



LYMPHOMA FOUNDATION of AMERICA

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TRANSCRIPT OF WEBCAST: RADIOIMMUNOTHERAPY DR. MARK KAMINSKI October 14, 2010

BETSY de PARRY: Hello everybody...and on behalf of the Lymphoma Foundation of America, welcome. I'm Betsy de Parry, a non-Hodgkins' lymphoma survivor, thanks to radioimmunotherapy, about which I'm so excited to be talking with Dr. Mark Kaminski. Dr. Kaminski is a professor of internal medicine in the division of hematology/oncology at the University of Michigan Health System. He's also the director of the Multidisciplinary Lymphoma Clinic at the University of Michigan Comprehensive Cancer Center, and he happens to be my doctor. Dr. Kaminski, I know that so many people have questions about radioimmunotherapy – RIT for short – and I'm so thrilled that you're with me to talk about it. Welcome.

DR. MARK KAMINSKI: Nice to be here. Thanks for inviting me.

BETSY de PARRY: I'm really glad you are here! Before we get started, I'd like our listeners to know that your knowledge of RIT dates back to its early days. As I understand it, back in the 80's, you and a small handful of scientists were trying to develop RIT to treat lymphoma, and that it was ultimately your concept - co-conceived with Dr. Richard Wahl, who's now head of nuclear medicine at Johns Hopkins - that succeeded and became Bexxar, one of the two RIT drugs. Correct?

DR. MARK KAMINSKI: That's correct.

BETSY de PARRY: I also understand that you've treated more people with RIT than anyone else in the world – literally. Is that also true?

DR. MARK KAMINSKI: I believe it is.

BETSY de PARRY: Well, that means that you've observed more patients, in and out of clinical trials, who've taken RIT than anybody else, so I'd say to our listeners that there's no better person to arm you with accurate information so that you can have meaningful discussions with your own oncologists who know your individual situations. And I also want to clarify that when we talk about RIT today, we're talking about the treatment, not specific drugs. And one final thing. Dr. Kaminski, I don't know what you're going to say, but as we go through these questions, if for any reason you'd like to reference my case as an example, please feel free. We can leave HIPPA off the phone. So shall we start?

DR. MARK KAMINSKI: Sure.

BETSY de PARRY: Well, let's begin with how RIT works. Dr. Kaminski?

DR. MARK KAMINSKI: Well, let me give you a short explanation of what RIT is and especially as it's given for lymphoma. One of the principles behind how this all works is that our immune systems are generally patrolling around with antibodies looking for foreign invaders. This treatment basically takes an antibody that's manufactured outside of our bodies, and this antibody knows how to bind to a specific target on our CD20 positive lymphoma cells. That's the target – CD20. It's a protein. And when you inject it into the bloodstream, it basically homes to wherever the lymphoma is and latches on to it. And when it does land on the lymphoma cells, it signals to the immune system that this is a cell that needs to be destroyed.

The extra twist that comes with RIT is that these antibodies that we're injecting into the bloodstream have a radioactive isotope attached to them, so when they do bind to these tumor cells, then not only is the immune system alerted, but these antibodies are delivering radiation right in the immediate vicinity of where that antibody has landed. So you get a very targeted type of treatment, really avoiding the normal cells of the body and really trying to focus in on those abnormal CD20 positive cells that make up the vast majority of lymphomas. That's the way the treatment works.

BETSY de PARRY: So it's a dual action?

DR. MARK KAMINSKI: That's correct. It is.

BETSY de PARRY: That's a great explanation in lay language. How does this really differ from chemotherapy and Rituxan and what are some of the common side effects of RIT and how do they compare to the side effects of chemo and Rituxan?

DR. MARK KAMINSKI: The main feature that's different is that this is a one shot treatment. It is not given in repetitive cycles as we give chemotherapy. Chemotherapy is given every 3 to 4 weeks and it could be 6 to 8 cycles of that, so you can imagine going up to 6 months before you're actually ending the treatment. With RIT, you're really talking about – and we'll get into this maybe a little later – a treatment that is basically over within a week and really consists of only 2 injections of antibody - radioactive antibody - about a week apart. And that's the end of the treatment. There are no followup cycles. So that's a big difference.

With RIT, as opposed to many chemotherapy agents, you don't have hair loss. There's little or no nausea or vomiting, and we don't even prescribe any anti-nausea medicines during that time.

The main side effect of RIT is a lowering of the blood counts approximately 4 to 6 weeks after the treatment is given, but generally this is pretty mild and patients recover spontaneously. Now that's a little bit different from chemotherapy because you expect chemotherapy to lower the blood counts as well, but if you're giving 6 cycles of treatment, you're lowering those blood counts 6 times over the course of 1 treatment. In RIT, we're only talking about 1 suppression - 1 down period - versus 6. So that's one of the differences.

As far as Rituximab is concerned, this is an antibody also against CD20 but it is not radioactive, so it doesn't have that double punch that the radioactive antibodies have.

BETSY de PARRY: Just as an aside, and this is from a patient perspective, as you well recall, I had many horrible side effects from chemotherapy, some of which required hospitalization. So I'll just say that taking RIT in comparison was a walk in the park.

DR. MARK KAMINSKI: Your case is quite reminiscent of a lot of other cases that we've seen. RIT is given primarily in patients who, just like you, have had other prior treatments so they've been exposed to chemotherapy and they know how that works and how it works on their bodies. The most common complaint I hear from patients is, "Well, I didn't get sick from this therapy so it's probably not going to work." And as we'll talk about a little later, it does work.

BETSY de PARRY: It works pretty well! I'm a little over 8 years out now. So Dr. Kaminski, RIT isn't appropriate for all types of lymphoma. What types is it appropriate for?

DR. MARK KAMINSKI: Well, it's approved by the FDA for patients with low-grade lymphoma, or indolent lymphoma, B-cell lymphoma and those types of lymphomas - the low-grade lymphomas - that may have transformed to a more aggressive type, and it's also indicated for patients who have become, or their lymphoma has become, resistant to Rituximab. So those are the primary indications.

