Emerging Treatments in Follicular Lymphoma  
Webcast  
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INTRODUCTION

Andrew Schorr:  Hello and thank you for joining us for our special edition program on lymphoma. This is one of a series. We did one back in September with a well known doctor in the treatment of lymphoma, Dr. Julie Vose from the University of Nebraska. Today we'll have another, equally well known guest, Dr. Jonathan Friedberg from the University of Rochester and the Wilmot Cancer Center there. And then, of course, we have two other programs scheduled coming up; one probably very late after Thanksgiving this month, and then we'll do one in December after the big American Society of Hematology meeting, which will be in Atlanta, and I'm going to go down there, so I'll bring you the latest news. Now this is a live webcast, so you ask your question; not so specific that it just applies to you, but one that can help all of us. We've gotten 30 or 40 questions already. We'll do our best to cover the highlights, but without further ado, I'd like to introduce our guest today, Dr. Jonathan Friedberg.

Dr. Friedberg:  My pleasure. Thank you so much for asking me to participate in this.

Andrew Schorr:  Sure. Dr. Friedberg, lets zero in on follicular lymphoma. Put that in perspective for us related to lymphomas and also how do you diagnose it, and how does somebody know that in fact that's what they're dealing with?

Dr. Friedberg:  I think the first question is to really make sure everybody is clear with what lymphoma is. Lymphoma is a blood cell problem. Although it's a kind of cancer, it's very different from, for example, prostate cancer or lung cancer, which affects specific organs of the body. The issue with lymphoma is, is that one of the blood cells called the lymphocyte, which normally fights infection, has a mistake in it, and that mistake is that it's making too many copies of itself. Since
it's a blood cell it can go anywhere, and we see lymphomas in the blood, in the bone marrow, in lymph nodes, and in organs, and that's not surprising because it's a blood cell. I think what differentiates lymphomas from any of the other kinds of cancers is how complicated lymphoma is. It turns out that the word "lymphoma" really means about 40 different diseases. So, some lymphomas are so aggressive that we emergently admit patients to the hospital and treat them. Other lymphomas are so indolent or slow growing that we often don't even treat patients right away, and many patients never require therapy of the lymphoma. So, when you're talking about lymphoma, it's critical to know exactly what kind of lymphoma you're dealing with.

The term "follicular lymphoma" summarizes one of these kinds of non-Hodgkin's lymphomas, and the way you figure out what kind of lymphoma it is, is you have to do a biopsy and have a professional look at it under the microscope. One of the things I wanted to emphasize today was how important it is to have an expert who understands all these different kinds of lymphomas look at the biopsies that are performed, and usually these biopsies are of lymph nodes, and oftentimes with lymphomas we need a larger piece of tissue than can just be obtained from a needle, so it's often a surgical biopsy, a piece of tissue that's looked at under the microscope, and through a variety of tests that the pathologist can perform we can make a definitive diagnosis of follicular lymphoma.

Andrew Schorr:  
Okay. The diagnosis is so important. People often get caught up, you know, 'I have lymphoma versus something else' and they talk about stages, but knowing whether it's follicular lymphoma is critical to knowing what treatment might be right for you versus a different form of lymphoma, right?

Dr. Friedberg:  
You're absolutely right on. As I said, some lymphomas are curable, some are not. Then entire goals and specific treatments are becoming more diverse among the lymphomas because we're understanding the various mistakes that comprise the lymphomas much more, and therefore a lot of times people are concerned about things like second opinions for management, but oftentimes it's prudent to also make sure that everybody's perfectly clear with what this diagnosis is, and if patients are in a small center where they're often less familiar with some of these kinds of lymphomas, it may make sense to have the pathology reviewed by a larger center who often have experts who really focus on these lymphoma for diagnosis.

EMERGING APPROACHES FOR TREATING FOLLICULAR LYMPHOMA

Andrew Schorr:  
Right. I'm going to make a little Patient Power speech for a second. So, I sought out for my leukemia, different, but I actually sought out a subspecialist in consultation to arrive at a treatment plan, and even in my leukemia, like we're talking about follicular lymphoma, when do you start treatment? And I know we'll get to that. So I would urge people, nowadays and fortunately follicular lymphoma does fit in this category, things are changing, so don't you want to at least check in with somebody who has devoted their life to that? Dr. Friedberg is an example of that, Dr. Vose I mentioned, Oliver Press is out here in Seattle. They are people who
are particularly involved in this disease, and then also the pathologist who is knowledgeable about it too, and make sure you know what you're dealing with. That's my little soapbox.

Dr. Friedberg, let's go on because as I alluded to here is things are changing. So help us understand the landscape of where we are in the emerging approaches for follicular lymphoma. What changing? Where are we headed?

Dr. Friedberg:
Obviously that's a big question, so well get into whatever detail you want. I think to sort of summarize the landscape it's been a very positive last 10 years in this disease. Historically, follicular lymphoma is considered a disease that is not curable with the standard treatment. Now under very exceptional circumstances that may not be true, but clearly it's a very treatable disease, and for 30 years, up until about the mid-90s, although several new treatments emerged on the scene, the survival of patients with follicular lymphoma did not change, and happily that has now moved significantly in the positive direction. Over the last 10 years we have seen significant improvements in overall survival for patients with follicular lymphoma, and we're not 100% sure as to why people are doing so much better, but we presume a large component of that is this antibody treatment call Rituximab or Rituxan, which has clearly integrated itself into the treatment of patients with lymphoma, all lymphomas that are B cell, but specifically follicular lymphoma.

