NETWise
A Podcast About Neuroendocrine Cancer

Episode 18
High-Grade NETs and NECs:
Transcript

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Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. I'm Elyse Gellerman from the Neuroendocrine Tumor Research Foundation.

One of the most interesting and widely discussed features of neuroendocrine tumors is that in many cases they are extremely low-grade, meaning very slow to develop and spread. Often, treatment of these low-grade NETs can go on for years or even decades, like management of a chronic condition.

This is not the case for all neuroendocrine cancer, though. In rarer cases, these tumors can be very aggressive indeed.

Today we're going to turn the spotlight on the highest-grade and most aggressive neuroendocrine cancers, and talk about their diagnosis and treatment, which is very different from the way low-grade NETs are handled.

To begin with, it's really important that your particular neuroendocrine tumors are carefully examined before any treatment begins, because how they look and behave can completely change the treatment strategy. This is done by a specialist called a "Pathologist", who is an expert at evaluating tumor samples that have been collected from a biopsy or surgery. Dr. Laura Tang is a Pathologist at Memorial Sloane Kettering Cancer Center and a Professor of Pathology at Weill-Cornell Medical College in New York City:

> *Tang: "Making the correct diagnosis (is) extremely critical. I think it is the most important first step when dealing with this disease. The first impression is the architecture, how the tumor cells (are) arranged. That's one level, and then the next level is a cytological level. We look at how big the cells are, the ratio between the nucleus and the cytoplasm of the cell, as well as mitotic activities, as well as (what) we call nuclear pleomorphism. So these are the combination of features we evaluate all together."*

What a pathologist is trying to determine about the tumor really comes down to two characteristics — "grade" and

"differentiation". The first of these, grade, refers to how quickly the cancerous cells are multiplying,

> *Tang: "So the higher grade tumor tends to grow faster and they have a higher potential to spread."*

Grade is generally determined by using the "KI-67 Proliferative Index".

Here's Dr. Thor Halfdanarson, a Medical Oncologist at the Mayo Clinic in Minnesota.

> *Haldanarson: "So the way I think of KI67 is it's a tissue stain, so it's essentially a paint or a stain or an ink that stains tumor cells that are actively growing or proliferating. So you apply this, it sticks to a certain molecule on the tumor cells that's expressed when the cells are growing. So if you have a KI-67 of 20% in this tumor that we're looking at, 20% of the tumor is growing, 80% of it is not growing. But if it's 95%, it means only 5% of the tumor cells are resting, but the other 95% are actively growing. So it gives you an idea about how much of the tumor cells is actively participating in tumor growth and how much of the tumor is actually resting at any given time.*

> *Tang: "In general, a neuroendocrine tumor(s) have lower KI-67. Majority of them fall between less than five to less than 20. However, when it is greater than 20, we're dealing with a challenging issue."*

Grade is an important consideration when determining your treatment course, but even more important is the other indicator determined by the pathologist – your tumor's differentiation.

> *Tang: "Differentiation is how close the tumor cells resemble their lineage, where they come from."*

This terminology can be a little confusing. "Differentiation" refers to the process of cells becoming parts of distinct organs of the body: skin cells, lung cells, liver cells, etc. So a "well-differentiated" tumor cell is one that has successfully made itself look like a healthy part of your body.

> *Tang: "So (a) well differentiated tumor means that they are very similar to a neuroendocrine cell, a normal neuroendocrine cell, or neuroendocrine cell organ. So we can recognize easily the similarity."*

A "poorly differentiated" cell is actually more different from the surrounding cells – it has failed to differentiate into being similar to healthy liver or pancreas or lung cells.