So there are lots of different low-grade lymphomas out there. The most common form of low-grade lymphoma is called follicular lymphoma. By far and away, that's the lymphoma that has been treated the most with RIT and where most of the experience comes from. There are some patients who have been treated with marginal zone lymphomas or MALT lymphomas, some with Waldenstrom's, but that's a fairly low number of patients, but we have seen responses in those patients. It is not approved for patients who have aggressive lymphomas such as diffuse large B cell lymphoma by the FDA and it isn't appropriate for patients who have T-cell lymphomas because the CD20 protein is only seen on B cells, not on T cells.

BETSY de PARRY: You mentioned that it's not approved for patients with aggressive lymphomas. Are there any studies being done to see how it might work in those aggressive lymphomas?

DR. MARK KAMINSKI: Yes, there have been a number of studies and some are continuing to be done – some with what we call the conventional dose or non-myeloblastic dose of these agents. They're being used either alone or more commonly after getting a treatment first with chemotherapy and using this as a cleanup. In addition, there is a higher dose regimen where one gives a very high dose of these radiolabeled antibodies in the context of getting an autologous stem cell transplant – basically a rescue from the very high dose of the radioimmunotherapy. But those are all experimental uses and are only really available to people, or should only be done, in patients who are in clinical trials.

BETSY de PARRY: But there are some trials out there?

DR. MARK KAMINSKI: That's correct.

BETSY de PARRY: What about for elderly patients?

DR. MARK KAMINSKI: RIT is particularly attractive for elderly patients because the side effect profile is so good. Again, I mentioned the most disappointing thing that people will talk about is that it didn't give them any side effects, and that is true for older patients on whom chemotherapy can play a real major toll. And in fact, even though the treatment may be working, the treatment's worse than the disease in many of these patients. And also, just think about the fact that if you're elderly, you have to get back and forth from your home or wherever you're living or an extended care facility to the hospital or to the clinic to get treatment, and you're doing this repetitively with chemotherapy over and over again, whereas this is a one week experience - much more convenient for the patient and for caregivers as well.

BETSY de PARRY: Yes, it definitely is. So if I had a type of lymphoma for which RIT were appropriate, what other requirements would I have to meet in order to be a candidate for it?

DR. MARK KAMINSKI: Well, generally we have some restrictions as to the blood counts that you have. We want the blood counts to be within a certain range. They're not very restrictive but there are some criteria that we use. If you have less than 100,000 platelets, we generally don't give the treatment.

We also look to see whether your bone marrow has a significant amount of involvement by the lymphoma. If you have more than 25% of the bone marrow biopsy showing lymphoma, we tend not to give the treatment. The fear is – remember how this is targeting the tumor cells – if there's a lot of tumor cells in the bone marrow, they're going to act like a magnet for these radioactive antibodies and they may expose the normal surrounding bone marrow to an excessive amount of radiation and lower the blood counts further than we would like that to happen. But that's about it – just really the blood counts and bone marrow involvement.

There are a few technical things that we worry about such as radiation safety hazards in patients who are potentially incontinent or who are throwing up or have other conditions that would make handling radiation in that person a hazard, not just to themselves but to others. So we do have a few of those restrictions but those are very few and far between.

BETSY de PARRY: That really leads me into the next question that I wanted to ask you. I understand that every case really has to be evaluated on an individual basis, but generally speaking, are there any other conditions that would absolutely preclude the use of RIT – something like, say, osteoporosis or diabetes or anything else?

DR. MARK KAMINSKI: No. Diabetics, people with heart disease, lung disease – all those patients – this treatment does not really affect those conditions, whereas chemotherapy could obviously have a major impact, so patients who have other “co-morbid”- we call them – problems in which chemotherapy could make them a lot worse, that doesn't seem to operating in this therapy because it is so targeted.

BETSY de PARRY: Interesting. That's actually good news. So could you please explain how RIT is administered and what precautions patients need to take after they do have it and do they need to remain isolated?

DR. MARK KAMINSKI: Sure. Well, I explained a little bit earlier that it is really a one week procedure so sometimes it's best just to go step by step. So there are two infusions of the antibody. They are one week apart. The first infusion we term as a test dose, so we give some antibody that very first day, and then on that very same day, at least with Bexxar, where the radioisotope is called I-131, we do what's called a gamma camera scan. We just lay you down on a gamma table and they run a special machine that detects how much radiation is in your body at that one time point. It's like running a Geiger counter over you. That takes about 5 to 10 minutes at the most. Then we have you come back 2 or 3 days later and we'll repeat that scan - just take that machine and run it over you. And we get a second time point for how much radiation you have in you. And then we bring you back a couple of days later and do the exact same thing. And now we have 3 points in time, and that's telling us how quickly your body is eliminating the radiation. Everybody eliminates at a different rate.

So a week after we've given you the first antibody injection, we give what's called the therapeutic dose, and that's a much higher dose of the radioactive antibody. And it's scaled based upon how you cleared the test dose, so some people will get more and some patients will get less, according to how they cleared their radiation. And then the actual administration of both infusions is about an hour and a half, and this is all done in an out patient basis.

Once you've gotten what we call the therapeutic dose, you're free to go home. In the case of Bexxar, which is the radioactive I-131 radiolabeled antibody, we ask patients to pretend like they have the flu for about 5 to 7 days. And by that I mean keeping your distance from pregnant people, or from your spouse, etc., not sleeping with them, for about that period of time, just to reduce the amount of radiation exposure other people will have.

Now even if you did stand next to somebody for a prolonged period of time, we have to be cognizant of the fact that it is a very small amount of radiation - if we tabulate how much radiation they're getting, it's about equivalent of maybe flying from here to San Francisco and back - I'm talking about Ann Arbor - so it's not that much, but it is an unnecessary amount of exposure and we don't necessarily want people exposed if they don't have to be, so you need to be conscious of it.

