THE LACNETS PODCAST

With Randy Hecht, MD
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Transcription:

Lisa Yen
Welcome to The LACNETS Podcast. I'm your host Lisa Yen. I'm the LACNETS Program & Outreach Director as well as a caregiver and advocate for my husband who is living with neuroendocrine cancer (NET). In each podcast episode, we talk to a NET expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician.

Welcome, everyone! It's great to welcome you to The LACNETS Podcast. We welcome Dr. Randy Hecht who is our guest today. So before we get started, I thought I'd introduce our special guest, Dr. Randy Hecht who runs the GI oncology program at UCLA and is the Medical Director of the Neuroendocrine Tumor Program. He is very dedicated to clinical research and to patient care. And I want to add that Dr. Hecht and I have a personal connection. I've known him over the last seven years as my husband and I have been seeing him for his own personal care as well as in his journey with neuroendocrine tumor. So we're really excited to have you here today with us, Dr. Hecht. If you don't mind introducing yourself and telling us a little bit about how you got into the neuroendocrine tumor world.

Dr. Randy Hecht
Well, thank you so much. You all do such wonderful work. The idea that our conversation today can reach and hopefully help many people around the globe is really truly amazing. I really appreciate everything that LACNETS has done. So I'm actually originally a gastroenterologist before I became a medical oncologist. But I've always been interested in GI cancers. And I'm lucky to be at a place like UCLA, where I work with people who are wonderful physicians in many different groups. So that includes our surgical colleagues, our pathology colleagues, our radiology colleagues, and also our nuclear medicine colleagues. Being able to work with all of them really was part of what interested me in neuroendocrine tumors. You need that entire village in order to appropriately treat patients who have neuroendocrine tumors. Also, the patients tend to be extremely nice and you get to have personal relationships with them, which is another thing that I really enjoy. While we've significantly improved how we take care of patients with neuroendocrine tumors, there's clearly an unmet need, and there's a lot more that we need to do. And it's something that all of us, not just at UCLA, but all of us in the field are working really hard for.

Lisa Yen
Thank you for that and for really stepping up to meet that unmet need. And we know that you created the multidisciplinary NET team and NET tumor board there. You've really spearheaded that effort, so thank you for all you do. So with that, let's get started with our 10 questions for

today. Our first question for today is, do all NET patients need to be on lanreotide or octreotide? Also, what's the difference between the two?

Dr. Randy Hecht
If you step back, what we know is that almost all neuroendocrine tumors come from neuroendocrine cells. They are an awful lot like them. And what happens is that normal neuroendocrine cells are cells that make hormones. These hormones mostly, not all, but mostly help coordinate things like digestion. And the way that it works is that the normal neuroendocrine cell makes a hormone, and it affects another cell to do something. And once again, endocrine just means hormonal. And then that normal cell makes a turn off hormone, which is called somatostatin. In order for somatostatin to have an effect on the neuroendocrine cell, that there are neuroendocrine receptors. There are at least five different classes if you really want to get complicated, but basically, it acts almost like a satellite dish where there's a signal coming in. And usually that signals to turn off making those hormones. It almost works kind of like a thermostat where something is done. Then there are somatostatin receptors. Over 90% of low to intermediate grade neuroendocrine tumors also have somatostatin receptors. We can leverage that a number of different ways. One, we can leverage it by giving longer acting versions of that natural turn off hormone of which octreotide and lanreotide are two. They're the two that tend to be used in neuroendocrine tumors. There are others that are used for other reasons. And that natural turn off hormone only lasts for minutes. And that's what you would want in the body. But if you're trying to turn off a cell all the time, you don't want to be... In fact, in the original trials, people were walking around with IV poles and it was saving people's lives. But instead, first they came up with injections that you give several times a day. And now we have long acting versions that just require an injection once every four weeks or so. And what those do is that those basically signal through those somatostatin receptors. They are called somatostatin analogs or SSAs. Sometimes you'll hear [this with] people who say this a lot. And what happens is that they turn off those cells and they can turn it off a number of different ways. They can turn off the hormones, if that's a problem, that are made. And it can also, and this came out later, is that it can stop those cells from growing. That's one way we use the fact that almost all low to intermediate grade neuroendocrine tumors have somatostatin receptors. And we can also use those for imaging, like in dotatate scans, which also are basically radioactive versions of this. And we can also use this for treatment. And we'll talk about PRRT, if that hasn't already been talked about on the podcast, a way to actually kill these neuroendocrine tumor cells. But all of it takes advantage of the fact that almost all neuroendocrine cells have somatostatin receptors. The two drugs that are used for the treatment, the first one was called octreotide. That's basically an artificial long acting version of somatostatin. Lanreotide came out a little bit later. Once again, it's a long acting version. And both of them have been shown to have activity in tickling the somatostatin receptors to turn off hormones. In some patients who have neuroendocrine tumors, have functional tumors. If they're carcinoids, they can have carcinoid syndrome and these drugs are very effective in turning those hormones off. If they have pancreatic neuroendocrine tumors, some of them are functional and can have hormonal symptoms. And once again, these are very effective in turning those off. Even in patients who don't have hormonal symptoms, there are now trials to show that both of them will help keep the tumors from growing. They don't make the tumors shrink that much. It's uncommon for them to make them shrink, but they definitely can stop them from growing. The question also is one versus the other. I'm not aware of any true head-to-head comparison. They are a little bit different. One is is that the octreotide, which is also called sandostatin, is injected a little bit deeper. While the lanreotide or somatuline, which is theoretically deep subcu [subcutaneous], depending on the build of the patient. I'm not certain they actually go exactly where we think they go. Some people just seem to like one better than the other. Also some people will feel that they have more side effects with one rather than the other. I think there's less data from an anti-cancer standpoint about switching from one to another. There are things in the pipeline that are beyond this. For example, there are versions of

somatostatin receptors that are not deep subcu that are subcu alone. And there are already for other tumors, actually oral versions that block this that are being looked at. While these are helpful, they're incredibly helpful for those patients who have hormonal symptoms. They also are really incredibly helpful for stopping tumors from growing. I think that there's still a lot more to be done because nobody likes getting shots every four weeks. I think that, particularly, if we can get to the oral drugs, that will be a definite improvement for our patients.

