NETWise
A Podcast About Neuroendocrine Cancer

Episode 39:
Immunotherapy
Transcript

If you're new to NETWise, we highly recommend you go back and listen to the first episode in this series. It goes over the basics of neuroendocrine tumors and how they're treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, where you'll also find infographics and videos that expand on this material.

If you have a story to tell about your own NET journey, please email us and let us know – podcast@netrf.org.

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Laurie Littlepage and her husband, Steve, are in the waiting game.

> ***Laurie Littlepage:*** *It's the kind of thing where we're literally waiting for a phone call and then we'll hop on a plane and go get the injections.*

Steve has pancreatic NETs, which he was diagnosed with in 2018. Since then, he's run the gamut of standard-of-care treatments.

> ***Laurie Littlepage:*** *First he did surgery, so he had part of his pancreas removed, two thirds of his liver, his spleen and gallbladder…He had a long time in which he didn't have any obvious tumors. Then another one appeared on his liver and, um, he had another surgery. He's also done capecitabine, temozolomide, he's done PRRT.*

Each time, the cancer would progress, then a new treatment would knock it back. Then it would progress again. And Steve's tumors are complicated – not all of them express somatostatin receptors, which is what makes targeted treatments, like PRRT, effective.

> ***Laurie Littlepage:*** *He has this heterogeneous tumor condition. So it's made us and all the doctors, the wonderful doctors who have worked with us, have to really think outside the box.*

This includes trying treatment options that might not be considered standard of care.

And Steve has done something else: he's had his tumors genetically sequenced. This opened up another possibility:

> ***Laurie Littlepage:*** *We're about to try an immunotherapy opportunity with a personalized vaccine.*

This is the phone call they're waiting on. Once Steve gets final approval, he's going to get an injection that will – hopefully – help his immune system fight his NETs.

You're listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF.

In each episode of this podcast, we share expert information and patient perspectives to help neuroendocrine cancer patients and caregivers navigate their journeys.

Lately, there's been a lot of talk about immunotherapy, which has transformed treatment for patients with some kinds of cancer.

So far, patients with NETs and NECs have largely been excluded from these developments. But there's hope that the benefits of immunotherapy could one day extend to NENs.

In this episode of NETWise, we're going to explore current research into immunotherapy, and what it might mean for patients.

Welcome.

We should be clear from the outset: Steve and Laurie are not in a typical situation. The immunotherapy Steve is set to

receive is not standard of care for NETs – it is a new avenue he has decided to pursue.

> ***Laurie Littlepage:*** *They've been doing clinical trials on these personalized vaccines and they've been doing them on a number of types of cancer. NETs have not been done yet. My understanding is that he's the first NET patient.*

There's no guarantee it will work – but Laurie and Steve are hopeful it will have a positive effect.

Immunotherapy has revolutionized treatment for some cancers, and researchers are working to assess its potential in treating NENs.

But what exactly IS immunotherapy?

Like the name suggests, immunotherapy is a treatment that uses the body's own immune system to fight a disease.

Dr. Dan Halperin is a medical oncologist at Winship Cancer Institute at Emory University in Atlanta, Georgia.

> ***Halperin:*** *In broad terms, I think of immunotherapy as really any intervention that is directly intended to use the immune system to attack the cancer. And that can take any one of a number of different forms.*

The idea of harnessing the immune system to battle disease goes back thousands of years. It's what brought us things like the smallpox vaccine in the 18th century, and more recently, things like monoclonal antibodies that have been used to treat patients infected with COVID-19.

When it comes to fighting cancer, some of the most significant developments in immunotherapy have occurred over the past 50 years. In that time, our understandings of both the immune system and cancer biology have increased by leaps and bounds.

Recently, that knowledge has resulted in highly effective immunotherapy treatments for some cancers.

> ***Halperin:*** *It's been transformative over the last decade or more, really, to have a number of different tumor types where patients can be treated with specific antibodies that unleash the immune system and really can give durable control, meaning, you know, we're very careful with the word cure, but durable, durable control for patients for a very long time, if not forever.*

These days, there are many different kinds of immunotherapies used to treat cancer. Some cancers respond well, and immunotherapy is used as a standard treatment. Other types of cancer, including most NENs, aren't treatable with current immunotherapies.