In the case of Zevalin, which is the other radioactive antibody which is labeled with an isotope called Yttrium-90, there are some different characteristics of that radiolabeled isotope such that there's very little radiation emitted outside of your body, so there, it's just a matter of some handwashing, etc. and keeping a few things separate in terms of utensils, but not as much restriction. But either way you look at it, we're talking only a few days inconvenience and then once that period is over, you're free to return to work and do whatever activities you've had and done before.

BETSY de PARRY: Well, I'll just add to what you said, again from a patient perspective, that the few days after RIT that I had to take a few precautions were a whole lot less inconvenient than spending months in chemo treatment and dealing with all those side effects. That's just my little personal thought on that.

DR. MARK KAMINSKI: A lot of people don't appreciate how different this is. They know that they've had prior chemotherapy - they went through it - and then they say "Wow, I wish I had this earlier." Maybe we'll talk about that later.

BETSY de PARRY: Yes, it is easier - much easier. Dr. Kaminski, I remember your calling me six weeks after treatment, after my first scan, and telling me that my lymph nodes were in normal range, and I asked you if I were in remission. For the life of me, I don't remember now exactly what you said, but I do remember that by the end of the conversation, we agreed that I was "on vacation" from lymphoma. So the question is: How long after RIT does it take to know whether someone has achieved a partial or complete remission? In other words, does it continue to work beyond that first scan afterwards?

DR. MARK KAMINSKI: Generally what we see is - if we repeat a scan at six weeks - if the patient is going to be a responder, we will see a difference between the pre-treatment scan and that six week scan. If we don't see any difference, then it's unlikely for us to see a delayed effect. So the story is pretty much told very early on, and patients do respond very briskly. Patients, for instance, who have lymph nodes on their neck or in their groin that they can easily feel often say to us that right after the therapeutic dose - about 3 or 4 days after they get it - they really start to feel things just sort of melting away, so that's a good sign.

Now as for how complete that response is at 6 weeks, we've been doing some other studies more recently and looking at PET scans which are a little more sensitive in detecting whether a tumor or a mass still has live tumor cells in it or not, and we get some variable results. We still sometimes see an abnormal looking

mass, but it's clearly smaller but it's not normal, and when we look at the PET scan, and there isn't any uptake anymore in that area, so there's just dead tissue.

In some instances, there might be some residual abnormality there on the PET scan, and that can fade over time. And so on followup scans, some of these residual masses continue to get smaller, but I think more than likely what's happening is that the tumor's already dead and what's going on is that the body is sort of resorbing what dead tissue has remained, so it's sort of like it's still cleaning it up. And I've had patients come back with improved scans at 3 and 6 months afterwards. So you pretty much know if you are in a "complete remission" within the first 6 months after the treatment, and generally, we know whether you're on a good path very early on, within the first three months.

BETSY de PARRY: Good to know. So Dr. Kaminski, can RIT be used in patients who are heavily pre-treated with Rituxan or who are Rituxan resistant? And is there a waiting period following Rituxan?

DR. MARK KAMINSKI: Well, actually that's the main – one of the main – indications that the FDA approved these drugs, radiolabeled antibodies, for. So yes, definitely. And patients do respond, obviously, otherwise it wouldn't be approved. Now the response rates are very high. They're in the rate of about 60 to 70%, and the complete response rates are about 20 to 40% in these Rituximab-resistant patients, so it's definitely a very useful treatment for patients who've had Rituximab and for whom it's no longer working.

BETSY de PARRY: What about the waiting period?

DR. MARK KAMINSKI: That's a really good question. No, there's no defined waiting period. Generally, a lot of patients are getting Rituxan along with chemotherapy and so it's important to let the side effects or the suppression of the bone marrow wear off sufficiently before embarking upon radioimmunotherapy – between 3 and 6 weeks after getting the last dose of treatment. There is a concern that if there's a lot of antibodies still around, because Rituximab can circulate around in the blood for quite some time – for weeks - there may be some tumor cells that still have the antibody hanging on and so they may mask the additional antibody that one is giving for the radioimmunotherapy. So far we have not seen a dramatic difference in patients who've gotten treated right away versus waiting, but there hasn't been a formal clinical trial looking at that.

BETSY de PARRY: So it sounds like again, on a case by case basis.

DR. MARK KAMINSKI: Yes.

BETSY de PARRY: The National Academies states that RIT has "generally a fraction of the toxicity" of chemo and "comparatively limited and reversible toxicity." What does that mean?

DR. MARK KAMINSKI: Very fancy, but if you just think about it a little bit, a fraction of the side effects – remember this is a one time, or one session treatment, versus 6 times - so already, one sixth, and then as far as the different types of side effects are concerned, remember I mentioned that there is no hair loss, there is no vomiting, so there's a lot of things that chemotherapy has with it that this does not. So I think that's what the statement is trying to tell us.

BETSY de PARRY: That's a great explanation. Thank you. I've heard lots of myths about RIT over the years, as I'm sure you have, and I'd like to share the ones that I most commonly hear and ask you to set the record straight. You've already talked about that RIT knocks down the blood counts just once, but one of the concerns that I hear is that RIT knocks down blood counts to risky levels. All treatments affect the blood counts, so just to review this a little bit, how valid is this concern?

DR. MARK KAMINSKI: Well, let me just say that chemotherapies can vary as to how much they suppress the blood counts, and a lot of that has to do with how much prior treatment the patient has had. So for instance, if you've had 5 different chemotherapy regimens, you can imagine how weak the bone marrow must be at that point. So anything that you give, including RIT, at that point is bound to have more of an effect on the bone marrow, which is already weakened, than if you had used it earlier.

So yes, there can be blood counts that can go pretty low with RIT, but it is very rare for us to use any growth factors or transfusions in these patients. And again, we're only talking about one low blood count – one

time or episode – versus many. And the blood counts do recover. Especially you can see the vast difference in how patients recover when you've used this treatment earlier rather than waiting for the fifth or sixth treatment or using it maybe second or third line. These blood counts are really not a major concern for the patient. Most patients don't even know that their blood counts might have gone down.

BETSY de PARRY: No, I never did.

