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Non-Hodgkin's Lymphoma™ UPDATE

Patient Education Series

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

CONTENTS

2 Audio CDs
Program Transcript

FACULTY

John P Leonard, MD
Weill Medical College of Cornell University
New York, New York

Mitchell R Smith, MD, PhD
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Brad S Kahl, MD
University Hospital
Madison, Wisconsin

CME Certified

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Neil Love, MD
Editor, *Non-Hodgkin's Lymphoma Update*
Miami, Florida

Welcome to the patient education series of *Non-Hodgkin's Lymphoma Update*. For 20 years, our education group in Miami has been producing cancer education programs for doctors and nurses. On this launch edition of our special patient education series, three nationally respected lymphoma research experts present their approach to discussing this disease with their patients. This audio series can not only be utilized by oncologists, but also by patients who wish to better understand the complex issues surrounding a diagnosis of non-Hodgkin's lymphoma.

If you are a patient who has received this program from a physician or nurse or downloaded it from our website, **www.NHLUpdate.com/Patients**, please note that it is not meant to substitute for the individualized opinion that a personal physician can provide. The experts interviewed on this program can, however, be a valuable supplement to understanding this disease and are a credible source of information in the field of oncology.

Dr Leonard is the Clinical Director at the Center for Lymphoma and Myeloma and an Associate Professor of Medicine at Weill Medical College of Cornell University at New York Presbyterian Hospital in New York, New York.

To begin, we visit Dr John Leonard of Cornell University, who discusses the most common subtype of NHL, diffuse large B-cell lymphoma. To assist in this discussion, I asked Dr Leonard to track through the case of a patient with this disease in his practice.

DR LEONARD: Not that long ago, I saw a very nice woman — who is actually the mother of one of our nurses — who is in her early sixties. And she presented with really swollen lymph nodes, fatigue, weakness, just feeling poorly.

DR LOVE: How long had she felt poorly?

DR LEONARD: Felt poorly for probably two to three months or so before that. Had some shortness of breath that kind of gradually worsened over several months and fatigue, which is, I think, a fairly common symptom for people with lymphoma.

She had seen her primary physician, who examined her and felt the lymph node. And he was concerned, because he did feel lymph node enlargement. He got some blood work, got some CAT scans, and he sent her to a surgeon who went ahead and did a biopsy of this lymph node.

DR LOVE: Where was the lymph node?

DR LEONARD: Lymph node was in her neck.

DR LOVE: How big was it?

DR LEONARD: It was about three to four centimeters, altogether.

DR LOVE: So that's like a couple of inches.

DR LEONARD: Mm-hmm.

DR LOVE: Was the lymph node itself painful?

DR LEONARD: It was not painful. It was not painful, and it was something that she really didn't notice all that much. It was in a location —sometimes you can see lymph nodes very clearly. But this was in a location where it was kind of hiding. It was in her lower neck, kind of hiding behind her collarbone. And once they pointed it out to her, she saw it very clearly. But she didn't really notice it then.

DR LOVE: Now on the physical examination that I guess her primary doctor did, and that you followed up on, were there any other lymph nodes or any other findings when you examined her?

DR LEONARD: She had some lymph nodes in her groin. And she had some very vague kind of fullness in her abdomen, which I think is also common. She had some lymph nodes in that area. In examining her, it wasn't clear that this was lymphoma, but these kind of fairly vague, kind of feeling full at various points in time in her abdomen was something she noticed.

DR LOVE: And when you examined her abdomen, did you feel anything specifically, or was it just sort of distended?

DR LEONARD: Just some fullness. Just some fullness there.

DR LOVE: And what did the biopsy show?

DR LEONARD: Biopsy showed a diffuse large B-cell lymphoma.

DR LOVE: And what exactly is that?

DR LEONARD: There are a variety of different types of lymphoma. And I think one of the hard things for patients is that there are in the range of 30 or 40 different types of lymphomas. There are Hodgkin's lymphomas, which are a special set, and then the non-

Hodgkin's lymphomas. And within the non-Hodgkin's lymphomas, which are more common, there are in the range of 25 or 30 different types. And so it is hard for patients, because you may encounter someone with lymphoma or go on the internet or be in a support group or something like that, and hear a story about someone with lymphoma. And that may be someone who has a completely different situation than what one is dealing with, because they have a totally different type.

I tend to group the types of lymphomas, the many different types, into three broad categories: one being the indolent lymphomas, a second being the aggressive lymphomas, and then the third being a grab bag of much less common lymphomas, all of which have their own special type, their own characteristics, their own special features.

So diffuse large B-cell lymphoma, which this patient had, is the most common of the aggressive lymphomas, which is about 30 percent of lymphomas.

DR LOVE: What's the difference between Hodgkin's and non-Hodgkin's lymphoma?

DR LEONARD: Hodgkin's lymphomas have a particular appearance under the microscope, and they have a particular type of cell called a Reed-Sternberg cell. And Hodgkin's lymphomas are treated, also, with chemotherapy and sometimes radiation. But they're treated with different chemotherapy regimens than we tend to use in non-Hodgkin's lymphoma. So the distinction is very important.

DR LOVE: So this woman had what is really the most common form of lymphoma?

DR LEONARD: That's right.

DR LOVE: Now, why is it called diffuse B cell?

DR LEONARD: Most non-Hodgkin's lymphomas are B-cell lymphomas. About 90 percent are B-cell lymphomas. And that is just a characteristic. It's a description of the type of lymphoma and, in fact, where the type of normal cell in the body — the B cell — is where this lymphoma came out of.

Lymphoma is a tumor of the lymph tissue. And the lymph tissue makes up the immune system. The immune system is kind of like the army, the navy, the air force, the marines. These cells fight infections wherever the body comes in contact with them. And there are switches in the cells that tell them to grow, and then tell them to die off. And depending on where those switches get broken, one gets a different type of lymphoma.

So this form of lymphoma is a B-cell lymphoma. And it has a pattern under the microscope, which is a diffuse pattern. It's the way the cells arrange themselves within the lymph node, and they are large; hence, the name: diffuse large B-cell lymphoma.

DR LOVE: What do the B cells do normally, compared to what the other types of lymphoid cells, the T cells, do?

DR LEONARD: The B cells tend to develop into other cells, called plasma cells. And those make antibodies. And antibodies are liquid chemicals that are released into the bloodstream and help to fight infection. So they provide one arm of the immune system, whereas the T cells are kind of like the infantry. The T cells actually go out into the infected area and they themselves go and fight off whatever needs to be dealt with.

DR LOVE: Now in a patient like this, who has a B-cell lymphoma, are her B cells functioning normally? Can a patient like this respond to infection?

DR LEONARD: Normal B cells are present, and so in and of itself, the immune system does work. Patients with any sort of tumor and lymphoma, as well, just by nature of having the disease and due to the treatments of the disease, may be at more risk of having infections.

DR LOVE: Were there any other studies done on the biopsy tissue, or studies typically done in addition to looking at it under the microscope?

DR LEONARD: Pathologists will do a variety of different studies to confirm what type of lymphoma we're dealing with, and that's very important. In some cases, patients should be encouraged to get a second opinion on their pathology, because defining the pathology, the type of lymphoma, is the critical part of deciding what's the prognosis and what's the treatment. And sometimes it's frustrating to patients, because they may have to wait a week or two while the pathologist is working on the tissue. They do a variety of different tests on them.

One group of tests is called the immunophenotype. And if patients look at their reports, they see all of these CD numbers. And these are the equivalent of saying, "What's the hair color of the tumor cells? What's the eye color? What's the skin color?" and different patterns of hair color, eye color, skin color fit different patterns of lymphoma. So, the pathologist will do these tests to kind of confirm their impression that they see directly under the microscope.

And then there are a number of other what we call molecular tests that also help to confirm and to look for genetic changes in the lymphoma, that help to categorize it and to be sure that it fits the pattern consistent with a given diagnosis.

DR LOVE: So now this woman was seeing you as the primary oncologist.

DR LEONARD: That's right.

DR LOVE: And do you have your pathologist then review what the other pathologist has done?

DR LEONARD: Every patient we see, we have our pathologist review what other pathologists have done. And I would say, in our practice now, we have a group — an outstanding group — of pathologists. But probably 20 to 25 percent of the patients that we see, our pathologists have a different diagnosis. And, in fact, it's interesting when you

look at the original pathologic classifications, the studies that the pathologist did to categorize lymphomas, taking the expert groups of pathologists, getting 10 expert, world renowned pathologists to look at the same tissue, probably about 10 percent of the time, depending on the type of lymphoma, they disagree. So, it's not a cut-and-dry, black-and-white issue in some situations, and I think it's very important to get another opinion, even if it's an expert that's seen it. Others may have other opinions that are important to know.

DR LOVE: Are there any sort of types of situations where you more commonly see the second pathology opinion differing from the first?

DR LEONARD: I think that there are certain types of lymphoma where that's more common. In follicular lymphoma and large cell lymphoma, the two most common types of lymphoma, that is less common. But the third kind of grab bag type of lymphomas that I alluded to tend to be more difficult. So for instance, mantle-cell lymphoma, small lymphocytic lymphoma, or CLL, chronic lymphocytic leukemia, MALT lymphomas, or marginal-zone lymphomas —and there are a whole grab bag of names of these things, but these are types that are a little less common. They're harder to sort out. And these – because they're less common, pathologists see them less frequently and may be a little bit less familiar with them. So, those are particular scenarios where I think it's important to have another opinion.

DR LOVE: Now in this case, did your pathologist agree with the first pathologist?

DR LEONARD: This pathologist did agree, yes.

DR LOVE: Now, I guess the next step, once the diagnosis has been made, is to sort of identify where the tumor is located. What was seen in this woman?

DR LEONARD: This patient had what we call a staging evaluation. She had a bone marrow biopsy, to look to see if there was lymphoma in the bone marrow, the cavity inside the bone. She had CAT scans. She had PET scans. And all of these were put together to give us an impression of where her lymphoma was. And in her case, we saw a variety of locations of the lymphoma, both in the lymph nodes throughout the body. She had some involvement of her lung, as well as her spleen. So there were a few areas where the disease had gotten outside of the lymph nodes, but was in various organs.

DR LOVE: As you talked to her and reviewed her history, you mentioned the fact that she was tired, or fatigued. Any other symptoms that you felt were from the lymphoma?

DR LEONARD: I think that was the most prominent with her. Sometimes people have fever, weight loss. She really had not had those. But I think she just felt like she was kind of chronically run down as her main symptom.

DR LOVE: Can you talk a little bit about the specific tests that you just talked about in terms of doing this staging evaluation, first the bone marrow. What's done in that situation?

DR LEONARD: A bone marrow biopsy is something that is a simple outpatient test, but there is some discomfort involved with it. Some patients liken it to getting a filling from their dentist, in that we numb up the area. It takes about 20 minutes or so.

DR LOVE: What part of the body is it done on?

DR LEONARD: It is done in the hipbone or in the iliac crest, the upper part of the buttock area, the bone in the back.

DR LOVE: So the patient lies flat, prone, face down on the table?

DR LEONARD: That's right. Patients lie on their stomach. There is some cleaning solution to make the area sterile. There's some numbing medicine that — usually lidocaine, that's applied to the skin and to the bone, using small needles. And then basically the person performing the procedure goes into the hipbone a couple of times with a needle and samples the area inside the bone.

There are a few areas, a few times, a few seconds here and there, where there is some significant discomfort, because we can't numb up the whole area. But the procedure is done with in about 20 to 30 minutes or so, and it's not a very dangerous procedure, which is reassuring to some people, despite its discomfort.

DR LOVE: In this case, what was seen in this woman's bone marrow?

DR LEONARD: This woman did not have any involvement of her bone marrow. Bone marrow involvement is very common in the indolent forms of lymphoma. In large cell lymphoma, which she had, it's seen in the range of about 10 to 20 percent of patients.

DR LOVE: Now you mentioned, also, the CAT scan and the PET scan. What are these?

DR LEONARD: CAT scans are fancy x-rays, basically, that allow the radiologist to look at pictures of the organs and the sizes of the organs and the consistency of the organs inside the body. So it's basically looking at slices of the patient going down the body from the head to the toe. And that allows us to look to see are there areas of lymphoma involvement in different organs. Are there lumps in the different organs, and, more commonly, look at the size of the lymph nodes, and are there enlarged lymph nodes. Normal lymph nodes are about a centimeter to a centimeter and a half in size. So if we see a lymph node area that's about five centimeters, let's say, we assume that that's lymphoma, because it's enlarged.

The PET scan is a different sort of test. It's a complementary test. PET scans involve a small injection of radioactive glucose, radioactive sugar. And radioactive sugar, or sugar in general, is taken up by tumor cells, as well as some other conditions, like inflamma-

tion. And so this is kind of a double check of the CAT scan that this area, this test lights up in areas that appear to be involved with lymphoma. And so the CAT scan is better at giving size of tumor masses, whereas the PET scan is better at picking up the number of tumor masses and areas that perhaps might be still small, but are involved with lymphoma and, therefore, not picked up on the CAT scan.

DR LOVE: Now you mentioned that this patient had involvement in the lung. Could you see that on her regular chest x-ray?

DR LEONARD: You could see that on her regular chest x-ray, yes.

DR LOVE: Where in the lung was it?

DR LEONARD: It was in the upper part of her right lung

DR LOVE: And it was seen also in the PET scan and the CAT scan?

DR LEONARD: That's right.

DR LOVE: So was this a majority of the lung that was involved, or just a small part of it?

DR LEONARD: No. This was a small area. The two lungs together take up most of the chest area, and this was an area that was maybe the size of a golf ball.

DR LOVE: I'm curious about sort of this woman's emotional reaction to this situation. How did she appear to you?

DR LEONARD: I think she was worried, as anyone would be, because it's obviously a scary thing to be facing this sort of diagnosis. I think, to some degree, she was also relieved to know that. Because she'd not been feeling well, she was relieved to know that she had an answer to why she was not feeling well and, I think, to some degree, relieved that we have good treatments for her. And she was optimistic that she would feel better soon.

DR LOVE: Now, is she working?

DR LEONARD: She is retired. She is active, though, has an active social life and visits with her family, goes out with her friends, is very active in her social circles.

DR LOVE: Is she married?

DR LEONARD: She is married.

DR LOVE: Who came into the office when you met with her?

DR LEONARD: Her husband and her daughter came in.

DR LOVE: I would imagine that one of the things, maybe, that might have come up in this conversation was why did she get the lymphoma. What do you say to patients about that?

DR LEONARD: We don't know why patients get lymphoma. It's complicated, and it's particularly concerning because the incidence or the number of people who are getting lymphoma seems to be on the rise. Lymphomas have been associated with people with problems of the immune system. So patients who have immune deficiency states, whether it's from some infection, like HIV, or from other more rare immune problems that are occasionally seen, that's been associated with lymphoma. But most people with lymphoma really do not have a definable risk factor; they don't have a definable reason why the lymphomas seem to occur.

DR LOVE: Are lymphomas in any way communicable? I mean, should her family, her husband, be concerned about that?