> *Tang: "The poorly differentiated one is going to the different direction to the point that we can no longer recognize where it is coming from."*

This makes for a tremendous difference in how the tumor behaves. So much so, that it is common practice to refer to poorly-differentiated neuroendocrine neoplasms as a different

kind of disease — not Neuroendocrine Tumors, but rather "Neuroendocrine Carcinomas" or "NECs",

> *Tang: "For neuroendocrine tumor, it's always well differentiated, although it can be high-grade. But for neuroendocrine carcinoma, it's always poorly differentiated and almost inevitably high-grade. One must have a correct interpretation before treatment starts because clinically, the treatment is completely different.*
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> *Haldanarson: "The poorly differentiated tumor means that I need to get stuff going right now. So if I see a poorly differentiated metastatic tumor, that means I'm calling the chemo room, I'm asking them, 'When is the first available chemo slot you can give me?' I'm ordering a chemotherapy. With the well differentiated tumors, so you technically have weeks to think about the things and you can start looking for a clinical trial and things like that, and even have a person go for a different opinion somewhere else if needed, seeking out a trial or just another opinion, but with the high-grade neuroendocrine carcinomas or poorly differentiated tumors, we've got to move quick in most instances."*

The most aggressive of all neuroendocrine cancers is a variety of poorly-differentiated tumors called "small cell" NECs. Here's Dr. Namrata Vijayvergia, an Associate Professor of Oncology at

Temple University and Assistant Chief of Gastrointestinal Medical Oncology at Fox Chase Cancer Center in Philadelphia.

> *Vijayvergia: "And even in the high-grade, the small cells are the most aggressive versions of that with a very fast growing and multiplying rate. And these are patients that sometimes, if I hear about a patient on a Wednesday and we are going into a longer weekend, I sometimes admit the patients to get their treatment started. So this is, we call it one of the urgent situations in management of neuroendocrine cancers."*

And unfortunately, a particular kind of small cell NEC is actually far and away the most common kind of neuroendocrine neoplasm – small cell cancer of the lung. This is also one of the very few kinds of neuroendocrine cancer that has an identified cause. It's almost always found in smokers.

We're going to put small-cell lung cancer to the side, though, for the rest of this episode, because while it's technically a neuroendocrine cancer, it's an outlier because it has such a clear environmental risk factor, and because it's often discussed in the context of other lung cancers rather than other neuroendocrine cancers.

Aside from small cell lung cancer, NECs are very rare, and small cell cancers even rarer.

> *Vijayvergia: "Outside small cell cancers of the lung, only 10% of the neuroendocrine cancers are high-grade. And out of those 10 to 15% that are high-grade, about two or 3% of the small cell. So it's a very small fraction of patients."*

It's important to note that other kinds of NECs are NOT associated with smoking. This includes non-small-cell lung NECs and small cell cancers in places other than lungs. As with other kinds of neuroendocrine tumors, their cause is rarely known.

Like low-grade NETs, NECs can be found just about anywhere in the body, though there are a couple of primary sites they seem to prefer.

> *Vijayvergia: "In the GI tract, there'll be in the colon, in the pancreas, in prostate neuroendocrine cancers, as well as cervical neuroendocrine cancers, so female and male genital tract. And then also having an unknown primary is much more common for the high grade and the poorly-differentiated neuroendocrine cancers, than it is for the lower grade ones. Very often we see just disease all over, but there is no area where we can see where it started."*

Also like low-grade NETs, NECs most often metastasize to the liver, but NECs in the bones are also common, as well as the lungs and sometimes the brain.

Unlike the less aggressive tumors, they are often discovered because they are heavily symptomatic:

Vijayvergia: "So in contrast to the lower grade — you know, the NETs that we typically talk about — who, a lot of them, either they have carcinoid symptoms, patients, or they get diagnosed accidentally, right? When they had went in for something else and had a scan done or during a colonoscopy? Because they are not very symptomatic? High-grade neuroendocrine cancers are very symptomatic. Patients present with symptoms… the typical cancer related red flags we talk about: weight loss, loss of appetite, pain in area where they're progressing. These are the typical cancer symptoms in what we see… "B" symptoms, which means you have fever, night sweats and things like that. The patient presents with these symptoms and we end up doing testing and then we find out.

Haldanarson: "Unfortunately, a lot of them present with advanced disease with bulky liver metastases, dull abdominal pain, abdominal bloating, a liver that's enlarged and packed with tumors. If they are in critical locations, let's say some of the lower esophageal tumors, they can present with difficulty swallowing. In women with gynecological tumors, it could be vaginal spotting. In men and women with bladder tumors, could be blood in the urine. So it's a whole host of different things."