DR. MARK KAMINSKI: And I will tell you, and I've given a lot of RIT as you mentioned earlier, I can only count on one hand out of the hundreds of patients that I've treated, in which I've actually had to admit somebody to the hospital because of fever and infection.

BETSY de PARRY: But on the other hand, I remember you had to admit me twice for chemo-related infections.

DR. MARK KAMINSKI: Sorry about that.

BETSY de PARRY: Well, you did what you had to do, but I think what I'm trying to say – and we're saying the same thing – is that all of these drugs come with a certain amount of risk, and the point of it is that we have to weigh those risks and benefits.

DR. MARK KAMINSKI: Yes, I think we just need to be absolutely clear here. There is no treatment, including RIT, that doesn't have side effects, and that may be an immediate side effect but it can also be a long term side effect. There's nothing perfect in this world, but I think when we do select treatment, we have to weigh the pros and cons of the particular treatment versus others, and we really have to individualize the treatment.

BETSY de PARRY: As I was sitting here listening to your answer about knocking the counts down 6 to 8 times with chemo versus once with RIT, I thought of a question. If I understand you correctly, drugs such as Procrit are commonly prescribed to offset chemo-related anemia, but I know those anemia drugs have their own risks, so if I'm a patient sitting here trying to weigh my treatment options, wouldn't I want to consider treatments that minimize the need for additional drugs above and beyond the ones that used to fight lymphoma? Should this be a consideration?

DR. MARK KAMINSKI: Oh absolutely. Basically these are drugs to rescue you from the toxicity of the treatment, and if we didn't induce that toxicity in the first place, you wouldn't need the drugs. And that also has implications for health care costs.

BETSY de PARRY: Ah, yes.

DR. MARK KAMINSKI: You're talking big bucks when you're talking about these growth factors like Neupogen or Neulasta which are very commonly used in combination with chemotherapy. Now let's also remember, for instance, follicular lymphoma and a lot of the low grade lymphomas are diseases of – I don't want to say elderly – but of more advanced age. And those patients are at even higher risk for needing these growth factors if chemotherapy is given. So you can see where the dollars are going in terms of trying to protect the patients from what we've already given them.

BETSY de PARRY: Well, I always point to my own case. I don't have the exact dollar amounts, but I can pretty much quote them. My RIT treatment – everything, scans, doctors appointments, followup, everything – was about \$36,000 versus \$166,000 for everything that didn't work, and I never finished a whole chemo treatment. So it's really remarkable.

DR. MARK KAMINSKI: Yes, that's another myth that's out there. You were talking about myths. One is that this is so expensive, but if you really put it all together, just looking at it from the expenditure of resources to keep the patient alive during treatment, versus that one week treatment that we're talking about here – RIT – you can see that there is a logical cost savings.

But I also look at it also from a sociological standpoint because if you're running a business or if a business is reliant upon your presence, being not up to snuff for six months isn't the greatest thing for your

employer or for your employees, so the faster the treatment is over, the better it is and economically, it makes sense as well.

BETSY de PARRY: Right, we can get back to making money and paying our fair share of taxes. [Both laugh] On to another myth. Sometimes I hear from people whose doctors say that RIT will destroy the bone marrow and thus preclude the possibility of a stem cell transplant or any other future treatments if necessary. In other words, RIT burns bridges and should be used only as a last ditch effort. Does it burn bridges?

DR. MARK KAMINSKI: No. Short answer. That myth has been talked about or sent around so often, and I think it's a lot of misinformation. People just don't know the data. And there is, as we call it, life after RIT – there's plenty.

We've transplanted patients who unfortunately didn't have the best results after RIT – with their own stem cells – and we have also transplanted patients with somebody else's stem cells. And as far as other chemotherapy treatments are concerned, yes, we've given them and the patients have tolerated them.

In fact, if you think a single treatment with radioimmunotherapy is going to burn bridges, then one has to look at the data that says, "Well, how come there is a study out there that we've performed with other institutions in which we repeated the treatment when a patient relapsed after their first treatment?" And yet their blood counts really didn't change very much from the first time they got RIT.

So there is plenty of data now for both Bexxar and for Zevalin, and you can repeat this treatment, so that tells you that that fallacy is out there for I don't what reason. So, no, it does not burn bridges.

BETSY de PARRY: Well, if you think about it, R-CHOP burns bridges because you can only use that once.

DR. MARK KAMINSKI: Well, yes, because of the adriamycin.

BETSY de PARRY: Exactly, so if I understand you correctly, you've even used RIT more than once.

DR. MARK KAMINSKI: That's correct. Now that's on a clinical trial and the FDA package insert is a little bit vague on it. It basically states that the safety and efficacy of using a second treatment has not been evaluated. Does that mean you shouldn't do it? I think one needs to be individualized, and I think if one's options are limited, and one had a fantastic, long-term response with the initial RIT, and somebody's already gone through multiple lines of chemotherapy, why return to something that doesn't work? So I think we need to be selective about who we re-treat, but I'm just telling you it is possible.

BETSY de PARRY: You mentioned that you've used RIT before a transplant. Can it be used after a transplant?

DR. MARK KAMINSKI: Yes. In fact, in our initial trials, way back in 1990 – 20 years ago – we included patients who had undergone autologous stem cell transplants. That means, after high dose chemotherapy, patients were getting back their own stem cells, and these are patients who were obviously ill. We had about 12 to 15 patients like that in our initial trials. And although we do reduce the dose a little bit for those patients with RIT, the patients with follicular lymphoma did extremely well, and 4 or 5 of those patients are out beyond 10 to 15 years in remission after failing an autologous stem cell transplant. So it's definitely an option.

BETSY de PARRY: Wow, that's amazing. Well, this next question, Dr. Kaminski, has multiple parts. I've heard many people say that their doctors tell them they are concerned that the radiation in RIT carries a high risk for secondary cancers, and yet radiation is commonly used in the treatment of many kinds of cancer and nobody blinks. So if I use an example - if I had a stage I tumor or breast cancer - it wouldn't be uncommon to treat it with external beam radiation. So would you please put the amount of radiation in RIT into perspective compared to external beam radiation? What are the facts about RIT causing secondary cancers? And doesn't chemo carry a risk for secondary cancers, too?