So the last 10 years we've really spent, I think, on figuring out exactly the best ways to use rituximab and several things have emerged from the 10 years experience. In general we've learned that when you give chemotherapy, it's best to combine rituximab with chemotherapy, and I think we've also learned that rituximab as a single agent can be given in various ways to either create a remission of the disease or maintain a remission of the disease. I think there have been some other intriguing studies of more aggressive approaches including bone marrow transplantation for the relatively uncommon young patient who presents with an aggressive component of the disease. We have had two drugs called Bexxar and Zevalin that have been approved in the last 10 years for this disease, and numerous new agents in study. So I actually, looking ahead, would predict that our treatment paradigms that we discuss today will likely change, as you implied, over the next four to five years, and that's hopefully going to be a result of the clinical trials that are open now and some of these new agents hitting the market, and we can discuss at least a couple of these new agents in further detail I would presume later in the call.

WHEN TO START TREATMENT FOR FOLLICULAR LYMPHOMA

Andrew Schorr:
Right. Let's also frame a couple of issues. So one I want to put on the table, and we'll get to is, when do you start treatment? And is the idea of watch and wait, or watch and worry, dead? Where do we stand with that? The other thing is, is knowing that we're not able to cure follicular lymphoma, but you have new things coming down the pike. How do you have a treatment plan so that your initial treatment doesn't preclude you from benefiting from something later on? So I want to make sure we get to that.
The first question is, when do you start treatment? What's your thought about that?

**Dr. Friedberg:**
I think that that is an evolving concept. Historically, and I think the textbooks would still say, that follicular lymphoma like the other disease you mentioned, CLL, since it's not curable, the standard approach had been to not treat this disease unless there was a reason to treat the disease, and those reasons might include growing lymph nodes, lymph nodes that are large or in a spot that could cause a problem. For example, if a lymph node is blocking off a kidney that would be a reason to treat. Symptoms from the disease, which could include fatigue, fevers, weight loss, or night sweats, or blood count problems that would predict that the patient would become symptomatic soon, and when our standard approaches were chemotherapy, that fit very nicely because chemotherapy had a lot of side effects, and studies in the 1980s were done that suggested it was safe to withhold therapy until somebody became symptomatic. In fact, if you treated sooner, you really only gave the patient side effects and no real clear benefit.

I think the reason why this is now in flux is because with our new treatments we don't know if that concept is true anymore, and in addition, we have new treatments including rituximab that I mentioned briefly that have many few side effects. So the threshold to initiate treatment I think has clearly changed. I helped to coordinate a registry of patterns of care in the United States for follicular lymphoma, and still about 20% of patients with follicular lymphoma are observed or put on a watch-and-wait program, so I think that this is still being utilized but I think that for many patients there is more incentive to start treatment a little early in the course of the disease than there used to be.

**FORMULATING A TREATMENT PLAN**

**Andrew Schorr:**
Okay, and just my second question before we get into specifics of what you have available now is, how do you arrive at a treatment plan so that all of the benefits of newer medicines can accrue to you knowing that you may need them sooner or certainly later?

**Dr. Friedberg:**
You bring up one of the most important issues in the management of these indolent diseases, and the analogy I use for my patients is that this is a marathon, that you can't use all of the treatment that we have in the first six months when you're hoping that survival times will be for decades. So you definitely have to have a plan from the day you meet somebody and ensure that your initial therapy will keep the options open that are part of that long-term management plan and of course keep in mind that new things may enter the equation as well. I think simply put, I've approached each patient as an individual, and I think that plans may differ depending on patient age, depending on other medical issues, and so forth, but I think that that's where you want to make sure that you have a very careful dialog with your oncologist because certain treatments, for example stem cell transplantation an so forth, if the disease is not managed a certain way may not be available to a patient when they need it, and you want to make sure you have all the options open to you, and therefore you want to choose treatments in an appropriate order that would allow that.
EXISTING AND EMERGING TREATMENTS: RADIOIMMUNOTHERAPY

Andrew Schorr:
Okay. Let's get into what some of these existing and emerging treatments for follicular lymphoma are. Now you mentioned along the way Bexxar, and I know there's Zevalin. So these are radioimmunotherapies. I think of them as like a monoclonal antibody, like a Rituxan, that's a targeted therapy but it carries this sort of radiation payload to the cancer cell. Tell me if that's a good way to see it, and where are we? I've been hearing about these drugs for a while, but I don't know whether they've been underutilized.

Dr. Friedberg:
I think that they have been underutilized. That's the short answer, but you're absolutely correct. These are monoclonal antibodies. Both of them directed against CD20, the same protein that Rituxan is directed against, and it's a way that you can inject radiation into the blood, and it can find its way to the lymphoma cells and zap the lymphoma cells. It's a very easy treatment for patients in that it only takes one week to get. There are not recurrent visits and so forth. It all goes in over one week, and the side effect profile is relatively minimal. There is no hair loss associated with it. It's not chemotherapy and so forth. It does need to be given in a center that has some expertise, and there needs to be some coordination with radiation experts to help give this treatment, but most even medium size centers in the United States are able to do this. Both of these drugs are approved drugs. These are not in clinical trials. These are approved drugs and available. I should mention that as single agents they have among the highest response rates of any agents that have been tested in indolent lymphomas. So, that's all the good side. The question is why aren't more people getting these agents? I think there are a lot of complicated explanations as to that. Some of it is the very issue you just brought up. There's a concern that if you use these agents too early in the course of the disease that you may be closing doors to other treatment options. We actually don't know if that's the case, but that's obviously an issue that people need to think about. The other issue is that it is somewhat complex, and it requires an experienced treatment team, and therefore if an oncologist has never done this before, it can be a little bit hard to arrange. There are studies going on now that I'm optimistic will better define the role of radioimmunotherapy for this disease.