DR LEONARD: It is uncommon, but there are family members of patients with lymphoma who do develop lymphoma. So like most cancers, your risk of having a cancer tends to be a little bit higher if you've had a family member with it. So there are some, what we would call genetic, perhaps, relationships. But there's no evidence that they are, in fact, communicable or that being around a patient with lymphoma is going to result in getting one.

DR LOVE: How strong is the genetic connection? For example, should her daughter be concerned?

DR LEONARD: The genetic component of lymphoma, overall, seems to be relatively low with respect to family risk and family history. So other than routine medical care and medical screening, we would not generally do anything special as far as screening for a family member of a patient with lymphoma.

DR LOVE: In breast cancer, we have mammography; prostate cancer, the PSA blood test; colon cancer, colonoscopy. Is there anything that can be done to pick up lymphomas earlier, or is it of any value?

DR LEONARD: It's hard to know whether or not picking up a lymphoma early would make a difference in outcomes. There are some hints that that would be the case, but overall, it's hard to really argue that that would make a big difference. And so, in general, there aren't any particular screening tests other than getting routine checkups with one's doctor. And, obviously, if one has a symptom which could be seen in lymphoma — fevers, weight loss, night sweats, or lymph node swelling — that would certainly be a reason to go see one's doctor and have that checked out.

DR LOVE: What were the options of therapy that you discussed with this woman?

DR LEONARD: Well, when I see a patient with large cell lymphoma, the type of lymphoma that this woman had, we sit and talk about what's the prognosis and what are the treatment options.

And in large cell lymphoma, going back several decades, we have something called the International Prognostic Index. And it's a very simple index. We remember it by APLES, or "apples," as a way to remember it and think about it. And that is really five features that tells us how a patient is likely to do. Now, none of these things are perfect. None of these tests are perfect. But it

gives one a rough idea as to whether a patient is going to do better than average, maybe worse than average, or somewhere in the middle.

Large cell lymphoma is a curable lymphoma. And so the goal of treatment with large cell lymphoma is to give the treatment, which is primarily chemotherapy. Occasionally radiation therapy is part of it. And now rituximab is a common part of it.

But the question is, for the individual patient, what is the likelihood of that type of treatment working for them? And so the International Prognostic Index is a simple, five-factor tool that we use. And I sit with every patient and go through it with them, just so we get a sense of what to expect out of their disease.

The first two factors are age and what we call performance status. Patients who are older — over the age of 60 has been an arbitrary cutoff — and that's very arbitrary — and have what we call impaired performance status, meaning they're sick in bed and unable to walk around and do their normal activities, are less able to tolerate the disease and less able to tolerate the treatment — so patients who are older and bed bound or unable to do their activities do less well. So those are two of those five factors.

The other three factors reflect the biology of the disease to some degree. Those second three factors are what we call the LDH or lactate dehydrogenase, which can be easily measured through a routine blood test and really shows the turnover of the cells. It shows how fast the cells are growing. Having an elevation of the LDH is less good. Having multiple sites of what we call extranodal disease — that's the E in the APLES — extranodal disease suggests, in more than one place, such as the lungs, the liver, the bone marrow, suggests that the disease is acting a little bit more aggressively in that it's leaving the lymph nodes and going into other areas.

And then what we call Stage III or IV disease, when we have disease — and that's the S, or the last factor — if the disease is in various areas of the body, both above and below the diaphragm, or the waist area, that would make it Stage III or Stage IV.

And so those five factors give us a sense of whether a patient is very likely to be cured, less likely to be cured, or somewhere in the middle, and gives us a sense, for an individual patient, of perhaps what we can expect out of this disease and how we should approach them.

So a patient who is young, who has disease and is ambulatory, feeling well, doing all their normal things, who has a normal LDH, the disease is only in the lymph nodes and may be in only a couple of areas, those are patients who are likely to do very well with standard treatment.

DR LOVE: By "very well," what do you mean?

DR LEONARD: Well, cure rates for aggressive lymphoma in patients who have none or very few of those risk factors are in the range of 80 percent or so. Other patients, who have more of these risk factors — so, let's say an elderly patient who is sick in bed, who has a high LDH blood test and has disease that's in various areas outside the lymph nodes, may have cure rates that are much lower. And in some cases, that can be in the 20 to 30 percent range. And then other patients are somewhere in the middle.

DR LOVE: And when you say, "cure," this is primarily with chemotherapy and rituximab?

DR LEONARD: That's right.

DR LOVE: So what were the IPI, or APLES, findings in this woman, and what did you tell her about her chance for cure?

DR LEONARD: This patient had multiple adverse or poor risk features. She was over the age of 60. She was up and around, so she had a good performance status. She did have an elevated LDH. She also did have multiple sites of the disease outside of the lymph nodes. And she had Stage IV disease.

And so, when I talked to this patient about her disease, and we talked about the fact that CHOP chemotherapy and rituximab antibody therapy being the standard treatment for this situation. However, this was not something that – while CHOP and rituximab could be very effective, given the fact that she had multiple poor risk factors, I was worried about this lymphoma. And I was worried that that therapy might not be enough to cure her disease, and that there was a significant risk that because of these risk factors, that this therapy was not going to be enough for her, and maybe we should think about doing something more.

DR LOVE: Now understanding that it's pretty hard to give an exact number, in your mind, what was the likelihood that she would have been cured with the rituximab antibody and CHOP chemotherapy?

DR LEONARD: I think less than 50 percent. Certainly less than 50 percent. And patients and doctors sometimes want to talk about these percentages. I think it's hard to know – we see patients who have a 95 percent cure rate, but if you're the five percent, you're very unhappy. And if it's a five percent cure rate and you're the five percent, you're very happy. So I tend to look at those sorts of numbers, which some people like to have, as to, are our chances of success good and, therefore, we should probably stick with the standard treatments and, in fact, make sure we do them very well and try to minimize long-term complications, because we think there's a good chance that the patient's going to live a long time? Or are we not happy with what we expect out of this treatment? Should we think of something more, giving the treatment in a different way, a more intensive way, perhaps, or doing a clinical trial with a new drug as part of the treatment to try to improve those outcome possibilities?

And I think that she felt strongly

that she wanted to do everything she possibly could to A) get better and B) be cured of her disease.

I think it's hard for patients. Doctors tend to be overly optimistic about this. And when we see large cell lymphoma, and we know that we can cure it, we tend to overestimate things, because it's not fun to say to someone, "You're not likely to do well." And so we tend to be overly optimistic and say, "Well, if there's a chance, or a reasonable chance, let's plan to do it."

But I think it's important for patients and doctors to understand what the percentages are. And, in fact, there are some cases where, yes, despite the fact that it is a curable situation, the chance of actually getting to a cure may be relatively low. And we really need to think hard about doing something more.

DR LOVE: It's interesting to see how oncologists in different kinds of tumors approach situations. In breast cancer, they actually have computer models where they generate specific numbers. And they often actually show them to patients. As I listen to you describe this situation, and particularly as you went through the factors and the fact that she'd had so many adverse factors, rather than the specific number, I would have been getting the feeling from you, "Hey, maybe we need to think about doing something a little bit more intensive to try to bring those numbers up."

DR LEONARD: That's right. And that's what this woman said. She said, "Well, that's good that you can cure it, but is there something more? I'm not satisfied with those odds. I'd like to do something better."

DR LOVE: And so what did you bring up then?

DR LEONARD: Well, we talked about the fact that there are a variety of different approaches that have been done to try to improve the outcomes with CHOP or CHOP/rituximab-based chemotherapy.

One approach is to give the treatment every 14 days, rather than every 21 days. That adds some toxicity to it. The blood counts, in particular, you have to use drugs to boost the white cells, to give it on an every 14-day rather than every 21-day, schedule, which is the usual schedule for CHOP. But that's one approach.

DR LOVE: That's the dose-dense chemotherapy-type approach? Because that's used a lot, again, in breast cancer.

DR LEONARD: That's right. That is used in breast cancer.

DR LOVE: So normally — can you go through then what a typical rituximab/CHOP kind of schedule would be and how that would be different with this dose-dense approach?

DR LEONARD: Sure. This treatment is generally given — CHOP and rituximab are generally given as an outpatient. The patient comes into the doctor's office, has an intravenous line started. They may get some nausea medicines to prevent nausea as part of the treatment, in the vein and by mouth. The nurse hooks up an IV. The drugs drip in over various periods of time. Cyclophosphamide, or the C in CHOP, drips in over about an hour or so through the vein. Adriamycin, or hydroxydaunomycin, which is the H, is in a syringe. It's a red drug that's injected through the intravenous over the course of about 15 minutes. Oncovin, or vincristine, the O, is given in the vein. It's a yellow drug that given in it through a syringe in about 15 minutes. And then P is prednisone. And prednisone is taken by mouth for five days with each round of the treatment.

So on day one, the patient gets the four drugs, three of them in the vein and one by mouth. The addition of rituximab to this involves another drug. The rituximab is an antibody-based treatment that drips in over the course of four to six hours. So rituximab takes a bit longer to give, and it turns it into pretty much kind of an all-day treatment, or close to an all-day treatment. And that's administered — the whole CHOP-R regimen is administered typically for one day every 21 days, usually for six treatments. So it's given about four months.

In the CHOP-14 schedule, we're giving it more often to try and give the cells less of a break in between the treatments, and we're giving it every 14 days, rather than every 21 days.

DR LOVE: I would like you to dissect out a little bit about how each one of these parts of the therapy might add side effects. Let's start with the prednisone. Now that's a steroid, a cortisone-type drug.

DR LEONARD: That's right. Prednisone is a pill. It can sometimes irritate the stomach. It can sometimes make people feel a little bit moody. Many people may be familiar with prednisone, because it's used for other diseases, particularly allergic reactions and immune–autoimmune diseases — asthma. Sometimes people are familiar with it. It can sometimes elevate the blood sugar, so it can be an issue in people with diabetes. It can sometimes make people feel a little bit manic or a little bit energetic while they're taking it, and then, when they stop, feel a bit less energetic.

DR LOVE: And what about the chemotherapeutic agents, the Cytoxan, Adriamycin and Oncovin?

DR LEONARD: They have a number of different side effects. These are outpatient treatments. And I typically tell patients — and it depends on the situation — that most patients are 70 to 80 percent of their normal self while they're on chemotherapy. Some people are better than that and are able to work and do most of their normal activities. Others are more affected by it and kind of have to shut down or to lower their activity level. Fatigue is an issue with these. Adriamycin, or the hydroxydaunomycin, does cause hair loss. And so that's something that we typically see with this regimen. They affect the blood counts, and that's why we wait,

typically, 21 days in between the treatments, to let the blood counts go low and then come back up. And when we use it, particularly on the 14-day schedule, we have to give medicines to help the blood counts along, to boost up the white cells, in particular, to minimize the risk of infection. Oncovin can sometimes cause numbness and tingling of the fingers and toes, what we call neuropathy. It's important that patients drink lots of fluids while they're on chemotherapy, to flush their kidneys and flush their system.

The rituximab treatment is generally given with Tylenol and Benadryl. The main side effect of that treatment is that people can get what we call infusion reactions — fever, chills, shakes — that occur while they're receiving the treatment, not so much when they go home. And that's something that is more common the first time the patient receives the treatment and less common thereafter.

DR LOVE: Let's dissect out a little bit more some of these side effects that you discuss, beginning with the last one, the infusion reaction.

How severe is it, and, generally, are patients fine once they leave the office?

DR LEONARD: Usually these are mild to moderate symptoms. Occasionally, they can be more severe. It's something the nurses are very comfortable with dealing with when they occur for an individual patient. They usually stop the treatment. There are medicines that we can give. Some patients just sleep through the treatment and sit and relax and read or watch a movie or watch TV. Others are more affected by it.

DR LOVE: And does the rituximab cause any of the chemotherapy-like side effects, the hair loss, nausea, et cetera?

DR LEONARD: No. The rituximab does not cause those symptoms. It's interesting, in that the studies that compared CHOP versus rituximab plus CHOP really showed no major increase in side effects when you add the rituximab. So it's striking that the rituximab doesn't worsen, in general, the things that the chemotherapy does.

DR LOVE: Now these reactions that occur, is it similar to an allergic reaction or kind of like having the flu? What does it sort of feel like?

DR LEONARD: It's kind of like those symptoms. People can feel cold. They can have chills. Sometimes they get a little short of breath. And just kind of feel achy, shivery, would be a description of it. They typically happen while the patient's there, so it's not something that typically happens on the way home or the next day, but really while the patient's in the doctor's office. And because it's generally predictable, it's something that everybody there is used to dealing with. While it can be a little bit scary for the patients sometimes, in general it's very manageable and not a life-threatening thing.

DR LOVE: What fraction of patients have no infusion reaction, initially? And what fraction, once you get out to two, three or four cycles, are still having no problems?

DR LEONARD: Over half the patients will have some sort of reaction. But most of those are mild and manageable. You get down to a much smaller percentage, maybe 20 or 30 percent, as patients get through their further treatment.

DR LOVE: Now you mentioned hair loss, particularly as it relates to the Adriamycin. What typically happens? When does it start? How much hair is usually lost in this situation?

DR LEONARD: With this regimen, patients usually lose all of their hair, at least their — the hair on their head. There may be thinning of the body hair elsewhere. Usually this takes about a month to happen. Patients will notice on the pillow or on a brush that their hair is coming out. And then, when the treatment stops, usually within a month, it starts to grow back again, obviously, very short, and then longer thereafter.

DR LOVE: What fraction of patients have complete loss of hair on their head and what fraction have none at all?

DR LEONARD: It really depends. And that's something that patients ask a lot about with chemotherapy, it really depends on the chemotherapy regimen that one is using and the doses that one is using.

With the CHOP regimen, Adriamycin is the most important drug. And so we don't like to delete it. But Adriamycin is the one that really causes that particular side effect. And so pretty much everyone has near complete hair loss.

DR LOVE: What about nausea and vomiting? I know we have a lot better drugs nowadays to prevent that and patients receive these kinds of drugs. In spite of that, what fraction of patients have problems with nausea and vomiting?

DR LEONARD: Most patients have some symptoms of at least nausea. We have medications that we give in the vein and by mouth to help prevent that. And when patients go home, they usually take some of these medications for a couple of days. I would say that most patients, their symptoms are, with this regimen — and, again, it's very dependent on which chemotherapy drugs we're giving. But with CHOP, the Adriamycin is the drug, again, that's most important, and that is the one that's the most prone to give nausea.

With this regimen, usually patients eat lightly for a day or so around the treatment. Maybe they have a little bit of nausea. It's pretty uncommon for people to have vomiting, where they can't leave the bathroom and are having major symptoms. And if that's something a patient is having, that may happen under 20 percent of the time. If that's something that patients are having, they really need to speak with

their nurse or their doctor, because there are lots of different tweaks to the medications that can be done to prevent that.

DR LOVE: Now you mentioned that there's this newer approach, using the therapy every 14 days. When this approach is utilized, are the side effects worse, or different?

DR LEONARD: Side effects are a little bit worse, particularly with the blood count. So we have to help them along with these extra drugs, what are called growth factors, to help boost, in particular, the white cells, to get them back up in time to give the next cycle of chemotherapy.