Treatment options are very different from the ones available to low-grade NET patients. For one thing, surgery is usually not a

good option, because it's very rare to catch NECs before they have metastasized.

> *Vijayvergia: "Typically, in low-grade neuroendocrine cancers, even if it's back to liver, if you can get it out, you should take everything out. In this disease, once it spreads outside the local area, there's definitely no role for surgery.*
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> *The most likely cause of death in these patients is not that the local cancer is becoming a problem, it's because it's spread to other places and causing problem there. And spread happens very early on in this disease. So even if you cut out the local area, the time it will take for you to heal up from that, that you would be considered for chemotherapy, it'll be too late and would have spread to other areas. And now, you have actually maybe more debilitated and unable to get chemotherapy for all that time, while we see the cancer's on the loose."*

In addition, treatments that make use of somatostatin receptors are not often useful with NECs.

> *Vijayvergia: "So somatostatin, you know (a) very small group of these patients are those who secrete any —or those who have carcinoid syndrome — that giving somatostatin analogues helps. For most of them, it really does not help and we don't think that somatostatin analogs alone can*

treat this disease by itself so we typically don't use them."

This includes PRRT as well as somatostatin analogues.

Vijayvergia: "A lot of these patients, even the ones who can get it, they don't have as good as outcomes with PRRT than we see with the low-grade cancer, low-grade NETs, or even the high-grade NETs, which are well differentiated. So I typically do not consider that as a good option at least at this time. Hopefully with time, we will have newer studies where we can amp up PRRT a little bit more, and then we might be able to treat these patients. But right now, we don't use that as much.

So what are the available treatments for NECs? Let's start with some that actually make use of the fact that these are such high-grade cancers. Because they are dividing so much, it opens the door for more mutations and genetic alterations to appear in their DNA. If these can be found, they can sometimes be targeted with medication, which can sometimes slow tumor growth significantly.

Vijayvergia: "So low-grade neuroendocrine tumors rarely have a lot of mutations. Okay, so there, the benefit of doing molecular testing, it's not as useful as it is for the poorly differentiated high-grade. These tumors are fast dividing cancers and they tend to Harbor a lot of mutations in them. What that means is that the genes in the cancer

cells, the DNA, it has a lot of new changes that is sort of stimulating the cancer cells to grow really, really fast."

Haldanarson: "So we now have these incredibly powerful tools to look at hundreds and hundreds of genes. And the tumor sample… we take a tiny little tumor sample, we sent it to a lab, and they look at hundreds or even thousands of genes and they find mutations or other kind of alterations. And sometimes we have a drug for this.

For example, a few years ago, there was a report I believe from Stanford, where they looked at patients with colorectal neuroendocrine carcinoma and found a mutation in gene called B-RAF or B-R-A-F, which we see in colon cancer and in melanoma and thyroid cancer fairly frequently. And now we have drugs that actually targeted this mutation. There is a gene called RET, R-E-T, which is commonly seen mutated in thyroid cancer and commonly seen with a fusion in other types of thyroid cancer. And there is now a drug that works for this. So we have seen patients with what's called RET fusion neuroendocrine carcinoma that have had a fantastic response to these new drugs.

These mutations are pretty uncommon, probably well under 5% of neuroendocrine carcinomas, but this is one of those things that if you don't look for it, you're not going to find it. There is nothing about the appearance of the tumor that would suggest this mutation being present. So I offer everyone what's called genomic sequencing, or deep sequencing, of these tumors now. I think everyone with

high-grade neuroendocrine tumor, especially neuroendocrine carcinomas, should have these tests done."

Patient Story:

Hammell: "My name is Hilary Hammell. I'm 38 years old. I live in Minnesota in the Twin Cities area. So, I'm a family physician primarily in a clinic setting, although I also work in a hospital setting as well. So basic primary care, children to older adults. I'm married to a wonderful husband and we have two kids, a nine year old and a seven year old. And I have neuroendocrine carcinoma, poorly differentiated. They think it's a lung primary. (I) was diagnosed stage four. On diagnosis, it was pretty much all over lungs, lymph nodes, brain, and bones.