EXISTING AND EMERGING TREATMENTS: BENDAMUSTINE

Andrew Schorr:
Okay. Let's go on now. Of course the standby, pre-Rituxan or even with Rituxan, has been chemotherapy. So, are there even older agents that are beginning to resurface that you'd like to call to people's attention even that are available now or may be or are a part of trials and how they fit in with what would be used for follicular lymphoma?

Dr. Friedberg:
Yes. I think of those agents that we're very excited about is a drug called bendamustine. A very interesting new agent to the United States but and old drug. This drug was developed in the last 1960s and early 1970s in the communist part of Germany and basically was only available in the communist world until the Berlin Wall fell in the 1990s, and at that time, when the Berlin Wall came down, doctors in the rest of Germany started using this drug and found it to be quite
active, and the drug is currently now under development in the United States for treatment of patients with follicular lymphoma and a recent study that has been completed and is pending publication suggests that this drug has very significant activity even in a group of patients where rituximab does not work any more, and that's historically been a rather difficult clinical situation to treat.

So we actually are optimistic that this drug will be approved by the FDA for that purpose in the year 2008, and I think that's going to likely be a drug that rapidly gets incorporated into treatment plans for follicular lymphoma.

Andrew Schorr:
Now, we have questions actually that have been coming in. People say, 'well, I'm on Rituxan. What do I do when Rituxan stops working?' We'll do a whole show about that probably later this month, but your comment on it, would it be that you can combine it with bendamustine and maybe use Rituxan again?

Dr. Friedberg:
Yes. I think that examples of what to do when Rituxan stops working, that's actually one of the most important clinical scenarios that oncologists deal with now. I think that radioimmunotherapy has clearly been shown to be active when Rituxan stops working, so that's one option. I think that chemotherapy, and often we still combine it with Rituxan is another option, and bendamustine is the first drug that will likely be approved with that indication of rituximab refractory disease. I think the other issues are is that for younger patients that's certainly a time when you may need to consider some of the more aggressive approaches like stem cell transplantation.

EXISTING AND EMERGING TREATMENTS: IMiDs

Andrew Schorr:
Now, we've got other drugs that are used for other cancers, like the so-called IMiDs. One of them is Revlimid, which I knew grew out of its sort of predecessor was thalidomide. Where does that fit in?

Dr. Friedberg:
Right. So another very important and very exciting class of drugs, Revlimid is a 2nd generation version of thalidomide, the same thalidomide that caused major birth defects in the 1960s when it was used for non-cancer indications. Thalidomide and more recently Revlimid have had a major resurgence in the treatment of a disease called multiple myeloma. Multiple myeloma is actually a 1st cousin, as it were, of indolent lymphoma. In fact, the malignant cell in myeloma is a lymphocyte, a plasma cell that is a mature lymphocyte. So, there are a lot of therapies that are sort of borrowed between the two diseases. Because of the successes in multiple myeloma, we've tested this in small numbers of patients with indolent as well as more aggressive lymphomas, and there's been an experience in CLL as well, and in all of those areas, the Revlimid seems to be quite active.
So now there are studies that are looking at optimal combinations combining Revlimid with drugs like Rituxan and even with chemotherapy. One of the exciting things about Revlimid is that it seems to work a very different way from chemotherapy. We're actually uncertain as to the exact mechanism of Revlimid but involved in it's mechanism is something called antiangiogenesis where blood vessels are actually affected, and there's a whole wave of research in oncology that has suggested that abnormal blood vessels help to support cancer, and if you can normalize these blood vessels, you may be able to help fix the cancer, and although the data on that in lymphoma is a little bit less than in some of the other cancers, I think it is becoming more and more clear that that is a reason why lymphomas can be stubborn to treat, and therefore we're optimistic that that mechanism may be very important in it's success.

EXISTING AND EMERGING TREATMENTS: VELCADE

Andrew Schorr:
Dr. Friedberg, so there's another drug that's also approved for multiple myeloma. It's a different kind of drug, a proteosome inhibitor, Velcade. Does that show any promise, or is that being studied in follicular lymphoma?

Dr. Friedberg:
Yes. So Velcade is a drug that not only is approved in multiple myeloma but recently was approved for the treatment of a rather uncommon form of lymphoma called mantle cell lymphoma. So, there's even more evidence with Velcade that it works against non-Hodgkin's lymphoma, it's very successful against one of them. In a couple of the early studies of Velcade, some patients with follicular lymphoma were included, and the response rates of those patients, many of whom had not responded to many other treatments, was about 40%, which is a very reasonable response for a single-agent type of treatment, meaning that 40% of patients had significant shrinkage of their lymph nodes following the Velcade treatment. Velcade, as you mentioned, is a proteosome inhibitor. The proteosome is sort of the wastebasket in a cell, and if you block the wastebasket, poisons can accumulate and help to kill the cell. It's sort of a different way of killing cells from some of the other chemotherapies that we use. There are a couple of studies going on now that I think will define the role of Velcade, including one that is combining Velcade with Rituxan, and I think that's often how Velcade may be given. It is actually an option now that is available, and I have used it in some patients with indolent lymphomas.

EXISTING AND EMERGING TREATMENTS: BCL-2 INHIBITORS

Andrew Schorr:
There are two other areas I want to ask you about, and then I want to remind folks of the telephone numbers too, and we will then devote the rest of the program as best we can to your questions.