DR LOVE: How about the other side effects, the fatigue or the nausea/vomiting, et cetera?

DR LEONARD: Those side effects may be a little bit worse with this form of treatment also.

DR LOVE: Now how does the rituximab and the chemotherapy work and the prednisone work against the tumor cells? How does it actually affect them?

DR LEONARD: It's hard to fully understand how all these treatments work. Chemotherapy affects rapidly dividing cells. And the tumor cells are among the more rapidly dividing cells. Some of the side effects of the chemotherapies, such as the blood count toxicities, occur because the precursors to the blood cells in the bone marrow also are dividing. And so those could be affected by the chemotherapy.

Different chemotherapy drugs tend to work in different ways to some degree, and so by giving them in a combination, you can kind of overcome the tricks, or some of the tricks, that the cell has to avoid the chemotherapy or to outsmart the chemotherapy, by coming at it kind of with different directions and different ways.

Rituximab works in a variety of different ways to kill tumor cells. It can work with the immune system to induce an immune response against the tumor cells. It can also flick switches in the cell, something that we call apoptosis. It's just a term, the scientific term that's used to describe this. But that flicking of the switches can tell the cells to die and not continue to grow. And there are some complicated ways where it appears that rituximab may sensitize the cells to the effects of the chemotherapy and, in effect, make the chemotherapy work better.

DR LOVE: My take is that rituximab is part of a wave of a lot of new therapies that sort of fall under the title of targeted therapy. They're more specifically targeted against tumor cells than chemotherapy. Is that your take?

DR LEONARD: Yes. I think that's the intention. And I think our goal is really to target the treatment towards the tumor cells, to have maximal effect, while minimize the targeting to the normal cells, which results in the side effects.

DR LOVE: So one option for this patient would be to get the conventional R-CHOP given every 21 days for six cycles.

A second would be to get it every 14 days. Now what do we know about the potential benefits of giving it every 14 days?

DR LEONARD: There have been some studies that were done, particularly in Europe, that used CHOP — this was before the R-CHOP became more standard — that suggested that CHOP alone on the 14-day cycle was better in some patients versus the CHOP alone on the 21-day cycle. We're still learning whether the addition of rituximab changes this in any way, or perhaps doesn't change this in any way.

We are still learning whether, now that we use rituximab quite commonly in the treatment of this disease, in combination with CHOP, whether or not the improvements that we're seeing in the 14-day versus the 21-day schedule still hold up.

DR LOVE: So is that an option that you've utilized in some patients, and did you present that as a possibility to this woman?

DR LEONARD: We discussed that. And that's something that we are looking at. And, in some patients, we do use that approach in certain situations.

We had a particular clinical trial that we discussed, and what this patient ultimately decided to pursue with her treatment. And this trial used the R-CHOP on the 21-day schedule in conjunction with a new agent that we were adding to try to improve the outcome.

DR LOVE: So this was an experimental study that you were doing at Cornell?

DR LEONARD: That's right.

DR LOVE: And what was the agent, and how was it utilized in the study?

DR LEONARD: The agent in this study is a drug called bortezomib, or Velcade. Velcade is a drug that's FDA approved for treatment of multiple myeloma. Multiple myeloma is a lymphoid tumor, or a lymph tumor, that, in some ways, is related to lymphoma, but it affects more, the bones and the bone marrow. Bortezomib has a complicated mechanism of action. But what it does — it is in a class of drugs that are what we call proteasome inhibitors. And proteasomes are organs inside cells that play a role in how the cell gets rid of things it doesn't need anymore. And so, by inhibiting the proteins using a proteasome inhibitor, such as bortezomib, you change the balance of certain proteins in the cell.

One of the important proteins in lymphoma and in other cancers is called NF-kappa-B. The name is not that important. But NF-kappa-B is the substance that might help "let" cells be resistant to chemotherapy and help keep them alive. So the concept behind this protocol is to give the bortezomib, which lowers NF-kappa-B levels in the lymphoma cells to make the chemotherapy work better. That's the theory behind it.

DR LOVE: So you were doing a study, sort of a preliminary study, to see

whether or not you could add in the bortezomib to the R-CHOP.

DR LEONARD: That's right. That's right.

DR LOVE: And at that point when you discussed it with her, what had you seen already with other patients?

DR LEONARD: She was one of the first patients to go on this study. And we have a lot of experience with bortezomib, or Velcade, in other settings, using it by itself, particularly in multiple myeloma. And there had been some studies with chemotherapy, but this is one of the earlier ones. And so we had treated a couple of patients on this protocol, and we had a pretty good idea of what to expect. But with any study, this was a relatively new combination. And part of the goal of the study was to say, "Can you give these drugs together? What is the right dose? What are the side effects? And how well does it work?"

DR LOVE: I'm sure she asked you how likely it was that she'd have more side effects or toxicity by adding in this additional agent. How did you respond?

DR LEONARD: Bortezomib, because it's FDA approved and it's been given to thousands of patients, we have a good idea of what its main side effects are. And those include neuropathy, numbness and tingling of the fingers and toes, and what we call thrombocytopenia, or a drop in a specific type of blood cell, the platelet count. And so those were the main side effects that we were worried about, in fact, because the R-CHOP regimen, in particular, the chemotherapy, can also cause some of those problems to some degree. So we told her that it was possible — and we were being very cautious in this study — it was possible that some of those symptoms may be worsened, because we were giving different sets of drugs that could cause similar side effects together and, therefore, the end result might be more in the way of toxicity. And so we discussed this issue.

We also told her that we couldn't be sure that other new side effects couldn't come about that we weren't expecting, and that that's why we're doing the clinical trial. But we were concerned enough about her lymphoma and the fact that we thought we needed to do something more, plus we were encouraged enough by the potential promise of this new combination that we thought it was an important consideration for her and an option that was worth pursuing.

DR LOVE: Now bortezomib is available. Physicians can prescribe it. Is this approach, combining the R-CHOP and bortezomib, something that any physician could do in practice, or really needs to be done as part of a clinical trial?

DR LEONARD: Theoretically, oncologists can prescribe drugs outside of their FDA indication, and so a drug approved for another indication, another situation, could be used in a variety of different places. Whether or not insurance companies would pay for that and deal with the cost of that is another issue.

Because this is a new combination, this is not something that I would do outside of a clinical trial, but something that I think is important to study. And perhaps, ultimately, depending on how this goes as far as safety and efficacy, it may be that we will have trials that would, down the line, potentially compare R-CHOP versus R-CHOP plus the bortezomib.

DR LOVE: Now when a study like this is done, I know that there's a sort of an external review of it to determine whether it's safe, whether it's ethical. I'm sure that was done in this case. Was that explained to the patient? And are there forms that are gone though, to go through that?

DR LEONARD: Any clinical trial follows what's called the protocol, where the doctors who are doing the trial and the whole group that is doing the study outlines in advance what they're going to do, how they're going to do it, why they're going to do it. And they include a consent form, which is, in some cases, a long document but goes through all the details of the disease, the treatment that's planned and the potential toxicities that are anticipated, and explains to the patient what the situation is, why the doctors, why the investigators are doing the study, what they can expect out of it. And the point is to be sure that patients understand what exactly is involved, why should they consider this study, and what are the potential downsides of the study. Because, by definition, any study is not a certainty. We're learning about a treatment regimen and, hopefully, how it can help patients.

DR LOVE: Now do physicians who participate in clinical trials like this benefit financially?

DR LEONARD: The way the clinical trials are supported is complicated. There are a variety of different clinical trial mechanisms. Some clinical trials are done and are sponsored by the National Cancer Institute. Many trials out in the community are done through what are called cooperative groups, where the National Cancer Institute organizes groups of both academic and community centers to do trials together, to answer big questions about how does one treatment compare to another.

Some trials are what we call investigator-initiated trials, such as this one. This is one that our group at Cornell developed and approached.

Other trials are conducted by pharmaceutical companies, or biotechnology companies, who have new drugs that they are trying to develop or trying to better understand. And those may be supported by companies who primarily provide support for doing the study to cover the cost of treating the patient, the nursing personnel, and keeping track of all of the data in the study. Every study that goes on has a complex series of regulatory pathways and issues that need to be dealt with. And there is a very extensive monitoring of

what's going on, the side effects, and to be sure that everything is being followed in the most appropriate way as far as the treatment program.

DR LOVE: So for example, in this study, were you deriving any specific revenue by this woman going onto it?

DR LEONARD: So I personally do not derive any revenue. The Cornell Medical College received some support for this study, to help to pay parts of the salaries of the people that are working on this and to pay for their activities working in conducting this research.

DR LOVE: So you discussed the option of R-CHOP dose dense every 14 days and this clinical trial. Any other options that you brought up to her?

DR LEONARD: We also discussed the issue of autologous stem cell transplant. Autologous stem cell transplant, or a stem cell transplant from one's cells, is a fancy way to give more chemotherapy. And it's a long discussion as to how this works and what's behind it, but the gist of it is that some of the bone marrow-derived stem cells, the cells that give rise to the blood, can be removed from a patient through a simple procedure, like a dialysis procedure, and put into the freezer and stored. And then the patient can receive high doses of chemotherapy, enough that would drop their counts down to a degree that would keep them low for several weeks, if not months. And then the stem cells are given back, like a blood transfusion. In short, this is a way to give more chemotherapy, to escalate the doses of the chemotherapy, but to try to minimize the blood count toxicities of this extra high-dose chemotherapy.

This procedure is something that is done in relapsed large cell lymphoma. So if this patient were to relapse from her disease, this might be something down the line that we can consider as a way of giving additional chemotherapy. And some patients can have their disease cured by this sort of procedure.

So some studies have looked at and some people have looked at the idea of doing this in high-risk patients right after the CHOP/Rituxan, not waiting for someone to relapse, but kind of as a one-two punch, to give the CHOP and Rituxan to get the disease into remission, and then the stem cell transplant to try to knock it out even further.

That's a debatable issue. There is actually a large trial going on right now in the US, a trial by one of the cooperative groups and the National Cancer Institute, looking at taking high-risk patients, much as this patient is, and looking at it in a randomized way, taking them and giving them R-CHOP in the standard, every 21-day schedule, and then randomly assigning them to observation versus autologous stem cell transplant in first remission, to see if the patients who get the autologous transplant in first remission do better. And so that's an important study, and that's something that we also talked about with this patient.

DR LOVE: So she decided to go on the R-CHOP/bortezomib study. Why do you think she decided that?

DR LEONARD: I think she wanted to do something more for her disease, and I think the idea of this form of therapy and the rationale behind it, without adding a lot of expected toxicity — although we can't be sure — that's why we're studying it. We did not expect that she would have major side effect problems from this, but that it offered a potential way to make the chemotherapy work better. And that was appealing to her.

DR LOVE: And what happened?

DR LEONARD: So she received the treatment. She tolerated the treatment very well. She finished her therapy somewhere in the range of about six months ago. So she started all of this in the range of about a year ago. She went into remission with the treatment. We monitored her with CAT scans and PET scans and laboratory work and physical examination. And she went into a full remission and has been in remission since that time.

DR LOVE: And, of course, we don't really know whether or not that might have happened, even if she'd got the R-CHOP alone.

DR LEONARD: That's exactly right. We don't know.

DR LOVE: I guess, in the long run, we'll figure that out.

DR LEONARD: I think, in the long run, we'll try to get a sense of whether or not this group of patients as a whole did better than we would have expected with the standard R-CHOP regimen, without the bortezomib. And then, if it appears that, perhaps, with the limitations of this sort of study that this regimen might be doing something better through the addition of bortezomib, we'll go on to study that in larger studies that could potentially more definitively show this.

DR LOVE: So when you say that the tumors went away, for example, when you examined her, how long did it take that lymph node in her neck to go away?

DR LEONARD: It took a couple of weeks for that lymph node to go away. And then when we repeated her scans, they really showed regression or shrinkage of the tumor masses over the course of several months.

DR LOVE: When you say "regression," was there anything there?

DR LEONARD: By the end, there was nothing abnormal on her scans.

DR LOVE: What about side effects? She lost her hair?

DR LEONARD: She lost her hair with the treatment. She was admitted to the hospital once with a fever and low blood counts. And that occurred despite having — getting these medications to help boost the white cells. Occasionally, it does happen, but she tolerated that. She was in the hospital for a day or two, was not sick, but was admitted for a fever and low blood counts as a precaution and to get intravenous antibiotics.

DR LOVE: Were you able to figure out where the infection was?

DR LEONARD: Most of the time when these infections happen with low blood counts, there's no clear source. There's no clear place. And, in her case, her counts came back up, the fever went away, and we didn't find what caused it.

DR LOVE: How long did it take her hair to grow back?

DR LEONARD: Her hair took several months to grow back, probably in the range of four months or so.

DR LOVE: What about nausea and vomiting? What did she experience?

DR LEONARD: She really did not experience much at all in the way of nausea and vomiting. She was very active. She felt a lot better. I mean, many patients are afraid of the side effects of chemotherapy and that's a reasonable concern. But some patients feel better despite the side effects, because the disease gets better, and they've been feeling poorly from the disease. And as the disease responds, the patient feels better despite getting treatment or because of getting treatment.

DR LOVE: Now, you said she felt fatigued. She didn't really feel very good when she started the therapy. Of course, then you had the effects of the therapy. But overall, as she started to get the treatment, did she feel worse or better?

DR LEONARD: Overall, she felt better.

DR LOVE: She actually felt better?

DR LEONARD: She was going out. She went to social functions and was out dancing with her husband and with her friends and traveling and doing well.

DR LOVE: While she was getting the chemotherapy?

DR LEONARD: That's right. Yeah.

DR LOVE: Hmm. Interesting. What was her sort of personal reaction, the reaction of her husband and daughter and family to this whole situation?

DR LEONARD: Well, I think that they were obviously concerned about the diagnosis and concerned that it was a serious issue to deal with. But she, I think, has been relieved that she has done well and is basically back to her normal life, doing her normal thing.

DR LOVE: Is this sort of a rare case? I mean, have you picked out a patient to discuss who did extraordinarily well, or is this pretty common to see in patients with large diffuse-cell lymphoma?

DR LEONARD: Most patients with large diffuse B-cell lymphoma are cured of their disease. And so this is typical in the way of how patients do. Now, unfortunately, everyone is not cured. And particularly the higher-risk group of patients, based on those criteria, tend not to do as well and tend to have disease that come back more often. But most patients with this type of lymphoma do do well and go back to their normal lives afterwards.

I think it's important to really have a good handle on what to expect out of the disease. And I think what we would call a risk-adapted approach, which is a technical term, which basically says, "Everybody with this disease is not the same. And yes, some people may do well, some people may do poorly, but everybody's not the same." And the key is to say, "Within the group of patients with this diagnosis and this disease, what is my individual risk?" And sometimes that's the pathology. Sometimes that's the doctor looking at the patient. Sometimes the scans and the blood work and the laboratory work give you some hints. But the key is, really, to figure out for an individual patient what is their particular scenario. Is it average, better than average, worse than average, or just in general? And then what can you do to maximize your outcomes?