So, we're coming close to a year now. It was April, late April, and I was sitting with my in-laws. We were chatting and I was rubbing my neck and I felt a rock above my clavicle. And I was thinking like, "What is that? That seems weird," and it occurred to me very quickly that that was not a good thing. I had had some vague symptoms prior to that. I had been feeling really tired and nauseated and I was blaming some of those symptoms on stress and whatnot. So, it all sunk in when I felt the lymph node that, "Oh, something's going on this time."

Got in, saw my doctor pretty quickly, ran some tests, had a chest x-ray done that showed a lung nodule, lung mass,

which led to a CT scan and the diagnosis of probable cancer. Although you don't know for sure from an imaging test, the radiologist thought it could be a fungal infection, possibly tuberculosis. And so I had a biopsy the following day, which ultimately confirmed neuroendocrine carcinoma.

It was really hard. Stage four cancer is not curable, and I know that, and I know how bad it can be. And so I went a little dark at that moment and it was not great. I think one of the first few things I was telling my husband, I went and assumed the worst. And so I told him, "It's okay if you get married again." And that's probably not, in hindsight, what my spouse wants to hear when I'm first diagnosed. So we had a lot of tears and a lot of those moments where you're just both dealing with this horrific life change together.

We didn't tell my kids right away, we waited a little bit and then sat them down and... my husband also got involved with a caregiver support group and I talked to a lot of friends and doctors and whatnot about how best to communicate with my kids… and so we were prepared that they'll ask questions, they'll ask, "Does this mean you're going to die?" And lo and behold, when we sat them down, that was one of the questions that they asked, so we needed to prepare to give them an appropriate answer to that, with a terminal condition. So we told them that… by that time, I think we knew that I had a treatment… and so we explained

that there's really good treatments and really good doctors and, 'right now things are going to be okay. If anything changes, we're going to let you know.' So it was a really hard conversation. I think I kept it together without bawling my eyes out, but probably did a lot of crying before then and after that.

So it was about five, six weeks before I finally got on treatments. What I did to cope as best I could is find as much information as I could. Reading everything I could, learning about what doctors I needed to see and trying to move along my appointments and advocate. I mean, that was a way of coping, I guess. In primary care, we see a little bit of everything and so I've been involved in patients getting the starts of a workup for cancer, and then I've also seen and managed patients who are dealing with cancer related side effects or complications in the hospital. So you see cancer quite a bit, but it's a very specialized field, oncology, and so the day-to-day stuff is not part of my world as much. And so I've learned quite a lot actually, being a patient.

I don't know if I've even had a patient that I've seen with NETs, or certainly, never diagnosed a patient with NETs, so I had to learn a lot. And then once we finally got me on treatment, then I felt a little bit better. That five, six weeks was pretty… pretty shocking.

There's other layers to that. I all also have a known oncogenic driver mutation: RET fusion. And so once we found out that I had that fusion, or that mutation, there's a newly approved RET inhibitor that's targeted therapy, and it was just approved a few years ago. And it turns out that no matter, it likely has a tissue agnostic indication, meaning whatever tissue it comes from, be it neuroendocrine cancer, be it thyroid cancer, et cetera, it tends to work.

So that was started right around June of last year and I've been on it ever since. So it basically, it shrunk all my tumors. I had six brain lesions, they disappeared on imaging. All the imaging sites, bones, lymph nodes, all disappeared except for, now I'm down to just a centimeter and a half lung lesion that remains. So it worked remarkably well, almost a complete response and I'm stable. Yeah, I know I'm really fortunate to have had something targetable. And I know that's not often the case with neuroendocrine carcinoma.

It's hard to parse out the data, but for those who have had previous multiple lines of treatment but go on this medicine, on average — or median — response is about 17 months before progression. And so eventually, I will progress on this, everybody does, but hopefully I'm on the opposite side of the median before I do progress. And I hope I can ride the wave of scientific progress for many years. And I try not to get too fixated on the prognosis other than that."

Because these tumors are so aggressive, the average prognosis for patients with poorly-differentiated neuroendocrine carcinomas is very different from patients with low-grade NETs

Vijayvergia: "Unfortunately, I have this discussion more often than I want to with my patients. We never want to play God, but from the data we have, we know that the average life expectancy for poorly differentiate neuroendocrine cancers is in the order of 11 to 14 months. With treatment, that's the survival. If we don't treat, it's less than three months or so."

