support, including financial assistance and co-pay. We also have online chats for patients and caregivers. So, please look at the flyer in your packet or go to lls.org/chat. These chats are moderated by oncology social workers and provide a good forum for patients and caregivers to share experiences and support with each other.

Please help me thank Dr. Kahl for volunteering his time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for sharing your time with us. Good-bye and we wish you well.