DR. MARK KAMINSKI: That's about 15 questions!

BETSY de PARRY: I know, I'm sorry but you've known me for about 9 years now.

[Both laugh]

DR. MARK KAMINSKI: I think I can handle it. Nothing is simple. Let me start with giving you a perspective on the radiation. This is a different form of radiation than external beam radiation. External beam radiation is coming in a big blast from a machine once a day for several weeks, and this radiation is not just getting to the tumor but is also traveling through normal tissue. Although we're getting better and better at pinpointing these radiation beams, there's still a substantial amount of scatter from the radiation so normal tissues are being exposed.

With RIT, this is a much more targeted form of radiation and it's more of a continuous low dose rate of radiation. It's a different biological effect. And so because the radiation is much more confined to where the tumor is, and is not very much in other tissues, those other tissues aren't getting exposed very much to cancer-causing radiation. We now have long followup, as you can tell – I mean, 20 years of followup – and the rate of other solid malignancies, such as colon cancer, lung cancer, those sort of things – in all the clinical trials, there's no signal at the present time to indicate that there's an increased risk for the development of those other cancers.

The one area that we continue to be cautious about is diseases that can arise, or cancers that can arise, in the bone marrow because that is an organ that is getting a fair amount of radiation, and that's where, for instance, the blood counts - when they go down - were affected by scattered radiation within the bone marrow. But when you compare it to what chemotherapy can do – which can also cause these secondary bone marrow diseases, such as, we call them, myelodysplastic syndrome or acute leukemia – the rate of development of those malignancies is no different with RIT than it is with chemotherapy.

And in all the studies that have been done with the exception of one, where it was used as a front line treatment, all the other patients had gotten prior chemotherapy, so we really can't tell whether – if they did develop AML or MDS – whether it really was the radioimmunotherapy that caused it or the chemotherapy or maybe a combination of both. It's not an alarming difference.

However, I think we need to continue to be vigilant and watch what's happening. Obviously the less prior treatment the patient has had, the less risk there is to developing MDS all over, not just from radioimmunotherapy but from chemotherapy as well.

So the short answer is it's a different kind of radiation. It's more targeted – less exposure of normal tissues, and the rate of developing bone marrow type of cancers does not appear to be any different than the rate you would see with chemotherapy.

BETSY de PARRY: Well, thanks for clarifying that. As I was sitting here listening to your answer, I'm also pretending that I'm sitting here as a patient weighing risks and benefits and trying to make a treatment decision for my next treatment, so would I be right in thinking that the risk of secondary cancers could increase with each additional treatment and that it might be logical to consider the treatment that would potentially give me the longest period of remission?

DR. MARK KAMINSKI: Yes. Definitely. The less treatment you get - the longer the remission you get - the safer you are.

BETSY de PARRY: That's what I thought. So Dr. Kaminski, I know that Bexxar and Zevalin use different radioactive isotopes and I've heard concern that the one in Bexxar can cause thyroid problems, but I understand that you can shield the thyroid to minimize the risk. So what is the potential problem and how great is the risk?

DR. MARK KAMINSKI: Yes, the radioactive isotope in Bexxar is Iodine 131, and iodine is essential for making thyroid hormone, and the thyroid gland is where that's all produced. And so some of the radioactive isotope can come apart from the antibody and can land in the thyroid because that's just a magnet. That's where the factory is. However, what we do is give some non-radioactive iodine prior to and during the treatment of Bexxar. So essentially it is like a shield against any radioactive iodine that might get loose. And the risk we have seen for low levels of thyroid function is less than 10%. So 90% of patients won't have any effect on their thyroid gland. And even if one does, this is a pretty common condition that a lot of people have who don't get radioisotopes. And it's treated by taking a hormone pill, a thyroid pill which is a natural hormone that the body is producing. We're just giving a pill to replace that and patients do just fine so I don't think it's a big deal. We do monitor it but again it's a low risk. It's less than 10% of patients who develop it.

BETSY de PARRY: Well, thank you for clarifying that. I'm going to get into something that you well know, which is: there's such an array of treatment options for the indolent lymphomas but no real standard of care, so that really leaves us patients weighing the risks and benefits of each option that our doctors tell us. So now that you've

set the record straight on these common myths, does RIT have any other risks that we should know about – but really, better yet, what are the benefits?

DR. MARK KAMINSKI: Well, I think that the major benefit is, first of all, the ease with which it is given and how easy it is for the patient to take. That's one. The second – and probably the most important thing – is how effective it is. That's the benefit.

And the response rates are very high, but probably more importantly, it's the number of patients who get into a complete response. To get into a complete response with these radiolabeled antibodies, these responses are quite sustained. We're talking in years and possibly decades. You don't really see that with chemotherapy, especially in the settings in which these RIT agents are approved by the FDA, that is, patients who have already gone through other therapies.

So the key here is that the risk that you're exposed to are outweighed, or can be balanced, by the very long term remission that you get and for the lack of need requiring other treatments down the line. So that's the primary thing that we need to focus on.

BETSY de PARRY: You mentioned the complete response rates, and I can't find any study that shows any treatment for the indolent lymphomas to achieve the complete response rate that RIT does – or the duration of response, which as you mentioned is often measured in years. There was one study, in fact, in which researchers from several institutions performed a meta-analysis of several clinical trials and reported that RIT had a complete response rate of 79% compared to 53% with chemo plus Rituxan. So again, if I'm a patient looking at my options, increasing the odds of a complete response by 26% would certainly pique my interest, so the question is: given that complete response rate that RIT is known to produce – and the duration of response – where should it fit in among the array of treatment options and when is it best used?

DR. MARK KAMINSKI: Excellent question. The figures that you were quoting probably reflect mostly the data that comes from clinical trials in which these agents have been used as a frontline treatment in follicular lymphoma, but when you look at the complete response rates of patients who have had multiple lines of treatment, they start to go down. They don't go much lower than 30% but they do go down.