So, here are the two areas. Let's pick them off, Dr. Friedberg. The first is Bcl-2 inhibitors. What is that, and what's their promise related to follicular lymphoma?
Dr. Friedberg:
This is a very exciting area. Once of the important questions when you're dealing with a cancer is what is the mistake that causes the cells to make too many copies of themselves? In follicular lymphoma at least a component of that mistake has been understood for some time. So very briefly, there is a switch of the chromosomes or the strands of DNA in the cell that result in an increased activation of a protein called Bcl-2, and Bcl-2 is a protein that is designed in the cell to prevent the cell from dying. So, the more Bcl-2 you have around, the less likely a cell is to die, and one of the problems with follicular lymphoma is there is too much Bcl-2 around. So, there have been a number of attempts to try to decrease the levels of Bcl-2 directly in the cells, but only in the last few years has the technology existed to make what's called small molecules or very small proteins that are actually targeted and designed to inhibit the expression of specific molecules like Bcl-2. So this is a very directed therapy that is available now orally in a pill, and three companies have Bcl-2 inhibitors that are currently in clinical trials, and very, very early preliminary results look extremely favorable, so we're very excited about this class of agents. I don't think it will be ready for general use for another four or five years, but we're optimistic that this class of agents could really change the way we manage the disease.

EXISTING AND EMERGING TREATMENTS: VACCINES

Andrew Schorr:
Okay and the other area I wanted to ask you about is the use of vaccines for follicular lymphoma. I believe there have been two in development and probably a number of people who are listening have been in trials. Where are we with knowing whether that's ready for prime time?

Dr. Friedberg:
I think we're going to have an answer in 2008. Very briefly, the concept is since follicular lymphoma, if you don't treat it, in about a third of patients you might see what's called a spontaneous remission where the disease seems to go away completely just on it's own. Unfortunately in most situations when that happens, the disease eventually will come back. For 30 years there has been the suggestion therefore that the patient's own immune systems can help to keep follicular lymphoma under control, and the concept has been made that if you take the follicular lymphoma out of the body, manufacture a vaccine, and give it back to the patient, you may be able to help generate an immune response against the patient's own follicular lymphoma. It's a very individualized therapy. Work had been done in the 1980s and 1990s perfecting this, and over the last few years there have been three, large, randomized trials where half of the patients after a treatment get a vaccine and the others get essentially a placebo. It's not quite a placebo; it's a nonspecific immune activation treatment, and we're waiting to see what the results of those studies are. I think that there are really two schools of thought on this. Some oncologists feel that the vaccines will likely play a critical role in the management of follicular lymphoma. Other oncologists feel that rituximab may have sort of been a more convenient way to help get this immune response directed against the tumors, and vaccines may add relatively little to rituximab-based treatment. I think we will find out in 2008.

Andrew Schorr:
Sounds like you don't want to weigh in just yet.
Dr. Friedberg:
I don't know if it's appropriate for me to weigh in on this call, but I will say that rituximab has set a pretty high bar for vaccines, and I think that one of the responsible things that the vaccines are going to need to do is if they look promising, we're going to have to figure out how to use them in combination with rituximab, and some of the studies were designed to answer that, so we'll see.

KEEPING FOLLICULAR LYMPHOMA IN REMISSION

Andrew Schorr:
So, now we've talked about a whole array of approaches. It sounds to me like as you've set out, it's an exciting time. Nobody wants to have this diagnosis. I didn't want to be diagnosed with leukemia, but when you are diagnosed with this, and you know that you're going to be living with it for the rest of your life is how can you keep the disease at bay and in remission and go on with your life with a high quality of life? It sounds like in most cases you have those tools, and you have something else to try if maybe the first shot at it isn't as effective as you'd like it to be.

Dr. Friedberg:
I think certainly they're coming, and I think we have many more options now than we used to have, and I think that's why patients are living longer. I think the other point, which hopefully patients will feel optimistic about, is many of the agents that we're studying now, these targeted designer agents, have many fewer side effects than the old fashioned chemotherapy regimens that unfortunately we still often have to use. So not only are we coming up with new promising agents to help treat this disease, but these agents as active as they are, seem to have many fewer side effects, and as I said, some of them are likely to just be pills that are taken every day, which is so different from coming every two or three weeks to get aggressive chemotherapy and losing your hair and having all of those issues. So I think that's one of the most exciting things for patients.

RITUXAN AS A HUMANIZED MONOCLONAL ANTIBODY

Andrew Schorr:
One quick question before taking a quick break, and that is so Rituxan, and I had it too for my CLL, as I understand made from a mouse gene, what is it when you're talking about a humanized monoclonal antibody, and where does that come into play? It may be related to what you were just talking about for side effects.

Dr. Friedberg:
Right. So rituximab is what's called a chimeric antibody, which means there are mouse components as well as human components on the antibody. You may be able to comment on this given your personal experience, but most patients feel that rituximab as a single agent really does not have significant side effects, although there may be some chills and shakes during the initial infusion of rituximab, and most patients are able to get through that.
Andrew Schorr:
Right. I had all that.

Dr. Friedberg:
And compared to our other treatments, it's really a pretty benign drug. But rituximab has been incredibly successful. Successful for not only indolent lymphomas but aggressive lymphomas, diseases as you mentioned like CLL and even some noncancer diseases. It's not surprising when a drug is successful that other companies start to get excited about trying to improve upon it because they see a big market potential, but we have seen over the last few years are attempts to try to make rituximab better, and one attempt is to get rid of the mouse component and make it fully humanized. Now, that does have the theoretical advantage of having a little bit less side effects, but as I said, I don't think that's a major motivator because as it stands, rituximab is pretty well tolerated. I think it's helped though that by making the whole thing humanized that you may be able to manipulate the human immune system a little bit better and have better activity against the cancer. There are three or four of these humanized anti-CD20 antibodies that are in clinical trials. I'm very interested. It's very hard to know until there's a head-to-head comparison whether these are really working better than Rituxan or not, but we're all eager to see how that goes.