Today, we're going to talk through some immunotherapies that researchers are studying for potential treatment of NENs. But before we get to that, we need to understand how immunotherapy works. And to understand that, we need to understand the immune system.

> ***Pelle:*** *So the immune system is something that we have to control that everything in our body is working properly.*

Dr. Eleonora Pelle is a medical oncologist. She's currently a postdoctoral fellow at the Moffitt Cancer Center in Tampa, Florida.

> ***Pelle:*** *So basically the immune cells are like soldiers, right? Going around and checking that every single cell is healthy. So every time that they see something that is not part of our body, they fight against whatever it is.*

There are many different kinds of immune cells that defend the body against infection and disease.

Dr. Mauro Cives is an associate professor of medical oncology at the University of Bari in Italy.

> ***Cives:*** *So the immune system is composed by different cells, including, for example, T lymphocytes, D lymphocytes, macrophages, monocytes, eosinophils, basophils, dendritic cells, and so on. It's a very complex system.*

One of the most important kinds of immune cells are T cells – Dr. Cives just referred to them as "T lymphocytes," which is a more specific name. T cells are a kind of white blood cell that play a central role in immune responses.

These T cells identify enemies by noticing when things don't look normal.

Cancer is characterized by unusual mutations, which the T cells can recognize.

> ***Pelle:*** *When a normal cell is becoming a cancer cell, it will start changing some of its features, let's say. So these cells start having mutations or a change in their, let's say, aspect. So the T cells – or in general, the cells that belong to the immune system – can literally see that on the tumor cell.*

When the immune system is working well, it identifies these mutations and attacks tumor cells that arise in the body. This happens all the time – our cells are constantly dividing, and mistakes are not uncommon.

> ***Cives:*** *So consider that every day, each of us develops, in our body, tumor cells. But we do not develop tumors every day, luckily, because we have a healthy immune system.*
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> *Whenever we smoke a cigarette, we're getting mutations in our lung. Whenever we are exposed to carcinogens, we are likely to develop mutations somewhere in the body. Whenever we go to the beach and we're exposed to the UV in the sun, we can develop mutations in the cells of the skin. And that can ultimately lead to the development of cancer.*

For the most part, the immune system is able to recognize tumor cells and control this development. But not always. Cancer is a complex disease, and it can trick the defenses of the immune system.

While cancer cells often express mutations that attract the attention of the immune system, they can also do the opposite: cancer cells can figure out how to camouflage themselves against the immune system.

> ***Cives:*** *One of the main mechanisms promoting tumor resistance to T cells, or in general to the immune system, is the expression of several proteins on the surface of the tumor cells. And these proteins are basically able to mask tumor cells [from] the immune system.*

There are a few different kinds of proteins that do this. They are called "immune checkpoints."

> ***Cives:*** *In particular, there are several proteins such as PDL1 or CTLA4. In particular, tumor cells, including NET cells, do express PDL1. And PDL1, by interacting with its receptor on the surface of T cells, is able to hinder the recognition of tumor cells by the T cells.*

In other words, these immune checkpoints flip a switch that tells the immune system not to attack.

> ***Pelle:*** *So when that happens, the tumor cells start growing and T cells actually are not able to control this growth anymore.*

This is where immunotherapy can come in to help.

> ***Pelle:*** *So what we do with immunotherapy is to try to restore this activity that immune cells naturally have against tumor cells.*

So how exactly does immunotherapy work?

We mentioned earlier that there are several types of immunotherapy. Each one works with the immune system in a different way.

The most established form of immunotherapy works to counteract those immune checkpoints we just talked about.

> ***Cives:*** *We can tackle the mechanisms that the tumor cells exploit by using specific drugs that are able to inhibit these surface molecules, which are expressed by tumor cells, preventing their interaction with the immune system.*

Remember, immune checkpoints are proteins that can flip a switch telling the immune system not to attack.

One of the big breakthroughs in immunotherapy was the discovery of molecules that could flip the switch back the other way, and allow the T cells to defend the body again.

> ***Cives:*** *And in this way, we unleash the potential of the immune system against the tumor cells.*

These molecules are called "immune checkpoint inhibitors." And this kind of immunotherapy is called "immune checkpoint therapy."