And achieving a complete response is really, in many cases, the equivalent of getting a durable response, that is, lasting years. So that's really a goal. So if you really put it all together then, the place where these radioactive antibodies need to be put is much more toward the front line than using it as a last ditch effort because essentially you may avoid all those other efforts if you use RIT earlier.

So I think the earlier the better, particularly, for instance, in patients who have had a front line treatment, for instance with chemo and Rituximab, and the response has been less than durable – for instance, less than two years. There's not much evidence that doing the same treatment or giving another combo of chemotherapy is going to do much better than that.

However, there is data to show that radioimmunotherapy can, in those instances, produce longer remissions than prior chemotherapy. So I think it's a really reasonable thing to consider in patients, I think, of all ages. Sometimes people shy away and ask what about young people – shouldn't they go to transplant? But I'm not so sure about doing that because we have plenty of patients now that have been treated in the way I just described, that is, they had a relatively short response to their frontline treatment and then got RIT and are still in remission without having to go to transplant. And as I said before, RIT does not bar you from going on to getting a transplant later.

BETSY de PARRY: I remember you once told me that since I was refractory to two types of chemo, that it just wasn't logical to use that same mechanism of action – that it was unlikely to work even if it was a stronger type of chemo – and I think really that makes perfect sense. It's logical.

DR. MARK KAMINSKI: And one of the things I think, to be perfectly fair, RIT is very appealing in this way and really should be entertained, but I also want to make sure that your audience remembers that there are lots of new agents that are also being developed and have a different mechanism of action. Some of them are even pills, and although they're very early in development, they look pretty promising. And I encourage patients to not only look into RIT – which I clearly urge – but also consider clinical trials if they're appropriate for them. That being said, I think that RIT has such a different mechanism of action – radiation – and these tumors rarely can get around radiation, and that's the reason why it works so well.

BETSY de PARRY: You mentioned that – if I’m hearing you correctly – that RIT is best used earlier rather than later in the course of treatment, but for us patients, that’s really a problem because RIT isn’t approved for first line therapy, except that Zevalin can be used in combination with chemo. So what are the approved uses for RIT and when is consolidation therapy appropriate? And you might want to explain consolidation therapy.

DR. MARK KAMINSKI: OK. Well, what consolidation means is that after you’ve gone through a planned course of chemotherapy or combined Rituxan plus chemotherapy, that this is an add-on, a kind of clean up of residual disease, no matter what your response is to the prior treatment. So that’s what’s called consolidation.

There’s another term out there and that’s called maintenance, and generally we’re referring to Rituximab being given for a period of two years every three months – that’s kind of a typical maintenance. The idea here is not to necessarily improve the degree of response, but to keep the disease stable or at bay. But I think one of the dilemmas right now is now we have clinical trials that show that when you give radioimmunotherapy as a consolidation after frontline treatment, that the duration of patients’ response is prolonged by over two years if you get radioimmunotherapy versus just observation. Interestingly enough, that’s about the same benefit that people are seeing with maintenance treatment but that maintenance treatment is given over a two year period of time, so it begs the question, when do we give radioimmunotherapy versus maintenance Rituximab? And so there’s still a lot of work to be done to determine in which patients this is best.

In my view, patients who get Rituximab plus some chemotherapy and at the end of their treatment, they had not achieved a complete response, I would definitely encourage the use of radioimmunotherapy in order for them to achieve that goal of getting a complete response so they have a long remission. After all, they went through all this trouble – what’s one more week, right? On the other hand, I wouldn’t encourage in that scenario somebody go through maintenance treatment for two years because already some of that treatment did not result in making them better, of getting them into complete remission. It’s unlikely to get them into complete remission.

For complete remitters, there is still a big question mark. The study that was done with consolidation radioimmunotherapy did show an improvement even in patients who had a complete remission. Although the numbers weren’t huge, I think that’s a positive signal, so one could consider it – again, versus putting somebody on maintenance Rituximab for a long time. I think that in the future we’re going to see some clinical studies that may, in fact, try to figure out which of those is the most useful, or which is the best. We’re hoping some trials will be done in the near future.

BETSY de PARRY: You’ve almost answered what I was about to ask you, but let me just review it because I think consolidation therapy has just added another layer of confusion to RIT, and I’ve heard several people trying to decide between maintenance or consolidation. So let me ask you if I’m hearing this correctly. Maintenance is intended to delay relapse by maintaining the best response to therapy whereas consolidation is meant to improve the response or eradicate residual disease. Do I have that right?

DR. MARK KAMINSKI: I think that’s a very good explanation. I think you nailed it.

BETSY de PARRY: I’m surprised. You taught me well!

DR. MARK KAMINSKI: After 8 years? [Both laugh]

BETSY de PARRY: Well, I’m a slow learner, but I guess then, if that’s the correct explanation, then here’s where the confusion comes in. If you’ve achieved a complete response with chemo, and I think all chemos now are combined with Rituxan, so if you’ve got a CR at the end of that therapy, why would you even consider RIT if you’ve achieved that response? How effective could it be? Would you have any CD20 markers left for RIT to target?

DR. MARK KAMINSKI: I think that’s a fantastic question. Yes, that’s a great question. It’s one that I am wrestling with also and that’s why I’m much more enthusiastic about doing RIT in patients who have a partial response - something that I know that I can tell that I’m making some kind of headway with.

For complete responders, I think there really needs to be a better randomized clinical trial to show whether there really is any benefit. In my mind, I have a big concern that there may be very little target for these radioactive antibodies to go after and therefore that might not be the best time to use these radioactive antibodies. Maybe it is better in the long run – and we’re always talking about the long run, we’re talking about survival here – to reserve the radioimmunotherapy for a rainy day, at the first sign when the disease comes back, for instance.

That may be the best time to do it rather than adding on at that particular time, but again, this is a thing for clinical trials.

BETSY de PARRY: We've talked a little bit about using RIT in front line therapy, and of course neither Bexxar nor Zevalin is approved as a single agent for front line therapy, but I know that you've got one trial that I believe you started in 1996 using Bexxar as the one and only therapy, and I think you just recently updated that study. The results are astounding. Would you share them?