Lisa Yen
Thank you for that really thorough answer and explanation of what's out there on the landscape and what we have to look forward to, as well. Our next question, how do I know what treatments I should be on?

Dr. Randy Hecht
Boy, that's a tough question. It's an easy answer, actually. It depends. One of the things that's really interesting about neuroendocrine tumors, and also very difficult about neuroendocrine tumors, is that there's so many different situations. For example, there are patients who can have their tumors completely resected. That's very different than someone who has tumors that cannot be cut out. Patients who have hormonal symptoms, as we were talking about, may have different treatments than patients who don't. Patient depending on if it's spread, where it has spread to, may have different treatments. For example, patients who have liver-dominant or liver-only may be eligible for liver-directed therapies. While people who have treatments in other parts of their body may not. I think probably the best thing is to talk to your doctor. The first thing that I would ask your doctor is, how many neuroendocrine tumor patients do you take care of? And I cheat because we get them referred in. Obviously, I'm saying this because I feel that patients are better taken care of by someone who treats a reasonable number of neuroendocrine tumors. You don't have to only do neuroendocrine tumors, but you have to treat a reasonable number of them. The other thing is, as Lisa was was pointing out earlier, is that it really does take a team to best treat patients. And for some patients, surgery is the best thing. Some patients medical treatment is the best thing. Some patients combinations of things are the best things. Working with our interventional radiologists. Sometimes patients have unusual tumors and working with our pathologists are really important. What I would say is that there is no one size fits all. And that's good. But what you really need is to talk to a group of physicians. You don't have one physician, you have one physician who is your quarterback who is backed up by an entire team. And then they can talk and decide what's best. I didn't really answer your question because there is not one answer to that.

Lisa Yen
That's helpful. As you said, it really depends. And getting to see a NET expert with a whole multidisciplinary team is important.

Dr. Randy Hecht
And to be fair, not every situation has a large randomized trial, the highest level of evidence. A lot of what we're doing is working with somewhat incomplete data. Now there are national and international guidelines. For example, NANETS has guidelines, that's the North American Neuroendocrine Tumor Society. The European ENETS, has guidelines, or even the Commonwealth one. There's also NCCN, which is a group of large cancer centers around the country. There's guidelines and all sorts of different types of tumors. But once again, it's not a cookbook. It's not one size fits all, but they're often very helpful.

Lisa Yen
With the quarterback that you or the patient is interfacing with...

Dr. Randy Hecht
It is quarterback season so yes, we can talk about quarterbacks.

Lisa Yen
So then they will help tailor the treatment for each individual.

Dr. Randy Hecht
Right. It's definitely not one size fits all.

Lisa Yen
Well, thank you for that. That's helpful. The third question is my doctor has recommended I take Everolimus or Afinitor vs. CAPTEM. What is the difference between the two? Everolimus, Afinitor vs. CAPTEM? How would I make that decision?

Dr. Randy Hecht
Both of those are medicines. That's first because remember I said they're a bunch of different ways that we treat neuroendocrine tumors--surgery, radiation, blocking off the blood supply. And both or all of them are oral. Everolimus or Afinitor or RAD001. We tend to use the generic names just so that you know that there is no generic of this. It blocks specific pathway, which is called the mTOR pathway, and is active in a number of different cancers. And that pathway is a signal to grow. And in fact, it's hijacking a normal signal to grow. And there are a number of different drugs that block this attack. These are derived from a fungus that was found from an organism that was found on Easter Island. And they have some activity in neuroendocrine tumors. In fact, there are randomized trials with everolimus in both carcinoids as well as pancreatic neuroendocrine tumors. While we often put NETs together, there are clearly differences between them. We tend to say, well, what what cells did they come from? Was it from the pancreas? Did they come from other parts of the body like the GI tract? Less commonly, did they come from the lung or even rarer parts with rare neuroendocrine tumors? There are commonalities but there are also some differences. While most neuroendocrine tumors will have some benefit from Everolimus (we were part of what was called the RADIANT trials), there does seem to be some difference.

Now, CAPTEM or CapeTem is a combination of two older generic chemotherapy drugs. Capecitabine is used in many different types of cancers, particularly GI cancers. Those are pills. The other name you'll hear is Xeloda with an x, because x's always sound cooler. That's also well tolerated and drugs that we use in frail elderly patients. It's combined with another drug which is called temozolomide, which is FDA approved for brain cancers. And a number of groups have shown that the combination of those two had significant activity in neuroendocrine tumors. Now, this is where the difference between where the neuroendocrine tumor came from. While there's some smaller trials that show that patients who have carcinoid or GI neuroendocrine tumors have activity, particularly grade one [or]grade two, basically neuroendocrine tumors tend to be very slow growing tumors, which is a really good thing. The way that we grade them is not just where they came from. That's one thing that we do, but also how rapidly they're dividing. And the ways that we can do that is a pathologist, not me, someone who does this for a living, looks under the microscope. You can go back to your high school biology and look at the number of mitosis or dividing cells, or there's an easier way, which is there's a stain called Ki-67. Or ki [pronounced "key"], some people say ki ("key") -67, I say "k" "i" 67. And that basically stains dividing cells. And we use somewhat arbitrary cut points, but many have very few. Those are Grade 1. Some have more but less than 20% of Ki-67. Those are Grade 2. Patients whose neuroendocrine tumors have greater than 20% are Grade 3, and there is not as big of a difference between Grade 1 and Grade 2. Grade 3 is divided into two different groups because we used to say, Grade 3 is high grade. But it turns out that there are patients who have Grade 3 neuroendocrine tumors that act a lot more like