Andrew Schorr:
All right. Thank you for that explanation. Lot's of things swirling about when we talk about follicular lymphoma, and that's why I recommend people do have a consultation with a subspecialist, if you will, someone who is really on top of it, like Dr. Jonathan Friedberg, our guest today, to really see what might apply to them now and in the future. We're going to take a quick break, and we'll be right back.

REPEATING RITUXAN THERAPY AFTER REMISSION AND DISCUSSION ON MAINTENANCE RITUXAN

Andrew Schorr:
Dr. Friedberg, here is an e-mail we got in from Edie in Pensacola, Florida. So Edie is a 65-year-old female and was diagnosed in 2003 she says with small b-cell grade-1 stage III indolent follicular lymphoma after she did have a surgical abdomen biopsy. Clean bone marrow, abnormal amount of lymphedema in abdomen. Anyway, her first line treatment choice was 12 treatments of Rituxan, and she has been stable since 2004, so she is wondering if she comes out of remission, do you just repeat the rituximab alone, and will that probably just do well or is it going to need to be combined with something else?

Dr. Friedberg:
That's been studied, and actually she's fortunate to have a very good response to Rituxan initially, and the response it sounds like has been quite durable for 3 years. That's really beyond the average, and that's a very good situation for her to be in. Frequently in that situation should the disease recur, and as I said we expect that it would, rituximab would be a fine option to try again depending of course on how aggressively it behaves, but she could certainly expect that under many circumstances you can respond to rituximab a second and even third time, and there is some even preliminary evidence that responses might last even longer the second time
compared to the first time, so I think that would be a very reasonable type of treatment option along with other treatment options.

**Andrew Schorr:**
Okay. Now, it's been controversial; at least a few years ago and I would like to know where we stand now; some doctors advocate, if you will, maintenance rituximab after you're already doing well. What's the latest thinking about that? What's your personal view?

**Dr. Friedberg:**
That's the 1000-dollar question both literally and figuratively. That's a very controversial area in the management of indolent lymphoma right now. I'll try to briefly summarize exactly where we stand as far as the data. We know that if you give what's called maintenance or prolonged rituximab treatment following single-agent rituximab. Usually rituximab is given weekly for four doses. If you then put a patient on a schedule where they get what's called maintenance rituximab or maybe a single dose of rituximab on a schedule every three months or sometimes it's every two months or even every six months, there's evidence that you can maintain a remission for longer than if you don't do that, but we don't know if that actually is any better than the scenario you just described where a patient gets treated with rituximab, is followed, and then when the disease comes back you get rituximab again. One small study suggested that actually the two approaches are pretty equivalent in keeping the disease sensitive to rituximab, and a large study in the United States called the Resort trial is seeking to really answer that question.

The other scenario where maintenance rituximab has been used frequently is after chemotherapy, and there is a study that clearly shows if you give chemotherapy without rituximab, and you get a response, that maintenance rituximab adds to that.

The real question that we don’t know is most patients in the United States who get chemotherapy get Rituxan with the chemotherapy. So for example, an R-CHOP regimen is a very commonly used regimen. Rituximab with CHOP. We don't know if giving rituximab maintenance after that regimen is something that affects the long-term prognosis of this disease or not, and it's a very important question that is being answered in a study that is completed accrual that has more than 1000 patients on it, and I expect that we should in the next several months have the definitive answer. Until we have that definitive answer, practice is really all over the place, and there are some physicians who feel that they don't want to withhold a potentially beneficial treatment that they see as having few side effects. I think there are other physicians who feel that we don't know the long-term side effect profile of prolonged maintenance rituximab, and there's also the theoretical concern of actually engendering resistance. If you take antibiotics every day, you know you're going to get resistant to those antibiotics. There's a concern that rituximab could be that way as well.

So, this is an area that we spend a lot of time talking to our patients, and I would encourage patients to have long discussions with their oncologists about this issue about why they should or should not be put on maintenance type of treatment program.
TREATMENT OPTIONS AFTER BECOMING RITUXAN RESISTANT

Andrew Schorr:
Now as we talked about earlier, a lot of this is different notes on the piano, different medicines being used together or one after the other. Here’s a question we got from Patrick from Boston. He said, ‘I received CHOP as a treatment in 2004 and a followup of Rituxan for 18 months, and then I relapsed. So in June I received Bexxar. My question is, should rituximab be resumed some time in the future? The Bexxar has been successful at this time, so where does Rituxan come in there?’

I know we can’t be so specific, Patrick. You’ve got your own doctor and all your lab results, and we can’t do this over the internet but just as a guide Dr. Friedberg?

Dr. Friedberg:
I think in general once somebody becomes resistant to rituximab, which it sounds like Patrick was describing where the disease grows despite rituximab treatment. Rituximab as a single agent is probably not something that is often used, but frequently rituximab may still be combined with chemotherapy in that setting, and you may ask why if Rituxan isn’t working why are you doing that? There is some evidence that even when rituximab isn’t working as a single agent it may help chemotherapy to work better, and therefore it’s likely that a patient or a patient like Patrick may get rituximab again, but it likely would be in combination with something else.

RADIOIMMUNOTHERAPY

Andrew Schorr:
Okay. Here’s a question relating to the radioimmunotherapy. This came in from Jan in Tacoma, Washington, and Jan writes, ‘what kind of results are you having administering Bexxar and Zevalin the second time?’

Dr. Friedberg:
There really is very little experience repeating radioimmunotherapy. A small study did it with Bexxar, and there are a handful of patients who have been treated with Zevalin. I think that for most patients right now there are probable other options rather than repeating radioimmunotherapy. I think the real issue is the one we discussed earlier that not enough patients are being offered treatment with radioimmunotherapy a first time, and I would say that whether somebody should get radioimmunotherapy a second time or not should be a very individualized discussion, but we don't have a lot of data on that at the present time.