Haldanarson: "This is where it gets really difficult because these numbers look bad. If I had 100 patients in my clinic today, all showing up today with metastatic high-grade neuroendocrine carcinoma, they would tell them, "Go home, get the treatment with your local oncologist, come back in February 2023." And less than 50 of them would come back, and probably a lot less than 50. Meaning that these are incredibly hard diseases to treat.

But sometimes they respond really well. And these are numbers derived from groups of people, not individuals. So I always tell my patients in the clinic that "You are not a group of people. You're an individual." And every now and again, as with other cancers, you just head it out of the park with the treatment and sometimes with chemotherapy, sometimes with immunotherapy. Increasingly we're finding

that the small minority of these have actionable mutations for which we can use some of our newer treatments.

So I'd say yes, average life expectancy is probably less than a year. The chances of being alive two years from diagnosis of metastatic, poorly differentiated neuroendocrine carcinoma are less than 20%. I think that's a very fair estimate that's been shown in multiple different studies… but huge variability. And I've seen people, and still, I'm seeing people in the clinic who are now on their third, fourth year, and still dealing with this, with to disease and responsive therapy. I think we can be sort of realistic and optimistic at the same time.

Susan Meckler-Plummer is a Registered Nurse who runs support groups for patients with NECs

Meckler-Plummer: "How long do I have? Nobody can answer that question. You can get dragged down with the fear and the stress of it all… but get to somebody who knows how to treat this disease. The right specialist will give you the most time you can get and will always have a plan when this fails. After a couple months, we'll go to the next treatment, and the next."

There are treatment options, though. And while none of them are curative, they can increase life expectancy and quality of life. The targeted therapies we just discussed work in a small

percentage of NEC patients. For the rest, the first-line treatment is almost always chemotherapy.

> *Vijayvergia: "These patients need to start treatment sooner rather than later, that's the bottom line. And chemotherapy is what works for them."*

We haven't talked much about chemotherapy yet in this series, so let's take a minute to learn about what it is and how it works.

All cells in your body multiply by splitting themselves in half – one cell into two, and then again, and then again. This is how your body grows and heals and replaces cells that are no longer functioning properly. The primary characteristic of a tumor is that the tumor cells are dividing faster than the healthy cells in the surrounding tissue. This creates an imbalance where there are too many of these new cells and they start blocking normal body function, which is what makes you sick.

Chemotherapy drugs are designed to seek out cells that are rapidly dividing and damage them in such a way as to prevent them from dividing further.

> *Vijayvergia: "Basically, these are drugs that go in and kill actively dividing cells. Because fast dividing cells need new DNA to be made; they need new DNA to give to the daughter cell. And so there are different processes involved when the DNA separate out, and the new DNA cell stuff comes in, and they attach and then they move on. And what these chemotherapy drugs do, in different phases of*

this cell cycle, they block different steps in that process. And when they arrest them, these fast-dividing cells die."

Some of the harmful side effects of chemotherapy occur because tumors are not the only fast-dividing cells in your body, and these agents don't do a great job of distinguishing healthy rapid cell division from cancerous rapid cell division.

Vijayvergia: "Part of their collateral damage, they cause damage too fast dividing cells of your body. So blood cells are the best example of that."

Haldanarson: "So white blood cells and platelets, they're constantly being produced in the billions every day. So the bone marrow is packed with blood forming cells. And the bone marrow gets hit pretty hard with the chemotherapy, as innocent bystanders will. So that's why we see, after the chemotherapy, you see a drop in the white blood cells and platelets.

Another example would be the hair follicle. We're constantly producing body hair. And once you disrupt all of that, you see the hair loss, which is very common with this aggressive chemotherapy. For platinum Etoposide, it's almost always complete hair loss."

Vijayvergia: "Linings, so the linings of the skin, the lining of the mucus membrane, in the mouth, nose, in your

intestines. You can get diarrhea, sores in the mouth. These are all from the inflammation."