Grade 1 and Grade 2 and are biologically much more like those. And to be honest, someone whose Ki-67 is 21%, their tumor acts a lot more like someone whose Ki-67 is 2% than they do with someone whose Ki-67 is 90%. They're different groups. There are ones that are called well-differentiated, meaning they look more like normal cells and have relatively lower Ki-67s, usually under 55%. And those patients act an awful lot like the Grade 1 and Grade 2. Then there ones are called poorly-differentiated, meaning they don't look like the cells they came from. And sometimes those are called small cell or large cell, depending where they look under the microscope. They often have very high Ki-67. They're a different beast. And they're really biologically different, genetically different. For example, they're much more likely to respond to chemotherapy.

Anyway, back to what I was saying, they are actually a little bit more likely to respond. For example, to CAPTEM. People have higher Ki-67s. Let's go back to the majority of our patients who have Grade 1 or Grade 2. We'll just say low to intermediate grade. If you divide not just by grade, but where they came from, and this is biology talking, patients who have pancreatic low to intermediate grade neuroendocrine tumors actually have a reasonable response, meaning tumor shrinkage or tumor not growing, to capecitabine and temozolomide or CAPTEM or Cape/Tem, I think that if you look at the data of patients whose neuroendocrine tumors are from the GI tract outside the pancreas, have a pretty low chance of benefiting. And we argue about this, but I think the data looks best. And in fact, the best data was from Pam Kunz's trial from the ECOG-ACRIN Trial, where the response rates were pretty high for either temozolomide or CAPTEM, and around 30% of patients had responses.

And let me define the term response, because my definition of responses and oncologist may not be the same as your definition of a response as a patient. We try to define things so we're all talking the same language. When you're in oncology, by response we mean a major shrinkage where the tumor has shrunk in three-dimensions by significantly less than half the original volume. That's not the same as benefiting our patients. We throw the words response rate out if someone's tumor shrinks a little bit, and they stay that way for a long time. Or even if someone's tumor doesn't shrink at all, but they stay that way, in good shape for a long time, that's sometimes called clinical benefit. But a lot of patients with pancreatic neuroendocrine tumors actually benefit from the combination of capecitabine [and temozolomide]. And I would say, if you asked my opinion that I think that's a much more active regimen than Everolimus; not that everolimus is not useful. But there may be other reasons why an oncologist would choose one or the other. But the major shrinkage rate with Everolimus this is kind of low, single digits. And I think that the amount of time spent on therapy is on average lower. Now that being said, it varies from patient to patient. I think back to a patient of mine who had a gastrinoma functional neuroendocrine tumor patient and he was on some of the original trials, and eventually we had to take him off because he'd been on so long the drug was already approved, and they had to finally say, it's closing time. We have to turn off the lights to the trial, but you can get the drug commercially. This person was on for more than five years. But that's uncommon. Was that a really long answer to a short question?

Lisa Yen
That was a really complicated question. That was really helpful as you helped us understand how you weigh those decisions. And let me throw out another one that's similar, but different. My doctor has recommended I take everolimus (afinitor) vs. PRRT. How would I go about making that decision?

Dr. Randy Hecht
The problem is that none of these have been compared head-to-head, which is really the best thing. The way I like to think about it is these are all tools that your oncologist and his or her team have in their back pocket. For example, most patients who have metastatic

neuroendocrine tumors end up on a somatostatin analog for a number of reasons. One, because often, though, not always, they're slow growing. Two, in general, the side effects other than being literally a pain in the butt, these drugs are generally well-tolerated. The question then comes, what happens if these stop working? And the trials have not been done to compare different options. But the trials were generally done in patients where a somatostatin analog like octreotide or lanreotide has stopped working. What I would say is that everolimus has been shown, as I've mentioned, both in pancreatic and other GI neuroendocrine tumors, and now more recently in other tumors, to have some some benefit, and that on average people, it takes longer for their tumor to grow than placebo.

Now PRRT. Let's go back to what I was talking about earlier. Remember, most neuroendocrine tumors have somatostatin receptors. And the question is, how can you tell? Well, one is statistically, most do. But remember, we can use them for imaging as well. Back a long time ago, they were called octreotide scans, which hopefully no one is ever using again, but you'll sometimes occasionally see. But instead, we have what are called dotatate scans. Dotatate scans are basically octreotide, where you've put a radioactive tag on it. It can be Gallium 68, or it can be, more recently, we have scans which are copper 64. The Gallium 68 is called NETSPOT. The copper-64 is called Detectnet, which we do at UCLA, and I think at UCSF. It's now beginning to spread around the country. I don't know if there are huge differences between them. And what those are, are basically, you inject those, and it has that tag, and it goes to cells that have somatostatin receptors on them. And using a special camera, they can say, well, one, does your tumor have those receptors? It's a functional way of looking at it. And second of all, where is it? And in fact, we found that a lot of people had spots of tumor in places we weren't really looking for that didn't show up on a standard CT or an MRI. And these are types of PET scans, but they're not the type of PET scan that most people get for tumors. Those are radioactive sugar or FDG. These are very specific ways of looking to see whether your tumor has the receptors. And if it does, then you would be a candidate. I'm not saying you have to have it right now. But you would be a candidate for what's called PRRT. PRRT stands for peptide receptor radiotherapy. But that's too long to say so we say PRRT. This has been done for decades with various hotter versions of that radioactive tag. I call it the "sriracha" version, because it's hot enough to actually kill the cells that it goes to. And a long time ago, they used other isotopes, we tend to use one which is called lutetium 177. And more recently, they've actually done the right thing, which is to treat it like a drug. Because as an oncologist, I ask does it make people live longer and feel better?