This is a complex treatment, and talking about molecules is just one way to understand it. Dr. Dan Halperin says the way he finally wrapped his head around immunotherapy was when a friend of his explained it like this:

> ***Halperin:*** *If you imagine, you know, the cancer cells and the immune cells are acting like a classic middle school dance. And both are sort of present in the same dance hall, but not really interacting with each other or doing anything. Everyone is just holding up the wall, looking quite awkward.*

> *You can imagine immunotherapy as that dance song that's just so good that it gets everyone out on the dance floor together. And so everyone goes from just being at the dance, but not interacting, to actually mixing and mingling with each other. And of course, as everyone knows, that's when things really sort of get interesting. And allows, you know, relationships to happen, and has long term implications for both the middle schoolers and the control of the cancer.*

This kind of immunotherapy has revolutionized the treatment of cancer. It can stimulate a long-lasting response in the body, keeping the disease at bay for many years.

It is highly effective in treating melanoma, lung cancer, bladder cancer, and kidney cancer, among others.

But so far, it has not proved effective in treating most NENs.

> ***Halperin:*** *As much as it pains me to say it, I think the most important thing to understand about immunotherapy in the treatment of patients with neuroendocrine neoplasms is that outside of a few fairly circumscribed circumstances, it's not part of the standard arsenal.*

This is because the kind of immunotherapy we've been talking about, immune checkpoint therapy, works best against cancers that have lots of mutations.

These mutations are the "red flags" that alert the immune system to the presence of cancer.

Immune checkpoint therapy reactivates the immune system's ability to recognize the mutations in tumor cells. So the more mutations a tumor cell has, the more effective immune checkpoint therapy will be. The opposite is also true:

> ***Pelle:*** *When we have a cell with very little red flags on the surface, the immune system is not able to recognize that cell as a cancer cell in the first place. So obviously when we give an immune checkpoint inhibitor, we*

are not restoring any activity because there was no activity to begin with.

To put it another way: when there aren't many mutations, not everyone can hear the music at the dance.

Neuroendocrine neoplasms don't tend to have many mutations, and in general, this means immune checkpoint therapy is off the table.

Pelle: *What we studied so far in neuroendocrine tumors are immune checkpoint inhibitors. Those are very intriguing weapons and they worked very, very well for other cancers. But the results that we had for neuroendocrine tumors are probably… let's say that they show limited efficacy.*

There is some nuance to this: every NEN is different, and the amount of mutations can vary. This means that in some circumstances, it *is* something that doctors might think about trying.

Halperin: *What I would say is that for patients with well differentiated neuroendocrine tumors, there really has not been very much that's encouraging there. It really does look like, whether you use a ball peen hammer or a sledgehammer, the nail is just not there to hit and it doesn't really matter how hard you do.*

I think for patients with poorly differentiated neuroendocrine carcinomas…the best way I could describe the data is actually a little bit confusing. Some of the trials did seem to show really nice results and others did not show particularly encouraging results. And so I think that in the right circumstances for the right person, it's something to at least consider.

The one exception to all of this is Merkel cell carcinoma, which you can learn more about in episode 29 of NETWise. Merkel cell is different from most NENs, since it does have a lot of mutations.

> ***Pelle:*** *Merkel cell carcinoma is a skin cancer and is most of the time driven by the infection of a specific type of virus. It's the Merkel cell polyomavirus. And also the development of these Merkel cell carcinoma includes other factors like, for example, UV radiation and immunodeficiency conditions. So those conditions increase the amount of mutations that you can have.*

This makes Merkel cell carcinoma highly responsive to immunotherapy, and it is used as a standard treatment.

> ***Halperin:*** *So it's a very special case for a very special reason. And we're really, really glad that those patients can benefit from that therapy as well as they can. But it is a- it's almost the exception that proves the rule because it's probably the most clearly immunogenic of any neuroendocrine neoplasm.*

Aside from Merkel cell carcinoma, the benefits of immune checkpoint therapy do not yet extend to NENs.

But immune checkpoint therapy isn't the only kind of immunotherapy. There are many parts of the immune system that can be activated or suppressed, and many different features of cancer cells that can be targeted.