Haldanarson: "Essentially, the cells in the body that divide rapidly, most notably the bone marrow, will definitely take some beating from chemotherapy."

There are a number of different chemotherapy regimens that have proven useful in treating NECs.

Haldanarson: "So they work in a slightly different way, but essentially all trying to mess up the multiplication of tumor cells.

For example, the platinum Etoposide drugs, these are called the alkylating drugs, and they essentially just glue the DNA strands together, in a sense. Some of the drugs actually are what's called antimetabolites, so they are drugs that look similar to building blocks of DNA. So the body will actually use them as building blocks, but they turn out to be pretty lousy building blocks. So the DNA can't really be replicated if the drug is being incorporated into that DNA."

There are oral chemotherapy drugs for some cancers — meaning they can be taken as a pill — but most of the ones used to treat NECs are given intravenously, so patients have to go to a hospital or infusion center in order to receive them.

Vijayvergia: "Typically, patients have to get blood work done beforehand. After the blood work's done, what they do is, you see the doctor, and the doctor approves that the patient's okay for treatment. We typically put a port in for these patients. A port is basically like a dime or a dime sized reservoir, in which it just gets implanted under the skin on your chest. One end of it goes into the big veins in the neck, everything is like a tunnel under the skin. And so then once everything heals up, you don't see anything on the surface. It's all under the skin. But you can feel that dime shaped reservoir. So every time you need chemo, they basically find that dime shaped reservoir and put a needle in it. And it's a much safer and a stable way to give chemotherapy so that the chemotherapy doesn't spill in the arm. And once they put it in, it can stay for blood draw, for the chemo, for the four hours, if they need fluids, everything. So it's just a one stop shop, sort of.

And then, so what they do is they go into the infusion room, and then they first get a lot of nausea medicines, and some medications to prevent side effects from the chemotherapy. It's called pre-medications. And then once that soon half an hour after that is when the actual chemotherapy drugs are administered."

Haldanarson: "So as an example, a platinum Etoposide was a very common regimen. If someone was starting on that today in my clinic, they would get two drugs today, IV will take

about three hours..."

Vijayvergia: "You know, so it's probably a half day affair, to get chemotherapy at a center. And with the wait times and everything, probably the whole day is what most patients spend there."

Haldanarson: "…and then we come back on the next two days with only one drug. And then they will go for three weeks without anything.

The one I'm using a lot, for pancreatic and colo-rectal neuroendocrine carcinomas, is a regimen called Folfirinox. So then now we use three different chemotherapy drugs, that are called Fluorouracil, a drug called Irinotecan, and a drug called Oxaliplatin. And then if you were starting that today, you would be in the clinic for about five hours, getting medications for nausea, things like that up front, the IV fluids. And then he would go home with a chemotherapy pump that slowly delivers chemotherapy for two days, or 46 hours to be precise. And then you would come back two weeks later and we would repeat this, and we'll do scans roughly every two months."

In addition to things like hair loss and low blood counts, these treatments can cause a lot of short-term side effects.

Haldanarson: "Everyone seems to get tired. Especially the days and week, maybe the first week, after chemotherapy.

That's where you feel really tired, and that's where people want to take it easy.

Some of them can cause diarrhea. This drug called Irinotecan can cause diarrhea in a number of patients, sometimes actually pretty severe diarrhea.

And then the platinum drugs, oxaliplatin, carboplatin, and cisplatin, can cause nerve damage. So it can be a transient disruption of nerve function leading to cold sensitivity. If you touch something cold, your hand may go all numb and tingly. If you drink something cold, your throat may go numb. Or with time, you can get this more real nerve damage, what's called the neuropathy. Numbness, tingling, you can't button shirts, do fine motor to tasks. And sometimes that is permanent, that doesn't go away.

Oftentimes it gets better over time, but some people are left with permanent nerve damage, so you got to be really careful with that. These are powerful drugs."

One piece of good news is that in the past, chemo was often accompanied by debilitating nausea, but there are new medications now that control that much better.