And they finally did a trial which was the NETTER-1 trial and the brand name for this is Lutathera, which you'll see. Which is lutetium 177 as the spice, the "sriracha" part. And that is FDA approved, and it's been shown to take a long time for the tumors to grow. It's harder to show overall survival because one, a lot of the patients who didn't get it initially ended up getting PRRT later. But it looks like patients probably live longer, and those are the things I care about. Then that would be another option. We don't know exactly when to use it because you can only use it so many times. And normally PRRT has been done a number of different ways. But the standard way is to give it once every two months for four treatments. You don't get really any treatment except for your octreotide or lanreotide in between. And the median, meaning the person in the middle, time before the tumor gets worse is generally between two and three years. Not everyone benefits and some people going significantly longer. That is one of the things that we can do. And the question is where to fit that in? And the answer is, I tend to do it earlier rather than later. But I would be the first person to say that those studies have not been done. There may be other reasons why you would choose one or the other, getting a little bit inside baseball. Oh, baseball season's over. But anyways, I tend to do it earlier rather than later. But there's some people that say no, I'd rather take pills, or it's hard for me to come in. There is no right answer for that. But if you were with me, I would say I tend to use it a little bit earlier. The other reason that sort of plays into the calculus of this is that you can only do it so many times. And as I said, you can be on Everolimus for years, though most people aren't

unfortunately. But there's mostly European data that after you do that, if the tumor does start growing, you can give salvage, and you can even give salvage again, there is no theoretical upper limit. But generally, it's been uncommon to get more than eight doses or cycles of this. And if I have patients who have very slow growing tumors, for example, who are really young, I may want to save that for later. If I have someone whose tumor I think is growing a little bit faster or I feel I need a response, I may use that earlier. As I mentioned a little bit before, I would say that pancreatic neuroendocrine tumors have a few more arrows in their quiver than carcinoid. For carcinoids, for example, I have fewer options. Once again a long answer.

Lisa Yen
This is really helpful. You and I have had many of these types of discussions about treatment decisions before. And I just wanted to follow up on one statement that you made, which is that you tend to use it earlier rather than later. And if you remember back, a lot of people used to try to keep it in their back pocket and use it last. What makes you say you would use it earlier?

Dr. Randy Hecht
When PRRT was finally approved, which meant the key thing was it was paid for. It's very expensive if it's not paid for. What was keeping it being done in the United States was not that it couldn't be done, it just wasn't paid for by insurance because it wasn't approved because it was done kind of locally. What happened was once it was approved, we had all these patients who had had multiple treatments before but had been waiting to get PRRT. They were getting it in their third treatment or their third anti-cancer treatment or their fourth or fifth. And now once those patients were sort of out of the way, the question came up what you just said. There isn't a right answer. And in fact, if you go to our guidelines, they list a number of different options. And this is when the oncologist really should talk to you as the patient. But at the end of the day, the patient is the boss. And our job is to help make suggestions and to lead and educate them. But as I said, I think that someone who had very slow growing cancer, for example, or neuroendocrine tumor, then you may want to wait a little bit and try other things. For example, NETTER-1, if you look, actually used a higher dose of octreotide. And there's European data. I don't think it was a placebo, I think it had activity in something that we do. Everolimus and CAPTEM is something that you can do. For my younger patients, I tend to save it a little bit. But if I have someone I feel that the tumor is growing more rapidly, or there's enough tumor that it's causing problems, and I feel like I need a response, I'm more likely to use it earlier. But in the average patient, and my average patient tends to be a little bit older. I have patients in their 20s and 30s. In the average patient, I tend to use it after patients have clearly progressed on a somatostatin analog like lanreotide or octreotide.

Lisa Yen
Okay, thanks for that. So that sounds like second line for you. This is good timing for the next question. Once I have had PRRT, what do I do next if the tumor progresses?

Dr. Randy Hecht
That's a really interesting question. Some of it depends on where the tumor came from. For example, if it's a pancreatic neuroendocrine tumor, I think capecitabine and temozolomide is a very reasonable thing to do. I just don't think that's a great option. Some of it may also depend on what the grade of the tumor is. The higher the Ki-67, the more likely you are to respond to chemotherapy, For example, someone who has a tumor with a Ki-67 of 20% and sometimes over time it does tend to go up a little bit. It doesn't go from 2 to 90, but it can go from 8, and then if you had a liver biopsy a number of years later, it might be 23% or something. And those patients may benefit from chemotherapy, different types, even carcinoid patients. The other thing is that there is salvage PRRT. And that has been looked at mostly in Europe because as I said, it's been available, meaning it's being paid for a lot longer. And usually what happens in salvage PRRT is that rather than giving the four doses that we would normally give, we usually

give two doses. And that's more because of side effects. Because the main side effects that we would see is if you give too much, tend to have to do with the blood counts. I can't say that there's ever been trials to show that two is different than one vs higher number. And if you look at the European data or repeat patients who've had a good response to PRRT, and in particular who have gone a long time before the tumor got worse, are more likely to benefit. I think patients who have pancreatic neuroendocrine tumors are also more likely to benefit them. And these cut points are arbitrary. They're not necessarily evidence-based. But at UCLA, if someone's tumor has gotten worse within a year after they started, they're probably not going to benefit as much or a lot less likely to benefit from salvage PRRT, and I'd be looking for something else. The other question that sort of comes up as interesting is that even patients where the PRRT has stopped working, we often were following these patients with functional imaging, meaning like a NETSPOT, or Detectnet, a gallium 68, or copper 64 dotatate, but they still maintain their positivity most of the time, which is interesting. One would think that you might lose that because you're killing the cells. But most patients who were dotatate positive at the beginning actually are DOTOTATE positive even if the tumor does grow eventually.