And researchers are working to find out if there are strategies or targets that could make immunotherapy an option for NET patients.

> ***Pelle:*** *We didn't give up when we saw that those treatments were not really working for patients with neuroendocrine tumors. And I'm very happy that there was a lot of big effort in trying to find other paths that are more suitable for the biology of neuroendocrine tumors.*

> ***Halperin:*** *There's a number of ways that investigators are trying to understand if it could be helpful for different groups of patients, and sort of looking at the problem*

from different perspectives, trying to get those transformative benefits.

At the moment, there are four new avenues for immunotherapy treatments that could potentially hold some benefit for patients with NENs.

The first of these new strategies is called CAR-T. You may have heard about it: there is some excitement around its potential to treat NENs.

CAR-T is an example of a kind of treatment known as cellular therapy.

Halperin: *So cellular therapy rests on the idea that if we could educate the patient's T cells specifically against a target on the tumor cells, then we might be able to induce a reaction. And it's worth noting that in other cancers, this has been really productive. And for some cancers we, you know, have agents available to patients that help them permanently clear their disease.*

Put more simply, clinicians can take T cells out of the body, and instruct them to attack and kill tumor cells.

Cives: *CAR-T cells are T cells that we get from the blood of the patients. Then the cells are grown in the lab, and then they are engineered in the lab. And then when they reach a clinically meaningful number, then they are reinfused in the patient. Then they circulate in the blood. They find the tumor cells, and they attack the tumor cells.*

The "C-A-R" part of CAR-T stands for chimeric antigen receptor. This is a molecule which is able to redirect the T cells against the tumor cells. With NENs, the T cells can be educated to look for targets uniquely expressed by the tumors, such as somatostatin receptors.

This is entirely different from immune checkpoint inhibitors, where a drug is infused into the body.

Cives: *So, in the first approach, we are actively reinforcing the activity of the immune system so that the same immune system of the patient is able to attack and kill the patient tumor cells. In the second approach, the CAR-T approach, we are infusing cells that have learned how to attack the tumor cells. Consider that, if you have an army, CAR-T cells can be considered a special forces.*

Halperin: *CAR-T, I think of as kind of the next step in the evolution, where we don't rely on the happenstance of that patient's tumor to tell the T cells what to react against, but rather we specifically tell them exactly what they should be targeting by introducing that receptor outside of the patient's body.*

NETRF has supported research into CAR-T. This has helped bring the concept from the lab, where it's been tested in mice, to the clinic, where it will be tested in people. There are currently two clinical trials set to begin testing CAR-T in patients with NENs.

Halperin: *I don't think anyone's been treated yet, to my knowledge, as of this recording. So we really have no way of knowing whether we will see the same thing in people that we saw in mice, because there is a wide gulf there for translation. But it is really exciting to think about the possibility of educating patients' T cells and directing them against the target*

So that's CAR-T.

The second immunotherapy approach researchers are investigating is called TILs.

TILs stands for "tumor infiltrating lymphocytes." Lymphocytes are a kind of white blood cell that is part of the immune system.

Cives: *So basically we get the lymphocytes from the tumor, then we grow the TILs in the lab, and then when they reach a clinically meaningful number, we re-infuse*

these TILs in the patient. These TILs will circulate, they will reach the tumor sites, and then they will attack the tumor cells.

The idea behind TILs is to increase the amount of immune cells attacking a tumor, hopefully making the immune response more effective.

Pelle: *So this way we can reactivate and restore the activity of these cells. So this strategy worked incredibly well in other neoplasms. For example, melanoma, and we are starting working on TILs in neuroendocrine tumors.*

There is currently one clinical trial underway investigating this kind of treatment.

The third immunotherapy strategy we're going to talk about today is known as BITEs.

Cives: *BI stands for bi-specific, T for T cell, and E for engagers.*

BITEs are molecules that essentially have two "arms." These arms can be instructed to grab onto different features of a cell. In this case, one arm can be told to grab onto T cells, and the other arm can be told to grab onto a tumor cell.