Haldanarson: "So nausea used to be a huge problem in oncology in years past. Now we have such great nausea medications that we can control nausea in most of our patients with chemotherapy by giving upfront the nausea

medications. And then in the days following the chemotherapy, on the regular schedule, give a certain, maybe two or three different types of medications for nausea. So there can be some nausea… the uncontrollable vomiting of chemotherapy in years past is rarely seen now, And I tell some of my patients with the chemotherapy I give, like platinum etoposide, or Folfirinox — which is really hard chemotherapy — I am not seeing much vomiting anymore."

The tendency of chemotherapy to reduce production of blood cells can also cause a wide variety of side effects, some quite serious.

Haldanarson: "Where we struggle the most now is platelets. We don't have a really good drug to bring up platelets. And if the platelets drop really low, you are at increased risk of bleeding. So when you have really low platelets, the type of bleeding you'll get would typically be like nose bleeds, maybe blood blisters in your mouth. You might see blood in your urine or blood in the stools. And little tiny dots called PPTI in the skin. So those would be the typical bleeding, but occasionally you can have a major catastrophic bleeding, like a brain bleed, or a bleeding into a massive bleed into the stomach. So that's why we need to be really careful with that."

All-in-all, the side effects of chemo vary quite a lot from person to person.

Meckler-Plummer: "It affects everybody differently. One person may be fine, and not have any symptoms. I know of people who sailed through chemo, never sick, never missed a day at work, just kept going, and going, and going. Another person may be in bed for 20 hours a day."

Vijayvergia: The body reacts differently to chemotherapy. So you might be somebody… and if you feel miserable and horrible, like if the chemo is making you feel more miserable than the disease, well that's the time to stop. It's not a one way street. It's not that, 'this is what I'm going to do. I have to continue it'. Take a treatment, see how you feel. If you don't feel well, we'll stop. If you feel well, we'll continue."

Chemotherapy can do a good job of slowing or even pausing the growth of tumors for a while, but unfortunately it is not curative, and inevitably becomes less effective over time.

Vijayvergia: "The problem is that whenever we treat these cancers, there's a group of cells that are not going to respond to chemo, because they're resistant to chemotherapy. And what happens is, the chemotherapy goes and kills the cells that are, (and) you see initial shrinkage in the tumor. What happens is the ones that are sensitive are killed, the resistant ones are not killed. Then what happens is, with time, it's just the resistant one that stays. And as a result, they become the dominant

variant and then start growing. And then, despite chemo, we are seeing the cancer start to grow."

So if it's only effective for a short time and has the potential to cause all of these side effects, why take chemo at all? The short answer is that the side effects of chemo, as bad as they might be, are often less severe than the symptoms of uncontrolled disease. And an increase of life expectancy from a handful of months to a year or more is a positive result.

Haldanarson: "A lot of patients come in very symptomatic, and they have a good response to the treatment, and they start actually feeling better. So I tell them that there are two goals in the treatment: one is to prolong your life, and the other one is to maintain or improve your quality of life, or at least maintain it or keep it from getting worse."

Vijayvergia: "I want to make sure my patients are doing the best. Why do I offer them chemotherapy for a limited benefit? Well, because I know that out of those 13 months, I can make sure that 12, 10 or to 11 of them, are going to be great. When you're going through the process, you know that this is a way that we can actually make you feel better."

And chemo is not the only option for these tumors. In some cases, radiation therapy might be used. This is a technique

where x-ray beams are aimed at a tumor, causing an effect that can be similar to surgery or ablation.

> *Vijayvergia: "Radiation is a less invasive version of local therapy. It's also slightly less effective than surgery, but it's also slightly less invasive. And as a result, we use that very often in localized disease. So somebody who had localized disease, and we gave them chemotherapy and they're doing great, we love to consolidate their treatment with some radiation, which means you zap the area up for whatever cancer cells. You know, I told you some other… You know with chemo there are some resistance cells? And with the radiation, we can go and kill those resistant cells locally, hoping that maybe those resistant cells were not the ones that spread anywhere else — If they did, unfortunately cancer comes back down the line — but hopefully, we can.*
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> *The other setting where radiation is used is actually in patients who have metastatic disease, but they have pain related to one area. So it's for palliation, which means that what it does is it can control that local tumor. And if control of local tumor can ease the patient off the pain, or if there's bleeding associated with the cancer, it can control those things very well."*

Another option that is often explored with these tumors is immunotherapy. While this has not been an effective approach to low-grade NETs, in neuroendocrine carcinomas, it may be an

option. This is where you are given medications that change your own immune response to make your body attack tumor cells the way it would normally attack things like viruses and bacteria.