DR. MARK KAMINSKI: Yes, I'd be happy to. I think they're even more astounding from the standpoint of looking at it in comparison to what is currently being advocated. Now we're not just talking about just Rituximab being added to chemotherapy, but now we're talking about Rituximab added to chemotherapy plus two years of maintenance of Rituximab, and some people are even talking about Rituxan plus chemotherapy plus radioimmunotherapy as a consolidation, then even followed by maintenance. So the pendulum has swung so far in one direction that one wonders: what about the simple approach? Did you forget about radioimmunotherapy alone? Maybe more is not better, and maybe the best time to use it is in the front line setting by itself.

And in fact we did a study in 76 patients here at Michigan and we now have a median followup of over 10 years. And 95% of the patients responded to the treatment. 75% of the patients achieved a complete remission. And for those who did achieve the complete remission – remember, that's 75% of the patients – the median progression free survival is 11 years. Only half of the patients have relapsed after 11 years. And when we look at the overall survival of this group, 82% are still alive at ten years. So with a one week treatment, this is what's been achieved.

That's a pretty big hurdle to go over, and to think that adding more might be better, it doesn't make a heck of a lot of sense to me unless you want to go back and actually compare: well, what about single agent radioimmunotherapy – Bexxar versus these more complex treatments? The problem is the pendulum has now swung so far that if you do ask a patient to do – we call them randomized studies so somebody is going to assign the treatment to you by chance – one is, one week of treatment versus more than two years of treatment. I think it's going to be a hard sell.

BETSY de PARRY: I'll just add that I personally know some of the people who were in that trial and who took Bexxar as long as 14 years ago....and I am still in awe that they beat lymphoma without a drop of chemo and with a treatment that took only a week. It's amazing.

DR. MARK KAMINSKI: Well, I'm not alone in wanting to get rid of chemotherapy. Even the field is moving in that direction, but I think that it is quite remarkable that we now have patients out more than 14 years off that clinical trial.

BETSY de PARRY: Right, it is. Something else that you mentioned, and I just want to clarify for our listeners. I think your number was 82% of the people in that trial were still alive. If I understand again correctly, that doesn't necessarily mean that they are not alive because of lymphoma. They could have died from any number of things - and I don't know what they died from - but some of them could have had a heart attack or a car accident or died from other natural causes.

DR. MARK KAMINSKI: Well, of those that did die, most of them were lymphoma-related deaths, but there were other cancers and auto accidents so it's not all.

BETSY de PARRY: I just want to clarify – sometimes when we as patients are reading these trials, or reading the studies – and we say, “Oh, but 18% of them died,” it doesn't necessarily mean that they died from the disease. It takes into account everything.

DR. MARK KAMINSKI: That's correct.

BETSY de PARRY: That's the point I'm trying to clarify. Sometimes I hear patients say their doctors are reluctant to use RIT because there's not enough data, and this always confounds me because, as you say, you started your clinical trials in April 1990, and that was a couple of years before the first trials for Rituxan began.

DR. MARK KAMINSKI: True.

BETSY de PARRY: So as a lay person, I ask what is “enough” for doctors to accept and incorporate new treatments into their practices, and in regard to RIT, hasn’t an awful lot data accumulated in those 20 years?

DR. MARK KAMINSKI: No question about it, and it puzzles me as well. I think the one thing that the critics point to is the lack of what they call randomized clinical trials showing a direct comparison between RIT and another treatment. Yet many of these clinical trials were done in patients in which another different treatment would not have been appropriate because they already failed them all. So I think that a lot of people forget about that. However, there are some randomized clinical trials that are now maturing and we hope that we’ll see the results soon and we’ll get more ammunition.

But I think that there’s still reluctance to accept this because radioimmunotherapy is not something that the medical oncologist or hematologist can give in his office. He has to refer this patient to either nuclear medicine or to radiation oncology because they have the license to be able to give those doses of radioactive isotopes. In many ways it’s just like somebody who has finished chemotherapy or has failed chemotherapy and now it’s time for radiation – we’re referring them for radiation. Yet there seems to be a kind of fear of radiation in general that still is in the medical community and of course in the public as well. So I think there’s still a lot of education that needs to be done and to remind people. I think updating the data about where we are now, especially in long term responses – which is underway, by the way – may reignite the flame here. But there are some other barriers and a lot of them are not really rational.

BETSY de PARRY: You want to expound on that or shall we keep going?

DR. MARK KAMINSKI: Well, there’s one thing. We talked about the myths earlier, and some doctors have said that this is too inconvenient.

BETSY de PARRY: I have to interrupt you. The hair on the back of my neck raises when I hear this, and my answer to anybody who says that it’s too inconvenient for them – my answer is this: having lymphoma is awfully inconvenient for us patients, too. Period.

DR. MARK KAMINSKI: Exactly. And in fact, that’s a myth. It is not inconvenient. When was it inconvenient to refer a patient to radiation oncology? It’s not inconvenient. And there are economic considerations here because doctors in private practice sell drugs. That’s the way they can keep their office going in many ways. They cannot sell this drug so I think: patient beware.

BETSY de PARRY: So get the facts. Let me bring you back to talking about the data, and this again is something that really confuses me when I hear that there’s not enough data about RIT. If scientific data gives doctors and patients the tools they need to assess the risks and benefits of any treatment, I’m curious why some of the newer treatments such as maintenance therapy or bendamustine or any of the other ones are more commonly used when they don’t have the body of evidence that RIT does. But the bigger question really is – since Rituxan is a component of Zevalin, does anybody really know how effective RIT is if someone becomes Rituxan refractory or what the long term risks are, if any, of these newer treatments, and specifically of maintenance therapy which is so common?

DR. MARK KAMINSKI: I think what you’re alluding to is that the more we’re exposing patients to these other treatments, including maintenance Rituximab, are we creating a monster, so to speak, that even a treatment like RIT can’t overcome because of all this resistance that might develop and the patients might lose a chance for a long term remission because people have been fiddling around with this other stuff? It’s a really good question.