Pelle: *So what happens is that these molecules, they work as a bridge. They physically connect the T cell and the tumor cell. And doing so, they activate the T cells and enhance the release of molecules that eventually lead to the cell death.*

Researchers think this kind of immunotherapy could have potential with cells that don't have a lot of mutations, like neuroendocrine tumor cells.

Pelle: *So, as I mentioned earlier, what happens is that the T cells are usually not aware that the tumor is*

there. So trying to restore the activity will not work because there is no activity in the first place. In this case, we are activating cells that were never active before.

Researchers are testing different targets on the tumor cells for the BITEs to grab onto.

Cives: *In particular, BITES targeting DLL3 have been tested in patients with neuroendocrine neoplasms, in particular, high grade neuroendocrine neoplasms, and there is a lot of excitement going on, and it is my personal opinion that this kind of treatment may be approved in the upcoming years. Obviously, we need to gather more evidence on that, but preliminary results look really promising.*

Lastly, there is a fourth and final immunotherapy possibility we want to talk about today. It's one that everyone is familiar with for other kinds of disease. And that's vaccines.

Pelle: *We can have cancer vaccines. When we give a vaccine as we do with, I don't know, a virus or any other vaccine. And what we do is to present, let's say, part of the tumor, an antigen or like dendritic cells presenting this antigen. And then this way we basically prime and activate the T cells against the specific molecule, meaning that after this priming, every time that T cell encounters that specific antigen, it gets activated.*

This is the same mechanism that something like the flu vaccine uses. It introduces small pieces of a disease into the immune system, teaching it to recognize and attack the disease if it ever appears in full force.

Cives: *We are working on deciphering the antigen landscape of neuroendocrine neoplasms. Antigens are small proteins produced by tumor cells.*

And if we are lucky enough to target the right antigens, maybe in the future we will have both prophylactic

> *vaccines and therapeutic vaccines. The aim of prophylactic vaccines will be to prevent the onset of cancer. The scope of therapeutic vaccines will be to harness the immune system in tackling the cancer cells.*

This sounds exciting in theory, but the reality is still a ways away. Widely-applicable vaccines are likely to be more successful in cancers with a lot of mutations, which we know NENs don't typically have.

But vaccine technology may be able to be applied in more specific instances.

This brings us back to Laurie and Steve, who we heard about at the beginning of the episode.

Steve is planning to get a personalized vaccine for his pancreatic NET, based on genetic sequencing of his tumors. Once he's approved for the treatment, he'll travel to the Mayo Clinic in Florida and get his injection.

> ***Laurie Littlepage:*** *Best case scenario, the treatment could be an opportunity for his immune system to target his tumors, or at least a subset of them, but maybe all of them. So, I mean, theoretically, he could be cured. That would be wonderful.*

Laurie Littlepage, Steve's wife, isn't just a caregiver. She's a cancer researcher herself. Her work mostly focuses on breast and prostate cancer. She says it's been eye-opening to see how much more research goes into treating more common cancers, compared to NENs.

> ***Laurie Littlepage:*** *It's been really interesting as a scientist, also really frustrating as a scientist because, you know, there's certain advances that have been made and, just the numbers of people that study some diseases, some types of cancer, like breast cancer or prostate cancer compared to neuroendocrine tumors.*

There is so much research still to be done, and so many treatments still to be tested.

Fortunately, within immunotherapy, there are many innovative treatment options currently being explored. CAR-T, TILs, BITEs, and vaccines all hold potential – and our understanding of the immune system remains incomplete, so there could be even more in the future.

> ***Laurie Littlepage:*** *I think it's frustrating for NET patients that the immunotherapy just is not standard of care yet, right?*
>
> *But there's so much effort going into immunotherapy. We're at a really critical stage right now in which we're just learning so much. And advances are being made and there are a lot of clinical trials right now. So these will be standard of care before too long.*

What's critical, Laurie says, is to make sure that neuroendocrine neoplasms are included in these studies. So that in the future, immunotherapy can hopefully become an effective, standard treatment for NET patients like her husband Steve. For now, the hope is that his experimental vaccine will at least buy them some time.

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Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF.

This episode was written and produced by Anna Van Dine; post-production by José Miguel Baez; executive producer, David Hoffman.

This podcast is made possible by the generous support of Boehringer Ingelheim and Novartis.

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Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

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