And I think that clinical trials are a very important part of all of this, because everything that a doctor — everything I've said to you today and anything a doctor tells a patient — comes from clinical trials. Everything we know about lymphoma, every treatment that we use, comes from clinical trials.

And clinical trials offer patients not only a way to contribute to that knowledge, which is important not only for themselves, but for patients coming along, but also offers a patient the possibilities of receiving drugs that, by definition, we don't know exactly if they fully work or how they fully work, but the possibility of perhaps improving outcomes for an individual patient.

DR LOVE: Did this woman verbalize to you that part of her motivation was to sort of move the field forward or help other patients?

DR LEONARD: I think that she felt good about that aspect of things. But I think most importantly, and appropriately so, she was worried about herself, and she looked at this as a way to — potentially not a sure thing — but potentially she was hopeful that this would improve her chances for a good outcome. And she was hopeful that it wasn't going to cause her any other problems. And it hasn't, thus far.

DR LOVE: That's interesting. I guess, really, it's going to be years before we really know whether or not, in fact, by her having gone in this trial, she really got a therapy that added benefit. I assume that what's going to happen is, at some point, you'll have to do an actual randomized study, where you compare, for example, something like R-CHOP to this regimen, R-CHOP plus bortezomib. Is that what you think is going to happen in the future?

DR LEONARD: Well, I think we'll see how these study results go. We're obviously hopeful that this will work well enough and that the signals will be that that's a strategy worth pursuing.

These randomized trials, which are the hardest ones for patients to think about, because something's taken out of their choice, it's almost a random decision, is really the only way to find out is a new treatment or a tweak on an

old treatment better than the standard treatment? And that's something that, while people can think they know the answer and try to pick which one is better, there are lots of examples in history and in lymphoma – and, in fact, decades ago in lymphoma there were new regimens that were more toxic. And, in fact, everyone thought they were better, but until the randomized trial was done, we didn't know that they were actually no better and, in fact, more toxic. And therefore, we don't use them anymore. So these are important studies to get done.

DR LOVE: Now this woman did have a complication of having to go into the hospital because of the fever and the low blood count. How often do you see that with R-CHOP and do you think it was, it's more common by adding in the bortezomib?

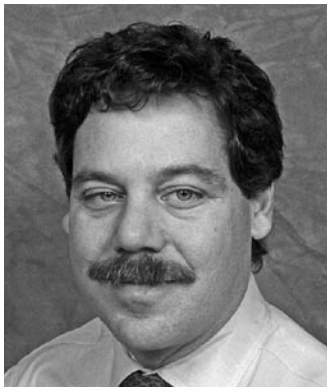
DR LEONARD: We see that with R-CHOP under five percent of the time. It's a little more common in older patients or patients who have problems with their blood counts. It happens a little more commonly the first treatment and less commonly thereafter. That's not been a major problem with the bortezomib addition, but short of a randomized trial, we couldn't really say is it more or less with that particular combination.

DR LOVE: You mentioned the growth factors to try to increase the white blood cell count. Was she given that from the beginning?

DR LEONARD: She was given that from the beginning.

DR LOVE: And is that something you routinely do when you give R-CHOP?

DR LEONARD: It's a debatable thing. I think that the use of the growth factors helps patients in some ways, but it's a debatable thing. And these are expensive treatments that I think are worth considering and need to be talked about and, in many cases, can be very helpful to patients. Certain patients, particularly older patients with low blood counts and with the first cycle, are at higher risk. And those tend to be patients where we are more definitive about using that the first time. But it's really an individual decision.



Dr Smith is the Director of the Lymphoma Service at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Another important variant of NHL was only defined in lymphoma classification systems in the last decade. Mantle-cell lymphoma seems to have a unique set of clinical and biologic characteristics, and I asked Dr Mitchell Smith, Director of the Lymphoma Service in the Fox Chase Cancer Center in Philadelphia, to describe a patient from his practice with this disease, and he discussed a patient who presented initially with enlarged lymph nodes.

DR SMITH: As with many patients, this gentleman presented with some enlarged lymph nodes. Goes to his local physician, ends up getting a biopsy and is told he has mantle-cell lymphoma, so — the subtype of non-Hodgkin's lymphoma called mantle-cell type.

And since the optimal treatment of this has not really been defined, he came for a second opinion. He was a healthy 52-year-old gentleman.

DR LOVE: What kind of work does he do and what's his family situation?

DR SMITH: He's married and works in a clerical job and wants to continue working throughout, needs to continue working throughout his treatment.

DR LOVE: And at the point you had seen him, he'd been recently diagnosed?

DR SMITH: I'd say recently diagnosed, had a lymph node biopsy, really had not had much in the way of staging evaluation at that point.

DR LOVE: "Staging" being trying to define where the tumor is located.

DR SMITH: Exactly. Lymphoma tends to be spread throughout the body, or can be, and so we need to stage, or define, where in the body it is.

DR LOVE: When you examined him, did you feel anything abnormal or pick up anything abnormal?

DR SMITH: He had some nodes in his neck and under his arms.

DR LOVE: Otherwise, he looked and felt well?

DR SMITH: Looked and felt well.

DR LOVE: What was his, sort of, state of mind at that point?

DR SMITH: He had started to hear a little bit from his local oncologist about mantle-cell lymphoma and the fact that it is difficult to treat, that it responds well to treatment, but almost always comes back, and that the average survival is not as long as we would like it to be. People quote different levels, but three years, four years, five years, and so he was looking for alternative treatments and what his best treatment options would be.

DR LOVE: And I'm sure he was very concerned. A lot of newly diagnosed patients with cancer in general feel tremendous fear and uncertainty. Where did he fit in, in that spectrum?

DR SMITH: He was keeping it pretty well together. He was clearly anxious about the diagnosis and what he was going to have to go through, but optimistic that lymphoma was treatable and that he was going to do his best to help us — go along with the treatment.

DR LOVE: And again, just by way of background, had he gone out and sought a lot of other information through the internet or telephone hotlines or anything else when he came to see you?

DR SMITH: What had happened is his local oncologist had called me to see if we had anything to offer and what we would offer and whether there was any reason to send him.

And I said, yes, we did have some research studies that he could well benefit from hearing about.

And so he knew — he had not been on the internet, but he had talked to his oncologist and said he was being sent here to talk about the different treatment options for his disease.

DR LOVE: How important, in general, do you think it is to get a second opinion in lymphoma, in general, and in mantle cell, specifically?

DR SMITH: I think there's two critical reasons. The most important reason, I find, is actually to get the pathology reviewed.

DR LOVE: In other words, what's seen under the microscope.

DR SMITH: Right. Because we find that usually, with the modern techniques of flow cytometry, et cetera, it's very rare to find that this is not a B-cell lymphoma. But the exact subtype can often be changed, depending on what we see and whether it's a mantle cell or some other type — I think we often see that there are changes in the exact subtype and, therefore, in the treatment recommendations.

DR LOVE: So you take the same exact microscopic slide and have two different pathologists look at it. And they may have different diagnoses or subdiagnoses.

DR SMITH: Absolutely. Even in some of the studies where expert hematopathologists, trained in lymphoma, get the same slides, they don't always agree. So certainly, if you have a pathologist in a community hospital who doesn't see the rare subtypes of lymphoma very often, that — having it seen by an expert hematopathologist, lymphoma specialist at a center, is well worth the second opinion.

DR LOVE: There are many different subtypes of lymphoma. Are there some, in particular, where you think it's really important to get a second opinion on the slides as opposed to others, where you don't really see that much difference?

DR SMITH: I think there's some fairly typical — sheets of large cells, it's large cell lymphoma. If you see a very typical follicular pattern, I think follicular lymphoma can usually be diagnosed pretty easily. But anything where it's diffuse infiltration of small cells — could be small lymphocytic, CLL type. It could be marginal zone. It could be mantle cell. I think those are the ones that pathologists have the most trouble with.

DR LOVE: So in this particular patient who was coming for a second opinion, one part of it would be to have a second pathologist look at it. Did that pathologist have the same conclusion as the first pathologist from the community?

DR SMITH: Yes. We did agree that it was mantle-cell lymphoma.

DR LOVE: And what's the other reason for second opinions?

DR SMITH: I think, because the treatment of lymphoma is evolving fairly quickly in terms of new treatments — and particularly in the indolent lymphomas — the choice of treatment is so vast that I think it's worth hearing about what the options are and the pros and cons of different treatment, and just an educational piece for the patient. They can usually go back to their local oncologist and be followed or get whatever treatment if they are not going to be treated on a research study. But having that education of understanding low-grade lymphoma, why it should or shouldn't be treated, how aggressively it should be treated or not, I think these are all issues which having a second opinion really are helpful.

DR LOVE: Now the concept of indolent versus aggressive lymphoma: "indolent" being a more slowly developing, harder to cure; "aggressive," more rapidly developing, maybe more likely to be cured. Where does mantle cell fit in?

DR SMITH: Right. So we usually think of mantle cell as having the worst features of each of those, so that it's not considered curable today with our standard chemotherapy treatments, which would be more like the low-grade lymphoma. But unfortunately, whereas with low-grade lymphoma you might live on an average of 10 years or more, with mantle-cell lymphoma, it's usually three, four, or five years. And the large cell lymphomas, the aggressive lymphomas, are potentially curable. Now if you're not cured, then your median survival — your survival's not very long, but at least there's the potential for cure. With mantle cell, we can't cure it, but even if you respond, it tends to come back fairly soon and that you're not going to live for many years. And certainly in the younger patients that's distressing news.

DR LOVE: So now, in this man, you have this diagnosis. You said you felt a few nodes. Where did you feel them?

DR SMITH: So in the neck and under the arms he had nodes. But he really did not have much in the way of symptoms. He hadn't lost weight. He didn't have night sweats. So he wasn't terribly ill from his disease. So we did proceed with the staging, which generally these days involves a CAT scan so we'll look for lymph nodes inside the body and a bone marrow examination, which looks to see if the cells have involved the bone marrow. Now you think about lymphoma, lymphocytes, – it's a cancer of the lymph system, and these lymphocytes circulate throughout the body. So it is perfectly expected, in fact, most patients do have cells in their bone marrow. And the mantle-cell type, in particular, almost always have cells in the bone marrow. So you have to be careful to think that this isn't the end of the world if it's in there. We just need to know it, so that we can know how we're doing as we proceed with treatment.

DR LOVE: Is it also important how much is in the bone marrow, how many cells are there?

DR SMITH: I mean, it's not so much how many, because that can be somewhat patchy depending on where

you stick the needle. But if your normal blood cells are normal — so if you're not anemic, if your white blood count is normal, then at least we know that there's enough normal bone marrow to make those cells. Then that's a good thing. If you have — all your normal cells are low because the marrow's replaced by these bad cells, then that's when we start to get a little bit more concerned that we're going to have problems.

DR LOVE: So in this man, what did his bone marrow show?

DR SMITH: His bone marrow was involved, to a small amount, with the cells.

DR LOVE: And how about the staging to try to find out where else there might be lymph nodes or tumors? What parts of the body do you scan and what did you see in this man?

DR SMITH: Right. So there are lymph nodes wherever there's blood vessels, but basically we look in the middle of the chest. There's a lot of lymph nodes along the major blood vessels and then in the back of the abdomen and in the abdomen itself. And then we also look at the liver and the spleen. The spleen is basically, can be considered to be a big lymph node. So this gentleman, his spleen was enlarged and he had some small lymph nodes, just as we felt outside the body, he had throughout inside. And that's pretty typical of mantle-cell lymphoma, to have sort of diffuse, enlarged lymph nodes, but they weren't pressing on anything. They weren't compressing any organs or causing anything that we'd be concerned about.

DR LOVE: Now sometimes when the spleen is enlarged, you can actually feel it on physical exam. And if the doctor's facing the patient, the spleen is in the upper right-hand part of the abdomen. Were you able to feel his spleen?

DR SMITH: Yes, I could feel it. What we do is we ask the patient to take a deep breath and when the lung fills up, it pushes the spleen down. And you could feel the edge of the spleen as it came down into the abdomen.

DR LOVE: And so at that point, you had enough information to discuss treatment options. Were there any other tests that you had to do?

DR SMITH: No. Some people, we'll do a PET scan, which is a new nuclear medicine scan. The CAT scan tells you the size of lymph nodes. The PET scan tells you how active they are. Are they taking up sugar? Are they metabolically active? And that can be helpful. It's not necessarily critical. It's often held for more at the end of treatment, to make sure that things which are still enlarged, that maybe shrunk 80 to 90 percent, but not back to normal, we want to make sure that it's likely to be scar tissue and not active lymphoma. Having a PET scan that's negative at that point can be helpful.

And PET scans are being used more and more. So most people these days will have a PET scan as a part of staging. This gentleman did not, actually, but more and more patients are.

DR LOVE: So at that point, you were ready to start discussing your perspective in terms of the options to consider. What options did you discuss with him?

DR SMITH: So typically, for aggressive lymphomas, we talk about a chemotherapy called CHOP. That's the initials of the drugs, C-H-O-P. And these days, we would usually add rituximab, which is a monoclonal antibody.

So what I would tell a patient, and what I told him, was that with Rituxan and CHOP, the response rate to mantle-cell lymphoma is excellent, over 90 percent.

DR LOVE: In terms of the tumors, the lymph nodes, shrinking down?

DR SMITH: Right. So the tumors would shrink in the vast majority of patients.

DR LOVE: And, for example, would the spleen shrink down also?

DR SMITH: Right. The spleen we would like to see go back to normal size. We would, if we were using this treatment, at the end of treatment, get another bone marrow specimen to make sure that this was now negative.

DR LOVE: So if you utilize that type of therapy, the R-CHOP, as the abbreviation goes, you would expect to see the tumors shrink down, maybe even go away temporarily?

DR SMITH: That's correct.

DR LOVE: And then what would you expect?

DR SMITH: Well unfortunately, on average, about a year and a half later the disease will start to grow back. And then that treatment would not work a second time, so we would need to give different treatments. The expectation is that might work for a little bit shorter time. And each treatment you give would work for a shorter time. And eventually you run out of treatments or the patient has side effects and can't get additional treatment, things like that.

DR LOVE: And what other options would be considered?

DR SMITH: So he was relatively young and otherwise healthy. And so there are some investigations or data with more intensive treatments, and there's one called R-hyper-CVAD, again, similar drugs to the CHOP given in a slightly different way and some more intensified doses. And that data looks probably best in terms of keeping the disease in remission longer. But again, it doesn't appear that we're curing many, if any, patients. So eventually, the disease will grow back after that treatment. And the downside of that treatment is it's more toxic, more risk of causing damage to organs, and it's much harder on the patient. They have to be in the hospital much of the time they get chemotherapy. So it's a major impact in their day-to-day life. He would not be able to work through much of this treatment. He would be at risk for coming back in the hospital

with infection and so forth.

DR LOVE: So with that type of therapy, the R-hyper-CVAD, as it's commonly referred to, how long would it be from the time therapy was started until the time the patient kind of felt better and had recovered from the effects of the therapy?

DR SMITH: The treatment takes roughly about four to five months. And then it takes a couple of months to really recover. So you're talking about at least six months of being out of action in terms of your normal life.

DR LOVE: And how does that compare to the R-CHOP?