Haldanarson: "It's almost like the system you have on your computer to detect spyware, so it's always running in the background, and they're waiting for an invader and what's typically would be an infection or something like that. And so it's essentially trained to attack the things that look different from the rest of your body.

But obviously, it's not seeing cancer cells. Cancer cells look very different from other cells, but for some reason, they escape this recognition by the immune system. So the immune system is up, the surveillance is on, but the cancer is growing quietly there in some corner. And the immune system is not seeing it. And one of the reasons for that is that the immune system is these effector cells and killer cells in the images. And they're held back by these natural brakes.

Because if they didn't have these natural brakes on, they would just run around and kill a lot of normal cells. And that's what is called autoimmune diseases, where you have your immune system out of whack, and it's actually attacking normal cells. So these drugs, and there are two broad categories of these drugs, interfere with these natural breaks.

So we sort of lift the brakes gently off the immune system, so now it gets a little bit more aggressive, and starts seeing, and successfully attacking cells. The interesting thing is that some tumors are much more sensitive than others. This all really started with the melanoma skin cancer, which is still to this day, a pretty uniquely sensitive tumor. One of the neuroendocrine tumors, which we haven't talked much about, is one of the poorly-differentiated neuroendocrine carcinoma called Merkel cell carcinoma. (It) starts in the skin, and immunotherapy is incredibly effective against it.

But the problem is, with immunotherapy is that when you lift the brakes of the immune system, now it starts attacking normal body parts. And that's actually what we've seen. These drugs can cause autoimmune diseases from pretty much every organ system, every part of the body. I don't think there's a single part in the body I have not seen attacked by your own immune system after we get these drugs.

But thankfully, mostly it's manageable. I will also say that, if you look at these side effects of immunotherapy and you compare it to the side effects of your classic multi-agent chemotherapy, on average, I'd say the immunotherapy side effects are quite a bit less."

Because this is a swift moving and incurable disease, all of these treatment strategies — chemo, immunotherapy, and so forth — are designed to help you feel as good as possible for as long as possible. Be open, as you're going through them, to all kinds of palliative care. Things like pain management can make a big difference in your quality of life and working with a palliative care specialist does not mean that you've given up on treatment, but rather that you're using every possible tool available to you.

> *Meckler-Plummer: "Don't turn pain medicine down if you need it. There's a lot of people that do that. Be comfortable. Palliative care is wonderful, which is something that I tell people from day one, from the day of diagnosis. Get palliative care involved, whether it's dealing with anxiety, pain, any kind of discomfort, any of the side effects from chemo or the disease."*

There are also lots of non-medical resources that are out there for people with serious illness and their families, things like support groups, social workers, and therapists. They can make all the difference.

> *Meckler-Plummer: "Because you can't do this alone. This is something you need a team, you need people.*
>
> *There's a whole community out there that will support you, that will be there for you, through whatever you need,*

through diagnosis, through end of life. And that can make an entire difference in what you're going through."

And know that many in the research community are working hard to come up with new and better treatment options.

Vijayvergia: "People had not heard of doing studies just specifically for poorly differentiated cancers, like never done. Now we have special studies just for the poorly differentiated neuroendocrine cancers. I am working… I have completed one, I have another one that's in the books that we are working on, because we understand it's a rare cancer, but it's such an important cancer that the area of unmet need is so high. And it's definitely a lot of work to be done there."

Thanks for listening to NETWise. I'm Elyse Gellerman, CEO of the NET Research Foundation. This episode was written and produced by David Hoffman of CitizenRacecar; Post-Production by Garrett Tiedemann *(TEE-da-min)*; Production Manager, Gabriela Montequin *(mon-ta-KEEN)*. It was made possible by the generous support of Advanced Accelerator Applications, a Novartis Company, and TerSera Therapeutics. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the Neuroendocrine Tumor Research Foundation, we're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer by funding

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