Lisa Yen
This is all very helpful. And as you know, you and I have had many of these discussions before. Would you also clarify for the audience, what salvage PRRT means?

Dr. Randy Hecht
Salvage means that it eventually stopped working. And as I said, we tend not to give the full dose. This has been worked out over years, over decades really. Two things-- one, that people do benefit. Now, that's not the case for most anti-cancer treatments that you're on all the time, that going back to something that didn't work often, not 100% of the time, but doesn't work. I think the reason that salvage, meaning giving it again, does work because remember, often patients can go for years after their last PRRT. And so it's not surprising that we don't eliminate the cells. We just kill a lot of them and eventually some of them grow back and they still have those somatostatin receptors so you can kill them again. Kind of like crabgrass.

Lisa Yen
Salvage is just repeating it again.

Dr. Randy Hecht
That's all it means. Thank you for correcting me. Sometimes I lapse into jargon. I'm always happy when people say please speak lay.

Lisa Yen
Okay, repeating it again. Of course, my husband had his first four rounds of Lu-177 dotatate PRRT and then he had it again, so that's salvage PRRT.

Dr. Randy Hecht
Exactly. It's mostly to say that we're not doing it for the first time. You could use other names-- repeat, doing it again.

Lisa Yen
That's helpful. Everyone's curious, how do I find out what new treatments are on the horizon for NETs?

Dr. Randy Hecht
There are a couple different ways. One is, of course, your doctor, and hopefully is the person who's been keeping up with this. They're extraordinarily human and certainly don't know everything. And one thing I would have to say is that if you're listening to this podcast, that

means you are active and you have agency and you're interested in your tumor. And while there's huge amount of disinformation on the internet, fortunately, they're actually very good places to find out information, which of course LACNETS is an extraordinarily good one. Other places are other similar groups as well. The other things that you could look at would be our national organizations like NANETS. Those tend to be not written in a format that's always patient-friendly. The more you go to people speaking jargon like "salvage" among themselves, sometimes is a little bit harder. One nice thing about the neuroendocrine community is this is an extraordinarily collaborative community. Starting at the bottom with the physicians and going to the top with the patients. If something works, the word gets out pretty quickly. Now, the question is, what's the definition of working well because at the end of the day, really what you want is a randomized trial to say that new treatment A is better than old treatment B. And sometimes it's new treatment A is better than nothing. If nothing is the right answer in that situation for those trials. Now, what I would say is that most of what we've been seeing is that I would divide new treatments up into two different groups. One, can we use the approaches that have already been shown to have benefit in neuroendocrine tumors? Are there ways to tweak and adjust those to make them work even better? For example, there are others [ways] like PRRT, which we just finished talking about. There are newer ways of trying to basically tweak the somatostatin receptor to try to use it. For example, using different emitters, like alpha emitters. Basically, different radioactive isotopes that you can hook on to something that will go to a cell that has somatostatin receptors. And that's been one of the things that there's a lot of research that's going on. There's a ferment of small and large companies looking at this, but that's basically the same pathway, the same way of doing it, but we know that it works? Can we do better? And I think possibly, but show me the data. And a little bit different than that, but also trying to tweak that, I actually happen to see at NANETS is using something that's been looked at in other cancers is trying to attach chemotherapy instead of radiation. In other cancers, people have been doing both chemotherapy and radioactive isotopes to kill cells. Historically, the chemotherapy attached has been more effective and only more recently, in a number of different cancers, for example, in prostate cancer has it been that radiation, which was the early front runner, has come roaring back. What I would say is that right now, that has not been that successful. There was a small abstract out of Emory looking at it. As someone who does this and other cancers, I would have to say that it's very warlike. The payload, or warhead that they used, I don't think it's a particularly active one. And I think that that there may be more umpf and that ways that have been looked at other cancers may be better so I wouldn't throw that out yet.

Other ways that we've been looking at to try to tweak things is that we know that drugs that hit the VEGF pathway, which is the vascular endothelial growth factor pathway, which is a pathway that your normal body uses to basically tell the body to grow new blood vessels. And we've known for literally for decades that drugs that block that pathway have at least some activity against neuroendocrine tumors. Antibodies have some modest activity, one called Avastin, or bevacizumab, though that has not been looked at as much recently. We know that there are pills which are sometimes called small molecule inhibitors. For example, sunitinib is actually approved in pancreatic neuroendocrine tumors. There are a whole bunch of these and what they do is that they block or muck up the signaling. These are different receptors, and different pathways that get turned on to grow new blood vessels. But the problem is that none of these are really that clean, and they probably hit a whole bunch of other pathways. And there are a number of drugs that are out there and some of them are probably more interesting than others. We know that some FDA approved ones like pazopanib or sorafenib, and I personally have had patients who have been on them, may get benefit. I don't think those are huge advances to be honest. I think the two that are probably being looked at the most, is surufatinib, which is a Chinese drug. It has some activity. I have to be honest, I was a little bit underwhelmed. I didn't think it was clearly that much better. It doesn't mean for an individual patient that it may not. I know they're going to the FDA to see whether or not they can get benefit. But if you told me that was clearly different and if you asked that data to me, looking at

it and it was some of it was recently published, is clearly different than the drugs that are already around. I'm not so certain. The one I think that I find most interesting is a drug that's already FDA approved, which is lenvatinib. Particularly in patients with pancreatic, there are some recent data that was just published with patients with pancreatic neuroendocrine tumors had a very high response rate. There was major shrinkage rate, and also had some benefit in patients who had carcinoids and other GI neuroendocrine tumors. That's not necessarily the easiest drug in the world. It's used in a number of cancers, particularly primary liver cancer, meaning it started in the liver cells. But all these are basically saying, can we do better with the pathways that we know about?