DR SMITH: Well, the R-CHOP is one day every three weeks. So it's much easier. You're not in the hospital. It still has the risk of infection and that sort of thing, but again, it's a much easier treatment on the patient, because the doses are less and the treatment is less intensive.

DR LOVE: So they're sort of not knocked out as much. But when do they sort of get back to normal?

DR SMITH: With the R-CHOP, again, most of us would give probably about six treatments, once every three weeks. So you're talking about five months and, again, another month or two. So again, it's about six months or so where you're having chemotherapy and not feeling yourself, although during R-CHOP most people can continue to work.

DR LOVE: So those would be two options that might be commonly considered by an oncologist in practice. Maybe the oncologist who saw this patient brought those up, I would guess.

DR SMITH: Yeah, I think so. And some oncologists have different levels — I mean, all oncologists are comfortable giving R-CHOP. Some are not as comfortable giving the R-hyper-CVAD, either because they haven't given it or, more commonly, because their hospital may not have the support systems in place for the sicker patients and blood transfusions and things like that. So the tradeoff in the R-hyper-CVAD is more impact on your lifestyle, more toxicity, side effects, but a longer duration of remission if you can get through the treatment.

DR LOVE: You mentioned the community oncologist, who's seeing every different type of tumor, and then the specialized oncologist in a cancer center, such as yourself, who focuses specifically on lymphoma patients. For the oncologist in general practice, how often do they see lymphoma compared to, say, breast cancer, and specifically something like mantle cell? Is this something where they might only see one or two cases a year or even less?

DR SMITH: Right. I mean, if you think about it, lymphoma is the fifth or sixth most common. Mantle cell is maybe one twentieth or one fifteenth of all lymphoma. So it's really very uncommon for the community oncologist to see; whereas a referral center, especially mantle cell, because doctors aren't as comfortable giving it, many patients at least come for a second opinion. So we see a fairly high proportion of mantle-cell lymphoma patients.

DR LOVE: So for example, in your own practice over a period of a year, how many new patients with mantle cell would you evaluate, would you guess?

DR SMITH: I would probably say about five to 10, depending on the year.

DR LOVE: Hmm. What other options did you discuss with this patient?

DR SMITH: So we discussed the R-hyper-CVAD having the best survival data and toxicity. And then we said, "But obviously, we're trying to do better."

We did discuss that some people are looking at getting a patient into remission and then giving high-dose chemotherapy with stem cell transplant. But again, the data there are not that mature and not that convincing that we're going to cure anyone, although, again, probably prolonging the remission.

DR LOVE: So that's, in a way, kind of similar to the R-hyper-CVAD, a more intense therapy, more side effects, with the high-dose therapy and stem cell rescue to try to sort of — you damage the bone marrow from the high doses of chemotherapy and kind of try to rescue it with the patient's own stem cells that you've collected ahead of time. That would be another situation where that might be a consideration, but there's really no proven value that it's going to be better.

DR SMITH: That's correct. So we discuss that as more may be better, but we don't know for sure.

And then what we discussed was a clinical trial, which is ongoing through ECOG, the Eastern Cooperative Oncology Group, looking at giving the R-CHOP and saying, "There's a very high response rate. We're not going to do any better in terms of response rate. But that there must be cells left at the end of that, even if we can't see them on PET scan and bone marrow biopsy and CAT scan. They must be there. And they're going to grow back."

So the question is: How can we get rid of those cells?

And so one way might be the high-dose chemotherapy, but that may or may not work. So what we've done in the ECOG is then to add radio-immunotherapy. That's a fancy word for saying, taking an antibody, like rituximab, which seeks out and binds to B cells, and tagging it with a bit of radiation, so that the radiation is given directly to the cell or the area around those cells.

Now we've chosen a drug called Zevalin which is clearly active, approved for use in non-Hodgkin's lymphoma, but generally used by itself for treatment. And so we're saying, "Let's not wait until the disease grows back and give it then. Let's give it now."

DR LOVE: And I guess, generally, when it's used in a nonresearch setting, it's

not used as the initial therapy, it's used later on after they've sort of gotten more progressed, the tumors progress after initial treatment?

DR SMITH: Right. So it's approved for use in patients who have previously had treatment and then the disease comes back and for the indolent lymphomas or transformed lymphomas.

DR LOVE: And so now, this study is looking at it in an earlier situation, as part of the initial therapy?

DR SMITH: Precisely. So let's not wait for the disease to come back. Let's see if we can get rid of every last little cell floating around at this point. And that's the rationale behind the study.

DR LOVE: You mentioned that this is a, quote, ECOG study. What is ECOG?

DR SMITH: ECOG is a cooperative group that includes research centers from all over the country. Actually, it's available through what's called a C-COP, a community oncology group, to virtually any oncologist who wants to participate. And for a disease such as mantle cell, where it's not that common, no one center is going to be able to ask these sorts of questions and get the information in a reasonable time frame. So what the cooperative group does is allow us to get many patients on a trial all over the country in a short period of time and get the answers more quickly, so that we can find out how to improve treatments.

DR LOVE: And that's the Eastern Cooperative Oncology Group, if anybody wants to go to the website and sort of find out more about that.

And overall, what fraction of patients with, let's say, mantle cell, end up going in a clinical research trial?

DR SMITH: Unfortunately, we have not, in this country, been as successful as we would like in getting patients onto clinical trials. Many patients are treated off trials, either because the physician doesn't discuss it with the patient or the patient doesn't want to participate in research. And I think most of those who don't want to participate, it's really our job to educate them, because there are concerns about research and being a guinea pig. And actually, most of these trials are state-of-the-art treatment, and you actually often get certainly as good, if not better, treatment on a study than off a study.

We understand patients are concerned about placebos and things like that, but most of these studies don't have placebos or they have active treatments, and it's not like, "Oh, I'm not going to get a good treatment."

This particular study, everybody gets the same treatment, and there's no randomization. There's no placebo arm, nothing like that.

So unfortunately, we've been slow in answering some of these questions and making progress, because not enough patients do go on clinical trials.

DR LOVE: It really seems like a shame in something like mantle cell, where you don't have that many patients, and really it's critical for — it's not like breast cancer or prostate cancer, where there are a couple of hundred thousand patients coming through. In something like this, it seems like every patient who has it ought to at least know about the opportunity. And as you mentioned, with some of the newer mechanisms, almost any oncologist in the country, theoretically, I guess, could put a patient on this trial.

DR SMITH: That's exactly correct. There's newer mechanisms, even if you're not a member of ECOG. There is a Clinical Trials Study Unit, CTSU, which allows oncologists to put patients even on trials for groups that they're not participating in. So there's really no reason why we shouldn't get more patients on trials and get these answers to these questions.

DR LOVE: Now, in this study and, incidentally, what's the number for the study?

DR SMITH: It's E, for ECOG, 1499.

DR LOVE: And you're the principal investigator leading this trial?

DR SMITH: Yes. That's correct.

DR LOVE: And in this study then, the patients receive what might be one of the standard options that you mentioned before, which is R-CHOP. And then I guess the experimental part of it is where, in general, in practice they would get the R-CHOP and wait and see what happened. In this trial, what you do is a second thing; at the end of the R-CHOP they get this radioimmune therapy?

DR SMITH: That's correct. So they're getting standard treatment and then an additional treatment. And the radioimmunotherapy is very simple. It's basically getting a rituximab infusion followed by a small amount of radiation on one day and then, a week later, getting another rituximab infusion and the actual treatment dose. And in between those two, there's a couple of nuclear medicine scans. But basically, the treatment's over in a week, and so it's not adding a lot of additional time or effort for the patient.

The side effects of this treatment are basically that about four weeks after, the blood counts go down for a couple of weeks, and you need to be monitored. Rarely will a patient need antibiotics or a transfusion, and then they come up, and then they're back to normal. So it doesn't really add a lot in the way of side effects. And we're hopeful it will add significant benefit.

DR LOVE: And in terms of antibiotics and transfusion, you're referring to the fact that the treatment can lower the red blood cell count, make the patient anemic, require a transfusion. The treatment can lower the white blood cell count, make them more susceptible to infections. How many patients actually end up having some kind of complication like that?

DR SMITH: It's very uncommon. Probably less than 10 percent will need anything. We monitor the counts. The counts do go down, but then they come up — they've come up in all patients who have gotten this protocol.

DR LOVE: Now the interesting thing I find about this study — and, of course, there are so many different studies in cancer, and some of them are very, very different in terms of sort of what's being presented to the patient. It sounds like this approach is not really offering a whole lot of additional risk to the patient. Is that your take?

DR SMITH: Yes, I think that is. I mean, there's a little bit of risk with the radioactive antibody in terms of the blood counts, but very minimal and, again, this is a disease that otherwise is going to come back and, while it may be treated a second or third time, is not going to be cured. And so the hope would be that this will prolong their remission at least, if not even prolong it for a long time.

DR LOVE: And what evidence do we have right now, that there might be some benefit to this approach?

DR SMITH: I think, right now, we don't have a lot of evidence other than theoretic evidence in putting two active treatments together. There are some other trials in low-grade lymphoma, another type, where giving CHOP followed by radioimmunotherapy does seem to be of benefit. So I think in other subtypes of lymphoma, it is clear that you can prolong the duration of remission, giving CHOP followed by radioimmunotherapy. So the concept works in other subtypes of lymphoma. So there's no reason to think it won't work in mantle cell, but the proof is in actually getting the trial completed.

DR LOVE: And I guess there may be patients who actually heard about the recent study that was published in the New England Journal, looking at radioimmune therapy again, as you mentioned, in indolent lymphoma. And that did seem to have some encouraging results, although, again, it was a little bit preliminary. What were your thoughts about that study?

DR SMITH: I think radioimmunotherapy is a very exciting area. It's approved for use in patients who have had previous treatment. And the recent study suggested that it has significant activity as the front-line treatment, initial treatment, in patients who have never previously been treated for indolent lymphoma.

The caveats, the cautions we need to keep in mind, are that the patients tend to be young and healthy, so not, perhaps, applicable to all patients with low-grade lymphoma.

DR LOVE: The patients who got into that study?

DR SMITH: Who got into that study, this is the one where patients who had never been treated with anything for their lymphoma got the radioimmunotherapy.

And so I think that it's exciting, but it has to be considered still preliminary. It's not that we should treat all our patients right now with these agents as initial treatment.

DR LOVE: Now that study that you're talking about was using the radioimmune therapy called Bexxar. The trial that you're describing uses radioimmune therapy called Zevalin. And those are the two that are available. What's the difference between the two?

DR SMITH: They both have an antibody with a bit of radiation on them. They have different bits of radiation. The Bexxar uses radioactive iodine, and the iodine has two different kinds of radiation. One just stays very close to where it is deposited on the lymphoma cells and the other actually is gamma rays, which you've probably heard about gamma cameras and things like that. And so the gamma rays actually come out of the body and allow us to see where the antibody is. That's the good news.

The bad news is, the gamma rays do expose people around the patient to radiation. So the patient, after getting Bexxar, has to be a little careful about sitting next to people for a long time, being around children, pregnant women, et cetera.

The Zevalin uses a radioactive piece called yttrium, and it only has the type of radiation that goes a short distance through the body. So basically, once that is in the body, nothing comes out. So the patient can be around their family members, et cetera, without any problem.

There are potential reasons why one might be better than another, but in practice, as I look at what's been done in studying these agents, I don't think there's a big difference between them in terms of how well they work. And so I think they both work well. Whichever one your doctors are comfortable using or whichever one is in the study that you are participating in, I think you can be comfortable with.

DR LOVE: And I've heard this described as sort of a Trojan horse type approach, where you're using one agent to sort of bring in the little particle of radiation therapy to give almost specific radiation therapy to a cell. Is that the way you visualize it?

DR SMITH: Yeah. That's a good analogy. Other people call it the smart bomb approach. The idea is, we know that lymphoma responds well to radiation, but we can't radiate your whole body. So if you have a certain area that's a problem, we can give you radiation, as we do for other kinds of cancers, from outside the body. And it works, but it has side effects on the normal tissues, and it's limited in how much you can give.

This is sort of giving radiation from the inside. So it goes in and, if you think about it — and we actually can see this — when the patient gets their treatment and we do these scans, we can see that the lymph nodes where the cancer is, where the lymphoma is, they're lighting up. And so we know it's going to the right spot and that we're not getting it to the normal organ, such as the lung and the kidney and places where we don't want it to go, and that's the reason for those scans, is to make sure that it's safe to give the actual treatment dose. And it's exactly the Trojan horse or smart bomb approach,

where you're directing the radiation only to the area where you want it and, therefore, not getting the kinds of side effects you get from radiation from outside the body.

DR LOVE: I think we should also point out that when you're talking about potential exposure to family members or other people related to Bexxar, that that's only for a short period of time. Is that correct?

DR SMITH: That's correct. The half-life is fairly short, so a week or two, at the most, is all you have to be cautious.

DR LOVE: Now, both of these therapies, the components of this trial, the R-CHOP and the Zevalin, are available. Why would maybe a physician or patient in the community might want to just decide that that's how they're going to be treated? Not as part of the study.

DR SMITH: Yeah. Well, unfortunately, that often happens when drugs are available, and that's one of the reasons we don't put as many patients on clinical trials as we would like to answer the questions, because then these patients get treated as if they were on the trial, but we don't have the information and we can't count them as on the trial.

Now the logistics of getting Zevalin is it's — the Zevalin and Bexxar are quite expensive, running about $25,000 to $30,000 for a dose. And since this is not an approved use, to use it as initial treatment, there's a good chance that your insurance company won't pay for it. If you get this on the clinical trial, it is covered. It is supplied. So you don't have to worry about your insurance company getting billed. And there are some practical aspects also. This is radiation. The person who administers it — it's under the guidance of someone who has a nuclear medicine license. And, in theory, they could get into trouble for using this in a setting in which it wasn't approved, and that's a — I've heard that from some nuclear medicine physicians, that they're concerned using it off label, as we often use many drugs off label, and this would be an off-label use of Zevalin. So they are concerned about that.

But for cost issues, for learning issues, for being followed properly, per protocol — the protocols are written in such a way that you have to get specific tests at certain times, and these are written carefully, so that we make sure that we are safe. And when you're doing it off study, some of those things can slip through and you might not be treated or followed appropriately. So there's many reasons why I think it's actually much better to be on the study than being treated as if you were on the study, but not actually on it.

DR LOVE: And I guess, actually, this kind of study is a little bit simpler and, I think, more appealing than some of the other kinds of studies out there, particularly the randomized studies, where a patient's going to have the computer decide which of two therapies, even though those are often great trials, important trials. It's a little bit trickier to sort of explain what's involved in this study, which seems pretty straightforward.

DR SMITH: Yes. I agree. This is what's called a Phase II study, meaning that everyone gets the same treatment and a certain number of patients will be treated, and we'll see how they do.

And this – you're right. This is much easier for a patient to understand and be comfortable with than a randomized study where, as you say, it's basically a computer essentially flipping a coin and deciding which treatment you will get.