BENEFITS OF RITUXAN THERAPY

Andrew Schorr:
Here’s a question that we got in from Jerry in Sherman, Texas, and he said, ‘I have NHL follicular lymphoma, and I was in a clinical trial for one of the vaccines, the Favrire vaccine as far as he understands, and at the 13th injection, one of my lymph nodes started getting larger, and so I was pulled from the trial, and I was told that I was getting the vaccine. I had four
treatments of rituximab about 2 years ago before I started the vaccine. My doctor said now to just wait and watch, and he said that I could do another clinical trial later. In your opinion, what would you do in the form of treatment when needed?'

Dr. Friedberg:
I think that's a scenario where it sounds like this patient; taking the vaccine out of the equation because that was really a trial; who was treated with rituximab, had a reasonably long remission, and now has slow disease that's coming back. I think it's similar to the other patient who we discussed before where rituximab or a monoclonal antibody based approach again is certainly an option. I think other clinical trials are potentially good options, and chemotherapy if need be if the patient needs to have a deeper response or a longer remission, and it's very hard to comment specifically except to say that the treatment that this patient has had so far really precludes nothing, and I think that's one of the advantages of single-agent rituximab is at least one of the treatment options is that you can give chemotherapy, you can do a transplant, you can do radiolmunoimmunotherapy, you can do all the kinds of treatments after that, so it does keep a lot of options open.

STEM CELL TRANSPLANTS AND FUTURE OPTIONS

Andrew Schorr:
Okay. Now that relates to our next question about keeping options open. Barry from Taos, New Mexico, writes in, 'I have heard that if you have a stem cell transplant, it doesn't leave a lot of future options if it doesn't work. Is this true?'

Dr. Friedberg:
I think in general there is some truth to that. I think the way to think about it is that stem cell transplant constitutes a lot of therapy, and the human body can only take so much therapy in a lifetime. So, the stem cell transplant is a way that you give a lot of therapy at once with the hope that the remission duration will be very, very long, and for selected patients it could certainly work that way, and that's why oftentimes we don't want to give stem cell transplants too early in course of the disease, but if you wait too long, oftentimes patients are not eligible for a stem cell transplant for one reason or another. So, figuring out the exact timing is a very individualized decision.

Andrew Schorr:
Let's talk about what else goes through your mind in that situation because Cheryl from Phoenix, Arizona, writes in. She said, 'I just had a recurrence of non-Hodgkin's lymphoma that shows up on the CT scan.' She has not had a PET scan done, and when she had it done in February it was negative, but she said, 'my hematologist is recommended stem cell transplant. Are there alternatives to consider as well?'

Dr. Friedberg:
I think there are definitely alternatives. I think that there clearly are a group of patients who benefit from stem cell transplant, and it's probably worth this patient's time having the discussion with a transplant expert to hear about exactly what's involved, but a lot of the alternatives to
stem cell transplant may be some of the clinical trials of the exciting new agents that we just discussed, and I think that for many patients that's another reasonable choice.

**SIGNS AND SYMPTOMS OF FOLLICULAR LYMPHOMA AND STAGING**

**Andrew Schorr:**
Here's a question we just got in from Adrian who is in Boise, Idaho, and he said he was just diagnosed with follicular lymphoma, and he has been told that it's slow growing and that there's not a thought that either radiation or chemo is needed just now, and he did go see a specialist, and he had blood tests, and the CT scan showed that he had a tiny growth in his neck and maybe a few other places, and he did have a nodule or cyst removed from his cheek just last month, and he's scheduled for a bone marrow biopsy. He doesn't have an appointment with the specialist for another five weeks, and he's wondering how do you know what stage your lymphoma is at, and are there certain signs or symptoms that he would notice as a patient?

**Dr. Friedberg:**
Let me answer the second question first. In general, if somebody has a very small amount of disease, and they're being observed, it's very unusual that symptoms will develop over the course of a couple of weeks. Frequently these patients can be observed for years. So, if a patient is seeing a specialist again in four or five weeks, I usually try to encourage patients to try to compartmentalize this and not worry that they're missing something within that four to five week period of time. This is not a disease that is sort of measured day to day. In fact, I often get more information if I see people a little less often because I can appreciate changes over time better.

To get to the first question, how is the lymphoma staged? Follicular lymphoma is staged like all non-Hodgkin's lymphoma, and basically stage I if there is a single lymph node involved. Stage II is if there are multiple lymph nodes in either the chest or the abdomen involved. Stage III is multiple lymph nodes on both sides, so the chest and abdomen. Stage IV is organ involvement including bone marrow involvement. Now, a good 60% or so of patients walking in the door with follicular lymphoma have bone marrow involvement. Stage IV does not have the same connotation in follicular lymphoma as it might in other cancers, so staging is somewhat helpful in guiding our treatments, but it doesn't quite have the prognostic information I think as it would in other cancers.

**CHEMOTHERAPY EFFECTS ON FERTILITY**

**Andrew Schorr:**
Here's a question we just got in via e-mail, and it's actually from Rochester, New York, where you are, sir. This is from Mary in Rochester. 'My wife is 28 years old and was diagnosed just last week with B-cell mediastinal non-Hodgkin's lymphoma, and she has a 9x4 cm mass in her chest, and the results of the PET CT indicated that her lymphoma was confined to that area only. My question is what types of, if any, advances have been made in terms of treatment with respect to long-term side effects and especially fertility because these are young people we're talking about.
Dr. Friedberg:
So, I'll be very brief on this answer because it's a little off the topic. Mediastinal lymphoma is an aggressive lymphoma that falls under the category of large-cell lymphoma, so it's really not follicular lymphoma as we're talking about today, but I will talk about the fertility issue because it's an issue that affects both follicular and aggressive lymphoma situations.