Now, the other question is, it's kind of like the old story about the drunk looking for his keys, and asks, Why is he looking, under the lamppost? Because that's where I can see. So, we keep going back to these same pathways over and over again. And I'm not saying that it's not useful and that better PRRT will help my patients and better small molecule VEGF inhibitors will help my patients. But the next question is, how can we do better than this? No one wants to have a small incremental, even though that helps patients. People want big incremental improvements. And in some cancers, immunotherapy has been really helpful. And unfortunately, for the vast majority of patients with neuroendocrine tumors, particularly those who have low to intermediate, the vast majority of these have been really a bust, I would say. And I think that the things that you see advertised on TV like Keytruda, which is pembrolizumab or Opdivo, which is nivolumab or any of the other 10 or 15 now very similar antibodies that have been looked at, the benefit in patients who have low to intermediate grade neuroendocrine tumors is slight at best. And we can have a separate podcast as to why that may be. It may be because those tumors actually don't have a lot of mutations and there's a correlation between number of mutations and clinical benefit. All those drugs basically try to get your immune system to identify the tumors as not you but as something that's foreign, and to kill it. And the problem is that not that that's impossible, have not been particularly helpful. And clearly, there are other things that we need to do to get your immune system to recognize that. Now high grade neuroendocrine tumors, and those patients unfortunately tend to do worse, they're more likely to respond to chemotherapy, but it tends not to last that long. Unfortunately, there is some data that the combination of two immunotherapies, nivolumab plus another one called ipilimumab, which has a terrible brand name of YERVOY. (They're running out of easy names and you can't do one that says "cancer be gone" or something so it has to be something that hasn't been used yet.) That combination is interesting, though the numbers are small. We were just talking about NANETS. There are a number of disappointing single agent trials or series of very small studies of looking at chemotherapy plus an immunotherapy or single agent immunotherapies in high grade. I would say that if you asked where I think the most interesting thing is trying from an immunotherapy standpoint, I would say because immunotherapies have helped in some cancers, there are lots of different immunotherapy trials out there. I would say that any patient with a high grade neuroendocrine tumor in particular, or who wants to do something else, a novel immunotherapy trial would be very, very reasonable for them. I think those patients are great candidates because we only have so many things that we can do, and we're trying to get that going.

The other place that I think we need to know more about is that we treat all these patients the same. How I divvy patients up could have been done 150 years ago by a pathologist. Count how many cells are dividing and what organ did they come from? And clearly, we would like to know which patients are going to benefit from which therapy, and are their patients who might benefit from therapies that we're not thinking about? Are there pathways that we can block? We know that blocking VEGF helps patients. We know blocking somatostatin receptors helps patients. There are lots of groups that are looking at this. It hasn't really borne fruit yet. I think it's reasonable, particularly for high grade neuroendocrine tumors, to do something called next generation sequencing, which looks at about 600 different genes. And most of the time, you don't find what's called an actionable mutation, something that would tell you to do something

different than you would do already. But occasionally you do. And those patients may have different treatments that are not in what we just talked about. And I think from a research standpoint, the genomics revolution, as it gets cheaper and cheaper, in order to not just look at 600 different genomes, but the entire exome, which is all the ones that are turned into proteins, or the whole genome, may lead to new treatments in the future. But as a clinical trialist, that's what I do also, in addition to taking care of patients. It's harder to do trials in 1% of a relatively uncommon tumor. We're still trying to figure out how to do that. Back to your question, we're going do what we're doing now better, and that will help patients. And we're desperately looking for new things, not just the same old stuff to help our patients.

Lisa Yen
Thank you for that. You're such a wealth of information. Thanks for giving us this overview.

Dr. Randy Hecht
Hopefully wasn't too much. I'm always happy to talk to people. And this is why it's really important for you to talk to your physicians, because if they can't explain it to you, then they don't understand it. And many of my patients understand things better than I do. Many of my patients with neuroendocrine tumors are extraordinarily well read and bright.

Lisa Yen
They are very empowered. The next question is would there be any treatments that negate future choices of treatment options or clinical trials, so I should I be aware of this in sequencing?

Dr. Randy Hecht
That's actually a really good question. I'm going to take that in two separate parts. One, are there treatments that I can get today that will mess up treatments I can get tomorrow that are already approved? And I'm going to put the other one a little bit to the side. And what I would say is not clearly, but theoretically. The one treatment that we haven't talked as much about, or I think I just talked a little bit about was liver directed therapies. And liver directed therapies have been around for a long time. And there are patients who benefit from liver directed therapies. And in fact, I would say neuroendocrine tumor patients probably benefit from liver directed therapies, more than just about any other cancer. One, that's often the only or dominant place where it goes. Two, because it tends to be slow growing, you get to have the advantage. If someone has a different type of tumor, let's say pancreatic carcinoma, cutting it out or destroying the liver doesn't really help a lot when it comes back in five different other places. But neuroendocrine tumors, those can be very helpful. And the problem is, because these are procedures, it's been very difficult to compare them against drugs. Remember, PRRT was finally treated like a drug. And they said, do people live longer and feel better? Which is what you care about. As opposed to, yes, we can do this. It's been harder to do that. Now, there are a couple of different ways that people do liver directed therapies. One, of course, is surgery. That's the original liver directed therapy. The liver is also amazing in that you can cut out or destroy two thirds of the liver and it will grow back in a relatively short period of time measured in weeks. There aren't any other organs that really do that. We sometimes block off the blood supply to neuroendocrine tumors, because they tend to actually trick your body into really, really filling it up with blood. Their blood vessels that grow to neuroendocrine tumors, and you can block that off, and that's called embolization. By putting a plug in of something to block off the blood supply. You can also put little radioactive beads that go to the little vessels in there, and that's called radioembolization. And usually the isotope that used is called y90. So if you hear people call y90, the y90 is just the isotope. It can be used for other things. There is some thought that people who get a lot of radiation to their liver from radioembolization may be some interaction between the two, though it's been really hard to show that in real life. The other possible interaction would be that some chemotherapy drugs can also suppress the