Now if the treatments on a randomized, Phase III trial are similar, it's not too bad. But sometimes they're very different — one with a bone marrow transplant and one with radiation or something like that. And then it is very difficult for a patient to understand why they can't choose which one they want or something like that. And I understand that there are patients and those are understandable blocks to getting patients onto a study, but both of the arms are generally considered good treatments in those cases. All of these trials are written by cooperative groups and pass through many levels of review to make sure that it's safe and ethical. The informed consent forms that the patient would sign, explain in great detail, sometimes hard for patients to understand, because they're very long, but exactly what's involved and what their options are and what to do if they don't want to go on the study or the opportunity to ask questions.

So we would encourage patients to look into these and ask their physicians the questions and see if they can understand and be comfortable with either of the treatment arms.

DR LOVE: And of course, I guess another issue in terms of this question of are you going to receive the treatment as part of a study or not part of a study is that, if you receive it as part of a study, hopefully, you're going to help future generations of patients by having information about what happens to you actually be analyzed and part of moving the field forward.

DR SMITH: Absolutely. And I think patients certainly don't want to compromise their own care, but if they can, in addition to getting good care on a study, also contribute to learning about that disease for future people and maybe members of their family – who knows who's going to get this? And it's a good feeling for them, and it helps advance the field more quickly. So that's a side benefit.

DR LOVE: And just, sort of looking at the overall, long-term strategy of clinical research in cancer in general and lymphoma specifically, I would assume that if, in this study, which is — there's a Phase I — where you sort of find out how safe it is to use, which, obviously, you're past. A Phase II, which this one is, where you just give it to every patient and sort of see how they respond. I would assume that, if you see encouraging results in this study of 50 or 60 patients, that the next step might be a randomized study,

where maybe the patients might get R-CHOP versus R-CHOP plus radioimmune therapy, or some other randomization like that. Would that be what you think will happen here?

DR SMITH: So I think that when you finish a study like this, there's really two ways to go. One is, you can say, "I'm very happy with the results, but we have to prove that we didn't select our patients by doing a Phase III trial," and that could be, probably, against R-CHOP. Or we might do something with R-hyper-CVAD, that sort of thing.

The other approach is to say, "Well, the results are good and it's a positive study, but we don't think it's quite ready for the Phase III. We think we can do better," and thoughts that we have sort of tossed around as well.

After the Zevalin, maybe we should give continued Rituxan maintenance, for instance. Which has worked in other diseases, lymphomas, to keep it away. So —

DR LOVE: And by that, you mean continue the Rituxan for a long term.

DR SMITH: Right. So after you recover from the Zevalin, say, on some schedule, keep getting the Rituxan, just to try to keep any cells there at bay, and you might get that for maybe a year or two or longer. And so we might do that. And then, maybe, compare those two, if that looked good. So there is a few ways we can approach it as to whether we think we're quite ready for the Phase III or whether we want to get even better Phase II results before we go on to the Phase III.

DR LOVE: And I guess that whole concept of how long to give the Rituxan and should you give it for a couple of years, or even give it longer than that, is something there's a lot of controversy about right now. There are trials trying to define whether or not that should be done. Without getting too far off the subject, how do you approach that when the patient's not on a study?

DR SMITH: So the idea of if you get Rituxan and the disease goes into remission, we know — again, talking here more about the indolent lymphomas, not mantle cell — but that the disease will come back. And we could wait until it comes back and then re-treat with Rituxan. Or we could say, "Let's not wait for it to come back. Let's give you Rituxan." And there are several different schedules that people have used.

And again, this is an individual sort of decision with the patient and their doctor. I tend to use a fair amount of scheduled retreating with Rituxan to keep the disease away, because I think the patients prefer to not have the disease come back and the anxiety that that provokes. And there's also the idea of doing something. They feel proactive. They feel that they're in control as long as we're doing something. And there's very little evidence of long-term side effects of continuing the rituximab. So other than the cost issues, I think it's — in my mind, the benefits outweigh the risks. So I tend to use more of it. Some of my colleagues do not. And again, some of it has to involve the patient and what they want to get.

DR LOVE: And some people use it for two years. Some people use it for longer. What do you usually do?

DR SMITH: So I think – as I look at things, the information's out there on two years. Not much data on more than that. And so in most patients, I will stop at two years, because I think eventually the disease will grow back. And if I stop and it's a year or two later, the disease comes back, we might still have the benefit of Rituxan. If I keep the Rituxan going and the disease grows while you're getting Rituxan, then there's not much point to giving more. So I'm hopeful — but again, it may be wishful thinking on my part — but I'm hopeful that by stopping at two years, I've gotten as much mileage as we're going to get and leave room to use it again in the future.

DR LOVE: So now, in this patient, you went through the options that he might consider without being part of a study and then this trial, particularly. How did that discussion go with him? How did he respond to those options?

DR SMITH: Yeah. He was very interested in continuing to work, and so the R-hyper-CVAD did not sound that attractive to him. And once he heard about the other options being really R-CHOP with what we know there is not the — as long a remission as we would like for a gentleman his age, he was quite excited about going on the trial and did consent and go onto the trial.

DR LOVE: And so you had – I guess, as part of that, as you mentioned, there's this long print informed consent that goes through the trial and risks of being in the trial. And I guess one of the most important things that those informed consents do is to reinforce that there should be no pressure about going on the study at all. If they don't want to go on it, that's up to them.

DR SMITH: Absolutely. Key in any of these is, right up front in the first couple of paragraphs, saying, "Please talk to your doctor about what your other options are." And statements that clearly say that, "If you decide not to go on the trial, this will not compromise your care. We're not going to kick you out for not going on the trial." So there is no pressure.

And even if you have agreed to be on the trial and somewhere down the line you decide you've changed your mind, you always have that option. And that's clearly spelled out as well, in the informed consent.

DR LOVE: Now did you discuss with the referring oncologist this trial and what your thoughts were about this man?

DR SMITH: Yes. So after we see him, we call the referring oncologist and say, "We could give R-CHOP, R-hyper-CVAD."

The referring oncologist was not comfortable in his hospital giving the R-hyper-CVAD, so was happy whichever way we went, to either have him

on the study through our institution or R-hyper-CVAD.

DR LOVE: And so I take it the patient entered the study?

DR SMITH: So he did go on the study.

DR LOVE: What happened?

DR SMITH: And he basically sailed through, got the Rituxan/CHOP every three weeks. Worked throughout. Felt fine.

DR LOVE: What kind of side effects did he have while he was on the R-CHOP?

DR SMITH: Well, his hair fell out, as expected.

DR LOVE: And that's from the Adriamycin that's the — it's actually the H, which is the — sort of the chemical name, but most patients know it by Adriamycin, the red medication. And that was the main thing, I take it, that was causing the hair loss?

DR SMITH: Exactly.

DR LOVE: Did he have a lot of hair to start with?

DR SMITH: Not too much.

DR LOVE: So — was that a major thing for him?

DR SMITH: He was not too distressed by that.

DR LOVE: Do you find that for other patients that is a major problem?

DR SMITH: Yes. I think, especially women find it very distressing to have their hair fall out. Or they think they will. Many of them, once it happens, find it less disturbing and are focused on other parts of their disease. But some do, especially if they have long hair and they've put a lot of care into it. It is distressing, no question about it.

DR LOVE: Any other side effects that he got from the R-CHOP?

DR SMITH: His blood counts did go down about seven to 10 days after each, but they did not go down into a range that led to a fever. He did not require any transfusions, did not require any hospital stay. He did get a little bit of numbness in his fingertips from the Oncovin, or vincristine.

DR LOVE: That's the O in the CHOP.

DR SMITH: The O.

DR LOVE: And when you see those changes in the fingertips, the what's called peripheral neuropathy, does that usually go away once the chemotherapy is stopped?

DR SMITH: Yeah. So the thing is about nerve damage, it takes a while to come on and it takes a while to go away. So you don't see it with the first dose; you see it with maybe the third or fourth dose. And when you stop, it gradually resolves. Some people, unfortunately, end up with a little bit left. But with this particular protocol, you actually only get four treatments of the R-CHOP, and so by the time you're starting to get the peripheral neuropathy, usually you're off it and it's not anything permanent.

DR LOVE: Now in this man, were there any functional problems because of the numbness. Were there things at work or at home that he couldn't do?

DR SMITH: No. It never got to that point. That can happen. And one of the questions we ask a patient is, "Do you have any trouble buttoning your buttons or things like that?" Certainly, if it's getting to that point, we would not give additional Oncovin.

DR LOVE: Now what happened to him in terms of nausea and vomiting related to the chemotherapy?

DR SMITH: So nausea/vomiting is probably, along with hair loss, the major concern that patients have. And these days, with new antinausea medicines, it is really a very minimal problem with most chemotherapy, and with the R-CHOP especially. There's virtually no nausea or vomiting with — if you get the antinausea medicines right before the chemotherapy, it's very rare to have any vomiting and minimal, if any, nausea.

DR LOVE: How about in this man?

DR SMITH: He had none.

DR LOVE: Was he able to continue work?

DR SMITH: Absolutely.

DR LOVE: Any other side effects from the treatment?

DR SMITH: Not really. He actually kept feeling like, "I'm doing too well." I would say, "Yeah, you're supposed to do well."

DR LOVE: Now in terms of the hair loss and potential nausea and vomiting, that's related to the chemotherapy. Those side effects are not actually associated with rituximab, if you use that without chemotherapy, correct?

DR SMITH: Correct. Rituximab side effects are primarily limited to reactions that occur while the drug is being infused. And so the way rituximab is given — it's a protein. It's an antibody. So it's far into your body, and you can have an allergic reaction to it. And anything you can think of, like if you are allergic to a bee sting or to shellfish or whatever, so it can be hives. It can be itching. It can be a sense that your throat is closing or asthma or wheezing.

But we start slow. If you do all right, we increase the rate. If you start to have a problem, we turn it off, and usually these effects go away within 10 to 15 minutes, and then we restart at the slower rate. So it can take several hours to get a dose of rituximab. If you are going to have a reaction like that, it's worst the first time you get the drug. It doesn't get worse as you go along. It gets better. So if you have a moderate reaction the first time, you'll have a minimal or no reaction the second time. So it actually gets better as it goes along.

DR LOVE: And you give this at the same time as the chemotherapy?

DR SMITH: Right. So usually it's a long day. You get the rituximab first, and then you get the chemotherapy right after that.

DR LOVE: And by the time the patient goes home, are there any residual

effects from the rituximab, usually?

DR SMITH: No. By the time we turn it off, usually they're fine and, at that point, they get the chemotherapy. And by the time they go home, they should be feeling well.

DR LOVE: Now in this man, did he have any problems with the infusion of rituximab?

DR SMITH: He had a little bit of itching with the first dose, and then nothing after that.

DR LOVE: So he got his four doses of therapy. What happened to the lymph nodes you were feeling in the neck and the spleen?

DR SMITH: So the lymph nodes and the spleen all shrunk. They were all pretty much gone by the second treatment. On the study, we get a CAT scan after the second treatment and after the fourth treatment. And the second one was probably 75 to 80 percent reduced. And by the fourth one, basically there was no disease to measure at that point.

DR LOVE: And then after he competed that four treatments, I guess, what? — a couple of months later he then got the Zevalin?

DR SMITH: Yeah. Actually, after the fourth treatment, about three weeks later, you get the CAT scan. Then we have to repeat the bone marrow to make sure that there's not too much lymphoma in the bone marrow. We knew there wouldn't be in him, because it didn't start out much and it got better, but that's just a safety issue. And then, probably about eight weeks after the last R-CHOP, he got his Zevalin.

DR LOVE: And just to clarify, if there are a lot of lymphoma cells in the bone marrow, that makes it more difficult or, in some cases, impossible to give the radioimmune therapy?

DR SMITH: Right. So if you think about the antibody delivering the radiation to where the lymphoma is, if there's too much lymphoma in the bone marrow, then you get too much radiation in the bone marrow. And the normal cells get irradiated as well as the lymphoma cells. And so the blood counts — it may be safe, but we're not sure. And so, to be on the side of caution, if you have more than 25 percent of cells of the area of your bone marrow being lymphoma, then we would not give the radioimmunotherapy.

DR LOVE: Now when you repeated this patient's bone marrow after he'd gotten the R-CHOP, what did you see?

DR SMITH: We saw nothing under the microscope but we did some sensitive flow cytometry tests so we could still detect a few mantle-cell lymphoma cells in the bone marrow

DR LOVE: And then he got the Zevalin. How did that go?

DR SMITH: Again he did fine with it. It's just like getting Rituxan. By that time he's had four previous Rituxans so he had no reaction. Starting at about three weeks after the treatment dose, his counts started to go down 'cause he did have a little in his bone marrow. And his platelets went down. But again nothing too dangerous range — he did not require any supportive care.

DR LOVE: He felt OK?

DR SMITH: He felt fine, again continued to work, and by about six weeks after his counts were on the way up, and he was out of the danger period.

DR LOVE: And how far out is he now?

DR SMITH: He's about six months out now and doing fine.

DR LOVE: So I guess he really hasn't got to the point where people typically might get into trouble or might start to see the tumor coming back if they just got R-CHOP.

DR SMITH: Right, that's correct. So we need a little bit more follow up on the patients on this study before we'll know the answer about whether the addition of the Zevalin was helpful.

DR LOVE: I think it's interesting too, having gone through this case, because a lot of people, I think, would find surprising what we just talked about — all the different sort of faces of clinical research in cancer today. And when you really analyze what happened in this trial, it sounds like a win-win situation. The patient's been exposed to a therapy that is promising. The patient's been able to contribute to the future care of patients. And it's really a shame that more people aren't given the opportunity to participate.

DR SMITH: Right. I think it's clear that you're right. Clinical research is not just for the researcher. It's a win-win situation for the patient and society and the research people.

Dr Kahl is an Assistant Professor of Medicine and Director of the Lymphoma Service at University Hospital in Madison, Wisconsin.

The third lymphoma expert I interviewed for this program was Dr Brad Kahl, Assistant Professor of Medicine and Director of the Lymphoma Service at the University Hospital in Madison, Wisconsin. Dr Kahl is principal investigator of one the major national trials in this disease. The RESORT study is evaluating the uses of rituximab or Rituxan in patients with so-called indolent non-Hodgkin's lymphoma, and Dr Kahl began our conversation by providing an overview of this condition.

DR KAHL: Indolent lymphoma is referring really to a group of diseases. And the term "indolent" is referring to the natural history of the disease. In other words, what would happen if no treatment was administered? And in the indolent lymphoma setting, patients can live for a long, long time, in general, without any treatment.

DR LOVE: And I guess that's totally counterintuitive to what we think about when we think about cancer.

DR KAHL: Most people, when they hear the word cancer, "I have cancer," they think it's a death sentence. And it's actually not the case for the vast majority of patients who are diagnosed with any of the indolent lymphomas. It's just not the case.