The regimen called CHOP chemotherapy that we frequently use to treat both follicular as well as the more aggressive lymphoma like this patient has frequently is not something that results in permanent sterility. The older the patient is when they get the chemotherapy the more likely they are to have problems in the long term conceiving a child. There are some things that experimentally may be able to be done to help to protect fertility, and it's certainly worth a discussion with the oncologist about some of these medical treatments, and there have been some studies looking at even egg harvesting and so forth, which we generally do not do because it takes a lot of time to do that, and a lot of times for somebody with a large mass in their chest that's not appropriate, but as I said, there certainly is hope, and in somebody in her age group I think there's a reasonable chance that she will maintain fertility.

CVP VERSUS RITUXAN

Andrew Schorr:
All right. Thank you for that. Let's take a call. Neil is joining us from California. What city are you in, Neil?

Neil:
Santa Ana.

Andrew Schorr:
Okay. So Neil, what is your situation, and what's your question?

Neil:
In 2004 I underwent CVP as part of the MyVax regimen to get into the vaccine clinical trial, and I had a CR. It lasted to get me in the program. I underwent the entire vaccine series and continued to have a CR for about 18 months after that where I progressed. Unblinded, I found out I did get the vaccine, and subsequently my question is, since I did have a good response from the CVP, relatively mild chemo, is there any record or going back to just CVP again or would you just go to something like CVP and Rituxan with everything being Rituxan oriented today?

Dr. Friedberg:
Right. I think that clearly CVP is another option, and historically there is a huge record of that. That's how we used to manage this disease. I think in this era though somebody in the situation that you describe almost certainly would be encouraged to get rituximab treatment either alone or with CVP or other chemotherapy. It clearly in randomized trials has far superior outcomes than the agents alone.
RESEARCHING RECURRENCE OF FOLLICULAR LYMPHOMA

Andrew Schorr:
Okay, that was great. Here's another question we got in from Lucy in Mandeville, Louisiana. 'What has been learned from research as to the recurrence of non-Hodgkin's lymphoma and the form in which it recurs, and followup studies that have been published relating to the above?' I think you mentioned earlier also, Dr. Friedberg, maybe a third of the time it doesn't recur, if I got that right? Where are we with that?

Dr. Friedberg:
No, no, I'm sorry. About a third of the time somebody may have what's called a spontaneous remission where the disease will go away by itself, but I think with follicular lymphoma, with the exception of some very unusual presentations, unfortunately this disease likely to come back. We don't think we have curative therapy. There are lots of thoughts on why this disease behaves this way. I mean, why should a disease be invisible for six years and then all of a sudden come back? It's really a very complicated question, and I think there have certainly been a lot of studies that suggest the immune system is an important regulator in that, and that's why all these studies and the vaccines and so forth have been done. I think there are potentially other things.

One of the other areas that people are looking at is what's called the microenvironment. What that is, if you biopsy a lymph node involved with a follicular lymphoma, it's not just cancer cells there. There are normal cells as well that create this follicular architecture that is characteristic of the disease, and the interplay between the normal cells and the follicular lymphoma cells appears to be critically important at keeping the follicular lymphoma cells alive. So in fact, another way to treat follicular lymphoma might be to disrupt that interplay and disrupt the normal cells, and that's something that we're clearly focusing some of our research efforts on even here. So, I think that all of those things are potentially targets for our treatments to try to prevent this disease from coming back, but as far as why exactly it's so resistant to our standard treatments I think people are somewhat unsure.

PROGNOSTIC MARKERS IN FOLLICULAR LYMPHOMA

Andrew Schorr:
My frame of reference of course is this sort of "cousin disease" chronic lymphocytic leukemia, and I know there we talk a lot about doing different kinds of test to say do you sort of have a more aggressive case even though it's not a particularly aggressive disease. What about with follicular lymphoma? Is there any test you can do where you can sit down with a patient and say, you know Mr. Smith or Mrs. Jones, from what we know of your particular cancer, it's more likely to recur sooner?

Dr. Friedberg:
See, CLL is an example of a disease where we have a lot of what are called prognostic markers such as proteins, for example, on the surface of the cell and so forth that can put you in one of those categories. We're not quite there yet in follicular lymphoma. There are some clinical
prognostic markers, and there's this scoring system called the FLIPI that if you have a lot of factors, patients tend to have shorter remissions than if you have few factors, and these clinical factors include advanced age, performance status, number of nodal sites, LDH value in the blood, hemoglobin in the blood, and stage of the disease. So depending on how many of those factors that you have, that gives you a score, and that score can help to predict how the disease is behaving. I think though that those clinical markers are really surrogates for what's going on with the cancer, and there have been some experimental studies that are looking at patterns of immune proteins that are in the cancer, biopsies for example, that help to predict outcome, but we're not quite at the level yet as we are in CLL where we can actually use these tests on a commercial basis.

UPCOMING INFORMATION ON FOLLICULAR LYMPHOMA

Andrew Schorr:
Yes, but there continues to be progress, and I want to come back to some of the things we talked about earlier just in summary. You have your big meeting of you and all your peers, the American Society of Hematology meeting that's coming up. So, what do you think is going to break there? Do you have any prediction of the news that people living with follicular lymphoma should listen carefully for?