bone marrow, of which temozolomide is the one that actually has probably the most suppressive. Capecitabine by itself, probably not. Everolimus and small-molecule VEGF inhibitors really don't. Some chemotherapy drugs that we use like 5FU and oxaliplatin a little bit, but really, it's the temozolomide and other similar drugs that we don't tend to use anymore. There are a couple ways. If someone's blood counts are low because of temozolomide, it may be harder to get PRRT. Flipping it around the other way, PRRT, especially in a patient who has a lot of bone metastases. Remember the blood, both the red and the white and the platelets, are made in the bone marrow. So if you radiate that, by having radioactive, basically octreotide going to that, it may make a little bit harder to do that. And then there is a feared complication with both of them. Both drugs like temozolomide can rarely cause leukemias, and radiation (PRRT) has less than 1% of people can get leukemias. A little bit higher percentage can get something called myelodysplastic syndrome, which is a pre-leukemic situation. And as we've discussed, the combinations of those two drugs at the same time may be worse, though there's a limited amount of data. But none of those are absolutes. What I would say is that this is the art of medicine. This is the art of what we do. And that I certainly have had lots of patients who've had both PRRT and capecitabine and temozolomide. You have to just look and see what you're doing. As for trials, right now, there are no trials with drugs that are clearly a homerun. Trials come and go. I would not change anything that I'm doing for a potentially future trial.

Lisa Yen
That's all very helpful. I know this is difficult question. Thank you for this answer. And I'm glad you brought up bone mets. Another question that comes up often is what does it mean if I have bone mets? Does that mean my prognosis is worse? Or does it mean my tumors are getting worse?

Dr. Randy Hecht
Well, it depends. It's been looked at a couple different ways. One is, until we did dotatate scans, we probably missed a huge number of bony metastases in patients that were never clinically important. In other words, people had some spots in their bones. We couldn't see it on cross sectional imaging, that means CT or MRI, and they're there. And in the vast majority of patients, they don't cause problems. I think those patients who have a limited number that we would never have found anyway, I don't think it makes a big difference. If you look at these large series, they probably are worse. Does it mean that it's worse just because you have new spots? Or is it worse, because there's something specific about the bone. People have argued both ways. What I would say is that some of those studies are older and use older ways of looking for bone metastases. I don't think it's a total apples to apples comparison, as to someone who has modern dotatate scanning and finds a single small spot in the bone. This is very different than someone who has lots and lots and lots of spots in the bone. It doesn't change necessarily what I would do from a anti-neuroendocrine tumor standpoint. I take that back. What I would say is that if you have someone who had just a CT scan, and had liver metastases, and that would look like there was all there is and then they end up getting a dotatate scan and there are a lot of bony metastases, I probably would be more likely to give something that treats the whole body than liver only. That's one way it would change what I'm doing. Patients who have pain from a bony metastasis, that's a completely different animal and that needs to be taken care of whether it's by radiating it and occasionally patients have fractures and need surgery, but the percentages are pretty small.

The other place that it has affected what we do is that neuroendocrine tumors are one of the few tumors that actually can get liver transplants. And what I would say is that we used to do more of those. UCLA historically was the largest liver transplant program in the world. We transplanted patients who had neuroendocrine tumors before we did dototate scans. But that's only for people who have nothing outside of the liver. Since we're finding patients who don't

have symptoms with bony metastases, and therefore that would make them ineligible for liver transplant. I would say we're doing a lot fewer. Also, we have a lot more options instead of liver transplant. We really aren't doing very many of those anymore. Though, I still have patients who are alive and doing well who had liver transplants. The other question, which is something I've actually I've been thinking about recently is, what do you do with those bony metastases that are not causing problems? And the answer is we don't know for certain. We know that for other cancers, there are drugs that you can take, particularly for breast and prostate and other cancers, that they're drugs that are actually the same drugs we give to mostly women, but people who have osteoporosis. There's a class of drugs called bisphosphonates, like Zometa which is the brand name for one of them. Or another drug, which is an antibody, which is called denosumab which is advertised as Prolia and in low dose, we give patients who have bony metastases is something called Xgeva. Same drug, different doses. And the question is how well do they work in patients with neuroendocrine tumors? And the answer is, we don't really know. My reading of the literature is, they may, but it hasn't been looked at probably as closely as I would like. There is no such thing as a free lunch. Even though these drugs are well tolerated, they do have potential side effects. There are rare side effects called osteonecrosis of the jaw. And people have had either radiation to the jaw, or lots of teeth pulled. I have never seen that, thank goodness, but that's a bad one. I'd do it by the seat of my pants, and I think someone who has increasing bony metastases, it's another tool in my toolbox. Someone who has modest number of bony metastases and may have potential reasons not to give it, I don't. And our guidelines are similarly kind of wishy washy about this to consider things.

Lisa Yen
Thank you for that. I think that's a great overview of everything to do with bone mets. You've given us a lot of information somatostatin receptors and a good understanding of it. What about people who don't have somatostatin receptors? Should they still have the gallium dotatate scan? And if not, what tests or scans would you recommend?