There are a variety of indolent lymphomas. The most common would be what's called follicular lymphoma. That term really just refers to how it looks under a microscope. There are some other indolent lymphomas. And what we, as physicians are learning, more and more, is that these lymphomas are different biologically. They respond differently to treatments. And more and more, our treatments are tailored to specific lymphoma subtypes. And that's probably a useful thing for patients to understand. So 10 years ago, most new treatment trials would just lump all the indolent lymphomas together. But nowadays, you're seeing more and more where the trials are separated and a trial will be designed just for follicular lymphoma or just for small lymphocytic lymphoma, which is another indolent variety, or just for MALT lymphoma. So there's a little more of that happening now, which is an important thing for patients to understand, "What kind of lymphoma is my indolent lymphoma?"

DR LOVE: What is the objective of treatment? I mean, if the disease really isn't going to threaten the patient, why treat?

DR KAHL: Well, the number one objective is to prolong the overall survival. In other words, we want our indolent lymphoma patients to live as long as they possibly can. Because the fact of the matter is, most patients who are diagnosed with an indolent lymphoma will die as a result of that diagnosis. And so you have to be careful here. Because it's indolent, that's generally considered to be a good thing, but I've heard some physicians explain to patients, "Don't even think of this as cancer."

I think that's the wrong message, frankly. Indolent lymphoma will shorten patients' life expectancy, and that's what we need to improve upon.

DR LOVE: Although in patients who are older, perhaps they might end up dying of something before that happens?

DR KAHL: That's exactly right. And so the management of an individual patient really has to be tailored. And if you have older patients, it is quite possible, could be even probable, that they would die of something other than their lymphoma long before the

lymphoma would cause problems. So particularly for those patients, it's important to not overtreat the lymphoma, because it could result in a detriment to their quality of life, unnecessarily.

DR LOVE: At what age would you say you start thinking about the fact that maybe this is really not going to be the problem that ends up taking their life?

DR KAHL: Well, the median survival for most of the indolent lymphomas – and I'm lumping them now. It's not the same for all of them, but it's usually around seven to 10 years. It would be a little better than that for the MALT lymphomas, a little worse than that for the small lymphocytic lymphomas. And that would be pretty much on the mark for follicular lymphoma. So if a patient is diagnosed in their seventies with this disease, I think there's a reasonable chance that they will have a normal life expectancy. But if you're diagnosed in your sixties and you're otherwise healthy, then there's a relatively good chance that this disease will be the thing that shortens your life expectancy, then we've got a problem that needs to be addressed.

DR LOVE: You mentioned MALT lymphoma. Can you explain what that is?

DR KAHL: MALT is an acronym, M-A-L-T, and it stands for mucosal-associated lymphoid tissue. This is a unique group of lymphomas that arises in any place but a lymph node. So typically, we think of lymphoma as a disease arising in lymph nodes. But the fact is, any place in your body that has lymphocytes is a place where a lymphoma can arise. And the fact is, you have lymphocytes in every nook and cranny of your body, and so people can get lymphomas arising in the skin or in the lungs, in the liver, in the stomach, in the small intestine, in the colon, in the conjunctiva of the eye. You name it, a lymphoma can appear there. And these malt lymphomas arise, characteristically, in places that don't normally contain lymphoid tissue, like the lungs, like the stomach, like the conjunctiva, the breasts. These are places where MALT lymphomas typically appear. Skin, for example.

DR LOVE: Do we know anything about the cause of the MALT lymphomas, as opposed to the other types of indolent lymphomas?

DR KAHL: There's one variety of MALT lymphoma called gastric MALT lymphoma, "gastric" meaning arising in the stomach. And that entity is highly linked to a certain infection with a bacteria called helicobacter pylori. And it just so happens that about 90 percent of gastric MALT lymphomas appear to be due to this chronic infection with this bacteria called H pylori. And the remarkable thing is that, once detected, with just eradication of the bacteria –

DR LOVE: Like, antibiotics?

DR KAHL: Antibiotic therapy. The lymphomas will regress about two thirds of the time. So there's a group of patients who might never need chemotherapy or radiation and can actually be treated for their cancer with antibiotics.

DR LOVE: So that's kind of a sort of outline of the indolent lymphomas. And I take it that the issue then is the oncologist will look at a lot of different issues and decide whether or not treatment is needed or whether or not they can just be observed?

DR KAHL: Exactly. Observation is something that we often do in patients who have a new diagnosis of indolent lymphoma. It's actually a hard thing for patients to accept, to be told they have a diagnosis of cancer and then be told, "But we're not going to do anything about it right now." And that's very understandable that that would be hard to accept. But the fact is, studies have addressed this question.

And so there are a couple of studies now in which there were newly diagnosed patients, and half of the patients went on to receive chemotherapy right away, and the other half of the patients went on to observation right away. And if you look at the proportion of patients alive at five years and at 10 years, it's identical in both groups. And so based upon that, it's reasonable for selected patients to just watch, initially. There really hasn't been a proven benefit to jumping in with chemotherapy, as long as the patient is not symptomatic from the disease and as long as they don't have a high tumor burden, meaning very large lymph nodes that look like they could start to cause problems in the near future.

DR LOVE: So for those patients, perhaps a patient who might be a little bit younger or a patient who has a lot of disease or who might have symptoms from the lymphoma, where a decision has made to use some type of treatment, can you talk about, then, where the option of participating in a clinical trial comes in that they might consider entering?

DR KAHL: Sure. Well, I would encourage patients to always ask their doctor about the opportunity to participate in clinical trials. Honestly, every advance that has been made in the past 40 years in the war on cancer is a result of testing of new agents or new combinations in the setting of clinical trials. And everything we know today about what to do is derived from that. And if we don't continue this, then there will be no further improvements for current patients or their loved ones or their children.

DR LOVE: So you're saying that a motivation to be in a trial is to help future patients?

DR KAHL: That's exactly right. I have actually had a few patients say to me how much satisfaction that they derive from just that fact, that they knew that they were getting state-of-the-art care, that we were trying things that were hot off the shelf, that were new, that were promising, and yet, at the same time, they knew that they were helping others at the same time.

DR LOVE: Do you think there's a benefit to the patient, themselves, who's in the

trial, from their own point of view?

DR KAHL: I think, by and large, yes, there is. For the most part, the trials are using drugs that are already proven, but we're just trying to optimize their use. We're trying to fine tune how best to use them. That's typically the case if it's a trial for a patient with a new diagnosis and is being treated for the first time. Or, alternatively, sometimes you get into the situation where a patient has already been through some standard treatments and the disease has come back. And maybe the options for treatment aren't so plentiful now. And by participating in a trial is a way for a patient to get access to new agents that are trying to kill the cancer cells in a brand-new way. So there are a couple of different ways patients can benefit from clinical trial participation.

DR LOVE: And I guess it's important for every patient to know that there's certainly no obligation or pressure whatsoever to be in a trial.

DR KAHL: That's right. It's completely voluntary. And if patients choose not to participate in a clinical trial, their doctor will still treat them the very best way they know how to treat them with available agents.

DR LOVE: Now, in this situation that we're talking about, with a patient who's about to receive their first treatment for an indolent lymphoma, we want to talk about two studies that they might consider going into, one of which you're actually running, and another trial. Can you talk about sort of the way these studies are broadly set up in terms of the idea of randomization?

DR KAHL: Okay. So there are two large studies going on right now in the United States for patients with indolent lymphoma. And they're both what are called randomized clinical trials. And the idea here is that two treatments are being compared against one another. And which treatment the patient receives on that trial is not chosen by the patient and it's not chosen by the doctor. It's actually chosen by a computer. A lot of patients have trouble with this concept, or they're uncomfortable with this idea that their treatment choice is being decided by a random assignment. It's important to explain to the patients why we do this.

Typically, when we're doing a randomized clinical trial, we feel like we have two very good treatments, two outstanding treatments, or at least two state-of-the-art treatments. And what we're trying to do is to decide if one is a little better than the other, to see if we can establish the new standard. And so the way I explain it to patients is "I think you would be getting very good treatment in either case. One of them potentially could be a little better than the other, but I honestly and truly do not know the answer to that. I don't know which one is better, and that's what we're trying to answer in this clinical trial."

DR LOVE: And I guess, if a physician sort of has a belief or a feeling that one therapy would be better for the patient than the other, probably they shouldn't be in the study.

DR KAHL: That's exactly right. So if the physician feels like, because of that patient's disease or their characteristics, like, one of the treatments would be more appropriate, then the physician is obligated to say that to the patient. And it wouldn't be appropriate to put them on the trial.

DR LOVE: Is there a financial incentive to physicians for participating in trials like these?

DR KAHL: Absolutely not. The trials come from a variety of sources. A lot of the trials are sponsored by what are called cooperative groups. And cooperative groups are large organizations of cancer centers and private practice oncologists who band together to try and answer important clinical cancer treatment questions. Those trials are funded by the National Cancer Institute. In other words, it's the patient's tax dollars that are funding those trials.

Some trials are funded by the pharmaceutical industry. And the fact of the matter is all new treatments for cancer have to come, eventually, from a company. There has to be a company with an interest in a new treatment if that treatment is going to go anywhere. But the companies themselves don't get to choose the patients for the trials. And so what they do is they provide the drug to the physicians who conduct the trial. Now the physician's office or group might get some financial remuneration for the conduct of the study. That would be used to pay study coordinators, data managers, but physicians don't derive income from clinical trial participation.

DR LOVE: And what I've heard physicians talk about is the fact that they like participating in the trials for their scientific value, for contributing to the field. I've heard people say they like them because they – adds a little more interest to their own practice. Some physicians, I've heard say, "Well, it increases the profile of my practice in the community, if people know I'm participating in research." But this isn't really a way for a physician to generate significant dollars in terms of income.

DR KAHL: That's correct.

DR LOVE: So why don't we start with a trial that you are running?

DR KAHL: Sure.

DR LOVE: If you can, talk a little bit about sort of what went into the thinking and then what happens to the patient who goes into this study.

DR KAHL: So I'm the principal investigator of a trial that's being conducted all over the United States right now. It's called the RESORT trial. And it has a number, too, and that's ECOG Study 4402. So if one were to look it up on, say, a website, they might find it under that heading.

DR LOVE: And you can find that in the NCI, National Cancer Institute, website and also the Eastern Cooperative Oncology Group, ECOG, website.

DR KAHL: That's correct.

And the RESORT trial is a study that is looking at two different ways to give the drug Rituxan to patients with indolent lymphoma. So Rituxan is a monoclonal antibody that targets a protein on lymphoma cells that's called CD-20. Rituxan is an attractive agent for indolent lymphoma treatment, because it doesn't have a lot of the side effects and toxicities of chemotherapy. And Rituxan has really changed the way we treat lymphoma.

There's a lot we don't know about Rituxan, particularly how best to dose it. So there have been some small studies now that have suggested that if a patient gets the drug Rituxan, that if they just keep getting it on a scheduled basis, perhaps that's a better way to control their disease, to keep it in remission and to keep the disease from causing problems.

On the other hand, it's not so clear that prolonged exposure to the drug on a continual basis like that is truly the best way to control the disease and keep it from hurting the patient. And it's possible that just giving the drug intermittently, when the patient really needs it, because the disease starts to grow again, might be the best way to control the disease in the long run.

DR LOVE: And this is given intravenously.

DR KAHL: It's given intravenously. It's an infusion. When the patients get their very first treatment, they get it four weeks in row. And for the patients who get the drug intermittently then, they would get the four weeks in a row every time the disease starts to progress.

DR LOVE: Initially, they get the four weeks, and then it would stop and wait until usually, the tumor would respond, would shrink down?

DR KAHL: That's right.

DR LOVE: And then they wouldn't get any more of the rituximab.

DR KAHL: They wouldn't get any more until we saw signs of disease progression, which, it could be 12 months, it could be 18 months, it could be longer. So they could have a long period of time free of any treatment in remission.

That would be the standard way to give Rituxan. That would be the traditional way.

The way that we would consider the experimental way or the newer way would be to give it and continue to give it; in other words, try and keep the disease in remission, don't let it recur. And in this trial, after the four weekly doses and the response, patients then get a single dose every three months, essentially indefinitely, until the disease starts to grow back despite the fact that the patient is continuing to get Rituxan. And that's called rituximab –scheduled, or another term for it is maintenance therapy.

DR LOVE: And also, I guess it's worth pointing out that, in general, if a patient weren't going to go onto this study or a trial and was going to be treated, almost for sure they would get Rituxan, either alone or with chemotherapy.

DR KAHL: That's right. The current standard of care in the United States is to give Rituxan either as a single agent or with chemotherapy.

DR LOVE: And so this trial is attempting to sort of refine down what might be the best way to give it.

DR KAHL: Right. Now an important point about this trial is that this trial is restricted to patients who have what we call low tumor burden. Rituxan is a great drug for patients, largely because of its favorable safety and side effect profile. It is not as active, however, as most chemotherapy drugs. So the probability of getting into remission is higher with an aggressive chemotherapy regimen.

DR LOVE: Chemotherapy alone or with rituximab.

DR KAHL: Either. And so if patients really have an indolent lymphoma that's acting more aggressively or they've got symptoms from the disease or they've got big, large bulky lymph nodes, it's probably not appropriate to get single-agent Rituxan without chemotherapy.

DR LOVE: So in essence, this is a situation where a patient might get Rituxan who's not on the trial, but they would go into the trial and have it randomly determined which of these two ways it would be given.

DR KAHL: That's right. And a typical scenario would be a patient who's diagnosed with follicular lymphoma, who has low tumor burden, has no symptoms, they feel fine. Most people, most physicians would initially watch that patient, which is appropriate.

Well, let's say you watched them for a year, and then they come in for a visit and it's clear that things are progressing. The lymph nodes are growing. And you're thinking to yourself, at this rate, this patient is going to be probably requiring chemotherapy within the next six, 12 months. That would be an appropriate patient for the RESORT trial. You could come in at that time and treat them with single-agent Rituxan. They wouldn't be getting any chemotherapy. And no matter which treatment arm they were assigned to, they would be getting treatment with Rituxan. And what we're really interested in seeing is which strategy delays that patient's time to chemotherapy. We think, ultimately, it would be to the patient's advantage if we could delay their time to chemotherapy, because there are some negative quality-of-life issues that occur when patients move on to chemotherapy. So if we can delay that, we think we'd be doing a good thing for that patient.

With Rituxan, probably the most common side effect is what's called an infusion reaction. And that, if it happens, typically occurs with the first infusion. And people can have fevers, shakes, chills, shortness of breath, pain at tumor sites, itching, throat swelling. I mean, it can seem all the world like an allergic-type reaction.

DR LOVE: Now this is during the infusion?

DR KAHL: It's during the infusion while you're at the doctor's office. And we're very used to seeing it. And the way we manage it is we give Tylenol and antihistamines before the infusion. If people start to have a reaction, we turn the drug off and we just sort of let things cool down, and then we just run it in at a slower rate and we increase the rate more slowly. So the first infusion can actually take a while. It can be a six- to eight-hour experience, if the patient is having problems with reactions.

DR LOVE: And if they are having problems with reactions, how do they feel by the time they get out of the office?

DR KAHL: Usually, they're pretty wiped out, because we've usually repeated their antihistamine, their Benadryl, so they're tired because they've gotten a lot of antihistamine and it's a long day. So if a patient ever has trouble with Rituxan, it's on that first day in the office. Usually by the next day they feel just fine.