Dr. Friedberg:
I think in follicular lymphoma we know a lot of the large clinical trials, and I think 2008 is going to likely be a bigger year than 2007. I think that a year from now we should have an insight as to whether the vaccine trials are positive or negative. I think that some other large clinical trials, as far as up front management of indolent lymphoma, are likely to be completely, and hopefully by the end of the year we might even have a signal on the maintenance question. So we could be a lot further along a year from now than we are now. I'm not certain that the ASH meeting or the Hematology meeting in December is likely to contain a lot of those. I think it's going to likely be somewhat more incremental, but the final program hasn't been published yet. I expect we'll actually see it in the next few days, so we might be pleasantly surprised by an abstract.

Andrew Schorr:
We'll be on top of that of course on Patient Power and with our future programs coming up maybe later this month. Watch our web page for that. I hope to see if we can have Dr. Armitage or Dr. Czuczman from Roswell Park to help us understand what they think is hot from ASH or their perspective on looking forward.

FUTURE TREATMENTS FOR FOLLICULAR LYMPHOMA

Andrew Schorr:
Dr. Friedberg, so all of you though seem to say that the future is promising. So, when you look back on that, is it just this array of approaches trying to get at the cancer cell from a variety of different ways either used alone or in combination that you have a lot to work with so you think you can beat the follicular lymphoma back and allow people to live a long time? Is that what's motivating that statement?
Dr. Friedberg:
I think there are two things. One is clearly that, that we have a lot of new agents, a lot of agents that are working and different mechanisms compared to our older agents. So just because certain chemotherapy doesn't work, it has no prediction as to whether these new agents will work because they're interfering with a different mechanism within the cell, but I think our biology and our science understanding of the disease has gone up significantly over the last 10 years, and a lot of that is somewhat sophisticated to discuss on a short phone call like this, but suffice it to say I think we're having a much clearer understanding of what keeps follicular lymphoma cells alive and what pathways may be able to be interfered with. So, that clearly feeds the pipeline. In other words, the more we understand what proteins are important to keep follicular lymphoma alive, the easier it is for a drug company to develop a pharmaceutical that inhibits that pathway that is involved, so that's a good direction.

The other thing is I think we'll likely have better understanding as to what certain patients may benefit from over others. The other thing is I think we'll likely have better understanding as to what certain patients may benefit from over others, so some of the types of tests that you implied you'd like to see done I think we're going to be able to do in follicular lymphoma. We may say, you have a subtype of follicular lymphoma that is likely to respond really well to a Bcl-2 inhibitor, so I'm going to start with that.

The only way we can accomplish this is with carefully constructed clinical trials and improved research, so obviously we try to support the research the as best we can, and we hope that collaborations between patients and physicians on getting these clinical trials done will happen.

PARTNERING WITH YOUR PHYSICIAN

Andrew Schorr:
I was in a clinical trial. I couldn't agree with you more.

Just one last thing I want to ask you about, Dr. Friedberg. So, we've covered a lot of ground today, and we will have the replay very quickly on our web site and then we'll add a transcript. People are going to say, 'well I want to discuss this with my doctor.' How do you have this discussion because it seems like this really gets at the art of lymphoma care today and not just the science. How do you have that so to partner with your physician or seek a second opinion to really have a treatment plan that you believe in and want to follow?

Dr. Friedberg:
I think the first thinks is to keep in mind that this is a marathon of a disease. I think that there are lots of opportunities to get a second opinion or another spin on management, and if somebody is in a situation where they're involved in a certain treatment program, it's not necessarily in their best interest to see five other people to see if they agree with it, and I think we have to also appreciate that there isn't one standard approach to this disease. That's good and bad. If there were, we would all do the same thing, but the good part of not doing the same thing is that we can individualize approaches, but as you say, that can be a little bit of an art, and I might decide that a certain patient would benefit from chemotherapy, and a very reasonable colleague might
say, 'I don't think so yet.' So, we have to appreciate that there are some differences. I think that all of those factor into that a little bit.

I will say that it's very important for patients to have an understanding, I think, as to how this disease behaves and what the rationale is, and that allows for a very productive dialog with the physician. This is not something that patients can learn overnight. It takes us years in medical school training to even become doctors much less oncologists, so you can't expect overnight to learn this, but you're going to have this disease for many, many years, and from the types of questions you ask me, you clearly have made an effort to understand your disease quite a bit, and I have many patients who it's the same thing, and there are a lot of resources out there, and over the course of the first few months of having the diagnosis after you've confronted the emotional aspects of it, I think it's important to try to get the fact, and then you're able to have a discussion with your doctor, and you're able to say, 'what about this approach' or 'what about that approach' and you know what questions to ask.

Andrew Schorr:
Great advice. I could not agree with you more, and that's our goal to help patients be smarter about, as you say, that you'll be living with it hopefully for many, many years but yet have a high quality of life.

Dr. Jonathan Friedberg, Associate Professor of Medicine and Director of Hematologic Malignancies Clinical Research at the Wilmot Cancer Center at the University of Rochester in Rochester, New York. Thanks so much for being with us, sir. You've been great and have helped, I think, demystify the latest science related to this illness. We wish you all the best with your research for our listeners because I know the work you do and your peers could make a bid difference over time. Thanks for being with us.

Dr. Friedberg:
It's my pleasure. I wish all the patients luck, and we'd be happy to help out in any way we can.

Andrew Schorr:
Thank you, and thanks for the devotion of a strong memorial in the University of Rochester there to this area of medicine.

We will be back hopefully later this month with another in our series of Patient Power program special editions for lymphoma, so take a look at the web page. Come back and look for the replay and we'll be adding the transcript, and tell your friends. As always, knowledge can be the best medicine of all. In Seattle, I'm Andrew Schorr. Have a great day.

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