Dr. Randy Hecht
There are two things. One, some places will still, and I've seen it but uncommon, do staining of the tissue, looking for somatostatin receptors, and that's not helpful. I have seen people say, someone did a stain and they're at least five different types of somatostatin receptors. The dotatate scan is the best scan from a functional standpoint. That's really the only thing that we really care about. And the reason is, because these pairs called theranostic pairs where basically same drug either a little bit radioactive so you can detect it on a camera, or very radioactive so it kills cells. But you're right, not everyone on a dototate scan is positive. And as I said, only about 90%. And what I would say is that, one, we don't know biologically enough about these patients as we should. Two, those patients should not get PRRT. What we know is that that would be toxicity without benefit. And there are different ways they compare. Interestingly, most of the original PRRT trials were done, if you remember with NETTER-1, with an octreotide scan, which is not a very sensitive way of looking at things. It takes three days, and it gives you blobs, and it's really hard to read. This is where I would also want my scan to be read by people who read a lot of them. You don't want to be at some tiny hospital out in the hinterlands. I know that sounds very elitist, but it really is true. They're both over and under calling things if they don't do a lot of dotatate scans. Before I would say that my scan did not show adequately. They used the liver and the spleen to compare with, called a Krenning score. And what I would say is that have it read or redone by a place that does an awful lot of them. The flip side we've also seen a reasonable number of overcalls, particularly what's called the uncinate of the pancreas or the knee of the pancreas where they're just normal neuroendocrine cells there. People are being told they have a metastasis, and the answer's no, that's being over read. Let's go to those 10%. I think that those are patients who unfortunately often are probably not. Their biology is a little bit different, and you clearly should not have PRRT. I'm going to flip that a little bit. We know that high grade neuroendocrine tumors generally do not

have enough somatostatin receptors to be useful. It's only about 10%. It's 90-10, 10-90, though it depends on on the trial. What I would say is that the patients who are in the minority of patients who are dotatate positive, particularly if it's a well-differentiated grade 3, those patients may benefit. Now the benefit, on average tends to be shorter. But if you're the patient who benefits longer, it's still worth doing. And there's a number of series to show that those patients who are dototate positive, it's worth doing, even if it's a grade 3. This is where it gets confusing. They tend to be FDG-PET positive. PET means nuclear medicine. FDG is radioactive sugar, and it goes to rapidly dividing cells. If 90% of your cells are dividing, those light up. Most of the time, it's one or the other. But there are some that are both PET positive and dototate positive. It's a useful thing, but my personal feeling is that if you're a place who doesn't do a lot of them and you're told your dotatate scan is negative, have your scan at least looked at or redone in a place that does an awful lot of them. Second is beware of overcalling, particularly in the pancreas.

Lisa Yen
That's some helpful practical tips. You've given us a really great overview of treatments that are currently available and treatments on the horizon and developments. Which of these treatments or other developments in this field are you most excited about? And lastly, what hope might you offer for those living with neoendocrine tumor or their loved ones?

Dr. Randy Hecht
What I would say would be, I think in the short term, we're much more likely to benefit from the tweaks. Whether better small molecule or VEGF receptor inhibitors or better PRRT, I don't think that there's anything right now, tomorrow or next year that is going to come out of the skies. People should continue to look. What we do is we do smaller trials before they do larger trials. And if you're unfortunately in that setting where the standard treatments have not worked or have stopped working, phase one trials or a small neuroendocrine tumor directed trial would be reasonable. If you're at a place that does not have multidisciplinary team -- I know this sounds like a broken and for those who are young, records are things people used to listen to that had a needle -- make certain that you get a second opinion before someone tells you that there aren't other options. Because often there are other options...if you squint. Now, for hope, what I would say is that the good news is that neuroendocrine tumors tend to be slow growing. And that's always great news for most patients with grade one and grade two. And what I would also say is, if there is a new treatment, everyone does not have to be helped. This is my doctor hat, which is that the person I care about most right then is the person who's sitting in front of me. And if that patient's helped, that's all that's important. I would say that I wouldn't do something that helps no one. That's not fair to you. But if there is a chance that something could help you, I would go ahead with it. And I think that the other thing for hope, which hope is so incredibly important and such an interesting word, is that if you went back 10 years or so there weren't a lot of people really looking in to the treatment or the care of patients with neuroendocrine tumors. There were were a couple isolated places that really had interest in it. And suddenly there is this explosion. Some of it has been the fact that we have active treatments. I think a large part has been because of the advocacy groups like LACNETS, and all the other advocacy groups that are out there, and people and patients and family members pushing and pushing. I know that there's a whole generation of bright young scientists and physicians and clinical translational people who are working on neuroendocrine tumors, when it was felt to not be that interesting 10 or 15 years ago. You have to go with the science. That generation of scientists are the ones that can come up with the new treatments. They're the ones who are going to tell us which treatments to use in which patients. And we were talking before we started that both of us attended NANETS virtually, when you look at the posters, all these bright young people in all sorts of different institutions who have decided to do their research in neuroendocrine tumors, is a really wonderful thing. And that generation, not even my generation, but that next generation, those are the ones that that I have hope for.

Lisa Yen
Wow, thank you so much for all of us. This has been so informational, educational, and hopeful. We have so much to hope for. In the last seven years that you and I have known each other we see how much has changed, treatments and developments, and the community as a whole.

Dr. Randy Hecht
Look how much NANETS has changed. NANETS is the North American Neuroendocrine Tumor Society and they used to hold meetings in very small conference rooms. And now, this is a large meeting that gets larger every year. And it's been powered by the advocacy community, and it's been powered by interest. Whether it's interest from government funded research, the government still does fund a reasonable amount of particularly, basic research. Or whether it's research from industry. There are companies that are out there specifically to look at and to treat neuroendocrine tumor patients that weren't out there before. That's just a perfect example of how things have changed in a relatively short period of time.

Lisa Yen
That's a really good point because there's more doctors, more physicians and experts like you.

Dr. Randy Hecht
Money is the mother's milk of research, and there is money out there. Whether it's from the advocacy groups or from the government or whether it's from industry, funding that research to help patients.

Lisa Yen
And like you're saying, more healthcare professionals in the room who are interested and willing to do the research, willing to fight and take care of patients and get the word out there and help us to live better lives. That's the bottom line. Thank you so much for all of this.

Dr. Randy Hecht
Thank you very much for inviting me and for all the work that you all do. Thank you.

Lisa Yen
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