DR LOVE: And in terms of the intensity of what this feels like, from what it's been described to you, is it kind of like the flu, worse than the flu, or not as bad as the flu?

DR KAHL: The reactions are very variable. And so for some patients, it'll be worse than the flu, but it's for a short period of time. But for most patients, it wouldn't be that bad.

DR LOVE: So people don't come back and say, "It was a horrible experience," or do they?

DR KAHL: Very rarely, they'll come back and say, "That was terrible." Most of the time, they get through it quite easily. But the good news is, even if it was terrible, it's very unlikely to happen with the second and third and fourth infusion. It's not an allergic reaction. It's a different phenomenon, and so it's very rare to get infusion reactions once you get beyond the first infusion.

DR LOVE: What exactly is going on then, if it's not an allergic reaction?

DR KAHL: So there's this system of proteins in our body that's called complement —it's part of our immune system. And we have a lot of these complement proteins in our circulation. So when a patient first gets Rituxan, the Rituxan is binding to B cells that are circulating in our blood. And that triggers this complement system, and that releases all of the chemicals in our body that we release when we get the flu. They're called cytokines, and so it causes a whole cascade of symptoms that would be sort of flu like. But by the time you come back for the next infusion, all of those B cells that were in your blood are, basically, have been cleared out by the Rituxan. And so this infusion reaction just doesn't occur with later infusions.

DR LOVE: So getting back to the trial, so then the patient would have to agree to sort of allow the computer to determine which way the Rituxan is going to be administered.

DR KAHL: Yes, that's right.

DR LOVE: How do patients respond to that idea?

DR KAHL: A lot of patients are initially very uncomfortable with the idea of randomization and that's understandable. Once I explain the process to them, they're usually a little more comfortable with it.

Randomized clinical trials are really the only way that we, as oncologists, can determine if a new regimen is better than an old regimen. There's no other way to do it and be confident that you're getting the right answer.

And the reason is, there's always the potential for what's called bias in trials. So this has happened repeatedly in the history of oncology, where a group of investigators at a single institution will come up with a new treatment for some cancer — let's say lymphoma — that they think is really promising. And they recruit patients from their own institution into that trial. And either intentionally or unintentionally, they end up recruiting patients who are younger, who are healthier, whose disease isn't so bad. And all of these things influence the outcome. So when they report the results, their reports look really good. And people might then run around and start giving that regimen, based upon the results of that institution's results that were published and that looked so promising.

And this actually happened in the 1980s in a different kind of lymphoma, called diffuse large B-cell lymphoma. There were three chemotherapy regimens that were much more aggressive and complicated than the standard regimen, that was called CHOP. And based upon small single-institution or limited-institution studies, these three regimens all looked much better than CHOP, very superior to CHOP, to the point where people basically stopped giving CHOP chemotherapy for a period of time in the 1980s and were using these more complicated regimens that were frankly more toxic. But doctors believed that they were curing more patients, based upon these published results.

Well, the National Cancer Institute, led by one of the cooperative groups, called the Southwest Oncology Group, got around to doing one of these randomized clinical trials that we're talking about. And the patients were randomly allotted to one of four treatments, one of the three more complicated toxic regimens or CHOP. And when that trial was ultimately reported, it turned out that the results were identical for the four regimens. In other words, the cure rate was no higher with the three more complicated regimens, and yet there were a lot more side effects and toxicities. And so for years, doctors were under the delusion that they were curing more patients, and they really weren't.

DR LOVE: And they were exposing them to more problems.

DR KAHL: They were exposing their

patients to more side effects and more toxicities. And we don't want to make those same mistakes over and over again, which is why, now, we really demand that before we accept a new regimen as an improvement over the old regimen, it really must beat the old regimen in a randomized clinical trial.

DR LOVE: And we all hope and we're looking to advances in therapy that are going to improve cure rates, improve survival, but when you think about it, those — I don't know — several hundred patients who participated in that study really had a tremendous impact on subsequent patients. There have been thousands and thousands of people treated since then, who didn't have to experience —

DR KAHL: That's right.

DR LOVE: — the side effects of the more toxic regimens.

DR KAHL: Those patients were heroes, truly.

DR LOVE: When you talk about, let's say, patients in the United States, for example — and this trial that you're talking about is an Eastern Cooperative Oncology Group, but it's also throughout the United States — can any oncologist, theoretically, participate in this study and put their patient on it?

DR KAHL: Yeah. Actually, they can with this RESORT trial. The trial was initiated in a group called the Eastern Cooperative Oncology Group. And only certain institutions are members of that group, but there's a new mechanism available that's called the Clinical Trials Support Unit, or CTSU. And the CTSU is a office that's funded by the National Cancer Institute to get trials like this available to all centers, all sites throughout the United States, no matter what that site's cooperative group affiliation is. So any office that has the capability of doing clinical trials can do trials through the CTSU, and the RESORT trial is available through the CTSU.

DR LOVE: Since it's like — I'm thinking about some of the commercials that you see, that pharmaceutical companies put on for various products, and maybe we could do a little commercial for clinical research by saying that maybe patients with indolent lymphoma ought to say to their doctor, "Are you part of the ECOG? Do you know what the CTSU is?"

DR KAHL: Right.

DR LOVE: Or, "Have you ever heard of the ECOG" — what's the number again?

DR KAHL: 4402.

DR LOVE: — "trial?"

DR KAHL: They would be — educated patients are actually, by and large, a joy. Occasionally, you'll get patients who probably have read too much and they're just confused. But by and large, educated patients are better consumers. They ask the right questions. It's easier to explain these concepts to them and I think anything we can do to educate our patients so that they're more informed is a good thing.

DR LOVE: I guess the other thing is that as much confidence as a patient might have in their oncologist, there's always sort of a value in a second opinion. And in a sense, being in a trial kind of provides that, because all their data is going to go into a center. They're going to check and see if they're really eligible for this therapy. There's sort of another set of eyes looking on their therapy.

DR KAHL: That's true. And the fact is that the trials undergo intense scrutiny before they're even able to be opened. I mean, they undergo review at so many levels for scientific merit, that I think physicians can feel very safe when they're opening a study that it's scientifically sound, and patients can feel safe that what they're being offered is considered state-of-the-art.

DR LOVE: Well also that it's ethically sound.

DR KAHL: Exactly.

DR LOVE: And I know there are committees that review these trials, to see is it really ethical to do the study and do this kind of randomization. And again, there are a lot of eyes that I see on the study designs and how they're run.

DR KAHL: I totally agree with what you just said.

DR LOVE: I'm sure you've talked to lots of patients about the possibility of participating in these randomized trials. In general, do most patients that you ask participate, or do some of them just say, "Hey, I'd rather not do that?"

DR KAHL: Not everyone participates in clinical trials and patients have every right to decline participation and, if they do, their doctor will continue to treat them in the very best way they know how. In fact, there may be settings where there isn't a trial available for a given patient at a given moment in time or where a trial wouldn't be appropriate. That can happen, too. But there are also many settings where there is a trial available and it would be appropriate and it would behoove patients to ask their physician, "Do you have any clinical trials available for me right now that you think would be appropriate?"

DR LOVE: And I guess one of the things that we've seen in general with cancer research is that, actually, relatively few patients enter clinical trials. Even if you look at those who are, there is a trial available, a relatively small fraction end up getting in trials. Is that your impression?

DR KAHL: Yeah. It's kind of sad. It's sort of unique to adults in the United States. In Europe, patients are much more likely to participate in clinical trials, particularly randomized clinical trials. And a lot of the progress, especially in lymphoma, that's being made right now is being made by our friends in Europe, rather than the United States leading the way, which is not the way it should be.

Pediatrics, pediatricians, pediatric oncologists are much better about

having their pediatric cancer patients participate in clinical trials. And it's amazing; probably 80 to 90 percent of all children diagnosed with a cancer will participate in a clinical trial. And if you look at the pediatric cancers, they have made steady, incremental improvement in almost all of their diseases over the past 30 years.

Now contrast that with adults in the United States, and the figure that I most often hear is that it's about five percent of adults with cancer, participate in a cancer clinical trial. And there are a variety of diseases where we have made very little progress in the past 30 years. And that's probably the biggest reason, is the lack of participation in clinical trials. So we can't get questions answered. We can't figure out if we're making improvements. We can't test new ideas. It's a huge barrier to progress.

DR LOVE: It is frustrating, and everybody has their own sort of theory about what the obstacles are or why this occurs. What's your take on it?

DR KAHL: I think that there are a variety of obstacles. I'll just speak candidly about them. The system of oncology care in the United States is not super well equipped to deal with clinical trials. The majority of patients are treated in private practice oncology offices, which are extremely busy, and a lot of patients coming through every day. And to put patients on trials takes time. It takes a lot of time. If it's a randomized trial, not only do you have to explain one treatment to the patient and all the side effects; you have to explain two treatments and all the side effects.

DR LOVE: And you have to go through a big long form.

DR KAHL: There's a consent form that the patients take home. Whenever I talk to a patient about a trial, I try to explain it to them as best I can. I give them the consent form, and then I make an arrangement that we'll talk by phone in a few days, after they've had a chance to read it. So it results in a long clinic encounter, as well as follow-up phone conversations. But I want them to understand what is being asked of them. And I don't think all physicians in the United States have the wherewithal or the motivation to spend that much time putting patients on trials. It really adds a lot to a busy physician's day. There's one barrier.

DR LOVE: And to some extent, I hate to say this, but sort of time is money.

DR KAHL: Time is money. That's absolutely true. And if a private oncologist's office is going to do trials, they have to hire research people. That costs money as well. So there is possibly a financial reason why the accrual isn't as good.

The fact is that most — well, just about every child that's diagnosed with cancer is treated at an academic center. And I think that's one of the reasons that more of them get on trial. So I mean, one of the things that we really need to do in the United States is to incentivize the whole process for the private practice oncologists, so that we don't have these barriers.

And most of the patients who have been asked about clinical trials and why they didn't do them, it was because it was never presented as an option.

DR LOVE: Yeah. We've polled patients with a variety of cancers, and that always is what we hear. At least two thirds have never even heard about a clinical trial.

I guess the other issue is particularly as it relates to the randomized trial, that the physician has to be comfortable that either way is okay. I've heard the term "equipoise," which is that there's an equal feeling about that. And I guess a lot of physicians have their own bias, that they think one treatment might be better than another.

DR KAHL: Right. That's a huge thing to overcome. For me, it's a very frustrating thing, because usually by the time something gets to a randomized trial, the literature is pretty clear that there isn't a better treatment. And overcoming the bias among individual physicians is a hard thing to do, but they just need to understand that the bias isn't helping the process.

DR LOVE: Another thing that relates to these trials is there's more to it than just trying to find out sort of which treatment might be better in these randomized trials. You're also looking inside the tumor, to see if you can learn things about the lymphoma that might correlate with treatment.

DR KAHL: The other thing that sometimes is hard for physicians, if you're putting a patient on a randomized trial, you're basically telling that patient, "I don't know what's best for you." And it's actually easier to take a more paternalistic tone with a patient and say, "This is what's best for you. I know what's best. This is what you need."

DR LOVE: And a lot of patients are asking for that, too.

DR KAHL: That's right. That inspires confidence from the patient. And when you do a randomized clinical trial, you can't do that. You literally have to say, "Here are two treatments. They're both good. I don't know which one is better."

You have to be comfortable saying that to your patients and they have to be comfortable with that fact. And that is another barrier.

Getting back to the question you just asked, we're entering a new era now in cancer therapy. And the term that we hear most often is the "era of targeted therapy." And there are a couple of drugs right now that are very good examples of that. And we're hoping to get away from the day where we give chemotherapy, which is more of a shotgun approach to treating cancer, and we'd like to have more rifle approaches. And you need treatments that are targeting aspects of the cancer cell that are unique, proteins or biochemical pathways that are unique to the cancer cell, that are not present on normal cells; whereas, chemo just

kills cells that are growing fast.

Well, for targeted therapy to work, you need to know what the target is. And to know what the target is, you really need to get inside the cancer cell. And that's one of the things that goes with clinical trials. We very often will be obtaining tumor tissue from the cancer cells or from the patient's blood that allows us to do what we call correlative studies. And it helps us figure out why the drug worked for these 10 people and it didn't work for these 10 people. And then it helps us to figure out where to go next when we're able to do these correlative studies and try and link that to the clinical outcome.

DR LOVE: We talked about randomized studies. What about other kinds of clinical trials that aren't randomized?

DR KAHL: So we usually apply the term Phase III when we're talking about randomized clinical trials. But there's actually two phases of study that come before that. So just to sort of take you through the process of drug development, let's say that there's a new compound that gets synthesized or discovered. And it typically would get tested in cancer cell lines and it might show some activity that looks promising. And then it would typically get tested in animal models, where you sort of work out some doses and some toxicities. And when it's ready for testing in humans, it is done in the setting of what's called a Phase I clinical trial. Those sorts of trials are usually done in patients who have advanced cancer, who really have exhausted their standard treatment options. And the purpose of a Phase I trial is really to establish an effective dose of a new drug.

And once a dose has been established and the side effect profile of a new drug has been characterized in Phase I trials, it then is moved on to what are called Phase II trials. And in the Phase II trials, you're really then targeting that drug in certain diseases. So in the Phase I trial, it would just be done in cancer patients in general, any kind of cancer. But when you do it in a Phase II setting, you're going to take drug X and you're going to test it in lymphoma patients, or you're going to test it in leukemia patients, or you're going to test it in breast cancer patients. Because now you really want to get a sense for, if I treat 100 patients with disease Y and give them drug X, how many of them will respond to this drug. And you need to do it in a certain disease then. Those are called Phase II trials.

And once a drug has established activity in a Phase II setting, then it may be considered moving forward into the Phase III setting, where it might be tested against a drug that's been around for a while and has a proven level of activity.

DR LOVE: Now when you talk about these types of trials, these patients often, if not always, had prior treatments. They have advanced-type situations. But even in a Phase I study, do patients ever benefit from the treatment itself, or are they just participating in it to help future patients?

DR KAHL: Occasionally, patients will derive clinical benefit from Phase I clinical trials. To be honest, that is not the normal situation, because probably, if you look at the history of Phase I trials, most of the Phase I drugs don't pan out in Phase II testing. So some patients will derive benefit from Phase I trials, but not the majority.

DR LOVE: Although I guess, at some point, there must have been a Phase I study for rituximab, for example.

DR KAHL: Exactly.

DR LOVE: And those patients, I guess, benefited.

DR KAHL: Exactly. In the Phase II setting, it's certainly true that lots of patients have derived lots of benefit from Phase II trials. And for it to be a Phase II trial, it doesn't just have to be a brand-new drug tested in a new disease. What it might be is you might take a regimen that has proven activity and works 40 percent of the time. And then you might combine that regimen with new drug X. And that's your Phase II study. So in that case, let's say that the regimen that works 40 percent of the time is the best regimen there is in that disease. Maybe that is the standard. And in that case, this Phase II trial, which has the standard regimen plus new drug X that might be the first treatment that patient ever receives. So there are many times where a Phase II trial will be the setting in which a patient receives their initial therapy, usually in combination with something that has a proven track record.