As far as resistance to Rituximab is concerned, both drugs, Zevalin and Bexxar, have been approved for use in Rituximab-resistant patients. However, when those clinical trials were done, they were not done on patients who were on maintenance Rituximab, who failed maintenance Rituximab – that’s a lot of exposure to Rituxan. We know that in a test tube, we can create, by exposure to Rituximab, resistant lymphomas. But anyway, in the non-maintenance patients, both RIT drugs work pretty well.

What’s interesting - and this is not a direct comparative trial, but just looking at the data side by side - the number of complete responses to Bexxar was more than double that of those to Zevalin in this particular situation, i.e., Rituximab refractory patients. And it might be because Bexxar uses a different antibody, a different anti-CD20 than Zevalin. Zevalin is essentially radiolabeled Rituxan. Bexxar is binding to a different part of the protein and it evokes a different immunological response than what Rituxan does. And so to me it makes more sense to try a

different antibody with radioimmunotherapy than repeating but just adding a little radiation with Zevalin in those particular instances. So that's my two cents worth.

BETSY de PARRY: I appreciate your explaining this because I think there are so many gray areas. Often time we don't have black and white, cut and dry answers. So you're the person who has the most experience with RIT and can explain it best.

DR. MARK KAMINSKI: Just one other thing. I often get patients who are referred here because they are interested in RIT and they're hoping that they're going to get RIT. And there are lots of patients in which I don't think RIT is appropriate or that they even need any treatment, so I think that we need to be very selective and I think the docs out there need to get more familiar with what RIT can and cannot do and then their comfort level in prescribing it will be better. But unless you get your hands dirty, it's not going to happen.

BETSY de PARRY: That's true. And that really leads me into the next question, and we're getting close to the end. I know I'm taking up more time than I had hoped to do. But studies are one thing. Real world results are another, and they do vary from practice to practice. I've heard patients say that their doctors have told them that in their practices, other treatments work "just as well" as RIT. And a few doctors have actually said that to me, but then when I ask how many doses of RIT they've given, they either don't answer or sheepishly admit to very few. So to me, that really means they're not as familiar or comfortable with RIT as they are with other treatments. So what would you say to anyone who says RIT works "just as well" as other treatments?

DR. MARK KAMINSKI: Well, there really is very little data to say that you can get the long term remissions with these other treatments that you can with RIT, and if you think that a treatment that takes six months to accomplish the same thing that takes one week to do is a better treatment, I beg to differ.

BETSY de PARRY: Get your hands dirty.

DR. MARK KAMINSKI: That's right.

BETSY de PARRY: Right. I think it's just been slow to be accepted, so as we get close to the end, if patients want to find out if RIT is appropriate for them, but their doctors either don't offer it or possibly don't have all these facts that you've shared with us, what in the world can patients do?.

DR. MARK KAMINSKI: I think that patients really need to be their own best advocates. Get educated. Go to websites and read about it. And also, if you're getting answers like "it's too inconvenient," or "I don't use it," or "this is dangerous," or "it's going to burn bridges," I think it's time for a second opinion. That second opinion may or may not confirm that you are an RIT candidate or not, but I think it's worth doing. And as far as where to go, I guess a starting point would be to look up a center that's associated with, for instance, the NCCN, or the National Comprehensive Center Network. The people there who are on the lymphoma panels are very cognizant of what RIT is, and if you look at the guidelines that they have for treatment of these lymphomas, RIT is all over the place.

BETSY de PARRY: Even as front line therapy.

DR. MARK KAMINSKI: Yes, even as front line in selected patients. So I think that you at least get a shot at getting a recommendation that I think is reasonable from an expert if you go to one of these institutions or somehow get information from them.

BETSY de PARRY: Let me just say to our listeners – the website for the National Comprehensive Cancer Network is www.nccn.org and you do have to sign up but it's free and you may have to kind of fumble your way through there but it does have every treatment recommendation for most of the types of lymphoma, and at the beginning of it, what Dr. Kaminski is referring to, is there's a list of doctors who meet every year and they set these guidelines so any one of them, I think, would be familiar with RIT.

DR. MARK KAMINSKI: I think that's a good place to start.

BETSY de PARRY: Yes, it is a real good place to start. Well, that's good information. So Dr. Kaminski, you have shared a wealth of information about RIT and I'm sure you've cleared up a lot of myths that we often hear. Before we close, is there anything else you'd like to say to our listeners?

DR. MARK KAMINSKI: Just keep your optimism up if you are a patient with these types of lymphomas. Not only is RIT very effective, but there are even other treatments that are coming down the pike. It used to be said that these indolent lymphomas were incurable. I'm becoming less and less of a believer in that incurable notion. I've seen patients who are living long periods of time without disease – beyond what we ever expected. This is a good time for patients with lymphoma and the options are out there. The trick is being able to maneuver with your doctor or doctors the right treatment at the right time for you.

BETSY de PARRY. Very good advice. Dr. Kaminski, so many people have had questions about RIT, and I know that everything you've said will help them understand it better and help them make more informed choices, so I can't thank you enough for sharing your time and expertise with all of us.

DR. MARK KAMINSKI: You're quite welcome, Betsy, and thank you for putting this on. I know how dedicated you've been to this and you're a consummate advocate and source of great pride and hope, and I thank you so much for all you've done. And good luck to everybody out there.

BETSY de PARRY: You're going to make me blush and I'm going to give you a compliment right back. Actually, before we close, I just want to say something that I've told you many times but I just want to say again now, and that is that those of us who live with lymphoma truly owe a debt of gratitude to you and scientists like you for choosing to spend your lives making ours better...So now we have the mutual admiration society.

DR. MARK KAMINSKI: I'm blushing now.

[Both laugh]

BETSY de PARRY: All right, well, as always, it's been wonderful talking with you, Dr. Kaminski, and behalf of the Lymphoma Foundation of America, I thank you again. And listeners, thank you for tuning in. This is Betsy de Parry, wishing you all an abundance of love and laughter.

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Reviewed and clarified for written transcript by Dr. Mark Kaminski