[MUSIC PLAYING]

GRACE CAMPBELL: Thank you, all. It's great to be here. I have my work cut out for me because I'm following several really great presentations, as well as following dinner. So hopefully, you'll all be awake enough to hear some of what I have to say.

I'm going to talk a little bit about peripheral neuropathy. And when I was asked to speak about this I was a little bit overwhelmed because this is an incredibly large topic. And so I've made a couple of decisions about what to cover here.

I'm going to talk about chemotherapy-induced peripheral neuropathy. Because in cancer survivors that's what we tend to see the most. And so I'm going to focus a little bit on that.

I have no financial conflicts to disclose. I do want to acknowledge my research funders, and I'm grateful for that support.

So let's talk a little bit about chemotherapy-induced peripheral neuropathy. It's one of the most common dose-limiting toxicities of chemotherapy, which is a little bit odd because it's not life-threatening like some of the others, like renal toxicity. But it really does impact people's lives as we have heard earlier today, and hopefully I'll talk a little bit about as I go.

Peripheral neuropathy from chemotherapy-- CIPN-- is seen in sort of three forms. There's sensory neuropathy. There's motor neuropathy. And then there's autonomic neuropathy, which is more about those nerves that innervate the body organs, the viscera.

We tend not to hear about autonomic neuropathy so much in cancer survivorship. But there is some emerging literature to suggest that it is actually more common than we think. And so some of our patients' symptoms, such as shortness of breath, may actually have a neuropathic origin, as well as from low blood counts and things like that.

So the pathophysiology of the CIPN is not well understood. There are a number of theories out there as to what may actually cause the CIPN. This diagram is from a nice review on the subject by Susanna Park. And I recommend it if you're interested in the details of this.

There have been a variety of theories, including disruption of the ion channels in the nerve cells for transport, inflammation, actual demyelinization from direct effect of the chemotherapy on the nerves, and mitochondrial dysfunction. And it's starting to look like the type of etiology varies based on the drug that's used. And so that is going to have obvious implications for discovering medications to treat and to potentially prevent CIPN.

So a brief note about epidemiology. So prevalence is estimated to be anywhere between 10% and 80% of patients receiving some of our most common chemotherapies-- platinums, taxanes, vinca alkaloids, as well as others-- experience CIPN. Well, OK. What does that mean? 10% to 80%? Why don't we have a better handle on this?

Well, again, just like the pathophysiology, a lot of the research into the prevalence-- the prevalence estimates tend to vary based on the drug that you're looking at, the cancer population that you're looking at, how you're defining CIPN, how you're measuring CIPN.

I would say kind of a good ballpark figure that I've seen a lot in the literature is anywhere between 40%, 50%, 60% of people will experience some degree of neuropathy at some point during or after their treatment. And there are a number of risk factors that increase the likelihood of getting CIPN. And I've listed some of them here for you. And these are documented in the literature.

So clinically, CIPN presents in a classic stocking-glove pattern, which means that it's mostly the hands and the feet. And it tends to have a distal to proximal progression. So it begins in the very tips of the fingers and the toes, and it progresses proximally.

There's a little bit of a debate in the literature as to whether it is actually symmetrical or asymmetrical. Some authorities in the field will tell you that it's always symmetrical, and that if it's an asymmetrical presentation that's something else, like a plexopathy.

I'm not sure I believe that. I'm not going to argue with authorities in the field. But I know many rehabilitation clinicians and many patients who really-- it does seem to be an asymmetrical chemo-induced neuropathy. And I see some of you nodding out there, so I think I'm not wrong here.

It presents most frequently clinically, at least as we describe it as clinicians, as numbness, tingling, and pain. There's also often allodynia, so things that should not be noxious stimuli cause intense pain and discomfort like bed clothes, things like that-- much like neuropathic pain from shingles. There's also some heat and cold sensitivity as well.

And then there may be some other descriptors though besides numbness, tingling, and pain that our patients use to describe neuropathy. I got interested in that idea when I read a qualitative study done in 2007 by Marie Bakitas. And she interviewed patients with CIPN. And it's really a very elegant study. And it's big, and I'm not going to go through all the results.

But one of the things that I found intriguing about this was that the words that patients use to describe their neuropathies often tend to be more clustered around sound-type words. So they describe sensations of buzzing, ringing, zinging. They even made sounds in their interviews to describe the sensation.

And so I became really intrigued by that. And I was looking at the literature a little bit more, and I found another study that was done. This was a quantitative study. Boyette-Davis's group looked at patients after receiving paclitaxel. And they measured them at two different time points. They measured them after completion of treatment, and then, I want to say, about six months later.

And what they did was they gave them checklists-- long checklists of descriptor words. And they had them just indicate which of those words most closely matched their experience of neuropathic pain or discomfort. And some of these are what we would expect. There's numbness, tingling, burning. But some of them are really kind of interesting. Spreading, tugging, drilling, flickering-- these are not words that I would have associated with CIPN.

And I saw some of this in a pilot study that I did recently where I had patients who would say to me, my legs feel heavy. And so that brings me to my first clinical pearl for today, which is that patients may describe neuropathy in terms other than sort of those textbook words that we as clinicians tend to look for.

So when we're interviewing a patient and we ask them, do you have any problem with numbness and tingling? They may say no, but I have this weird sort of spreading in my feet. OK. We're all thinking, OK, no neuropathy, and we're moving on. So the clinical pearl is that's a clue that maybe we need to stop and do some more focus-probing questions about what they're experiencing because it may be neuropathy.

I'm going to talk a little bit about assessment of CIPN. There are two sort of prongs in assessment. There's assessment of actual nerve function. And then there's assessment of impairments that sort of derive from nerve dysfunction.

In this picture, this is electromyography. That is sort of the gold standard assessment method for nerve function. It involves a probe either applied to the skin, or a needle inserted into the skin that applies an electric stimulus.

And then they're able to measure all sorts of things all along the path of the nerve, such as conduction velocity and amplitude of the wave. And they can measure action potentials and those kinds of things. And electrophysiologists and neurologists can actually interpret this-- and physical medicine rehab docs-- can actually interpret those readings and make a diagnosis about what kind of neuropathy is going on.

Well, it may not surprise you to know that people don't want to go and have this done. Does anyone really want to have somebody sticking a needle that's electrified into them? No. So it's really hard to get patients to go and have these tests done, particularly when they're in the middle of cancer treatment.

And also, there's a question of access. At UPMC we're very lucky. We have a lot of places throughout the system where EMGs are done. In rural centers, in small community hospitals, in areas where patients don't have a lot of economic resources to pay for co-payments to go and have these fancy tests done, there are some real access issues making them somewhat not practical for clinical use sometimes.

So there are other things that we can do. We can assess nerve function using some more sort of clinically bedside appropriate types of tests. There are certainly patient-report outcome instruments that are aimed at assessing neuropathy. And we use a couple of those in our research.

And there are also these sort of clinical bedside measures of CIPN including the monofilament test for light touch and the vibratory tuning fork for vibration sense. There are also hot and cold sensitivity tests, but those are a little bit more difficult. And these are the two that you tend to see most used at the bedside.

Now, then there's assessment of physical function and impairments related to the nerve damage. And yes, that is in fact me in the picture on the left. So, yeah, I had nothing better to do that day.

So this first picture on the left is what's called a NeuroCom machine. This is a computerized balance assessment tool. It lives here at UPMC in the Eye and Ear Institute. And what happens is you stand on those force plates, and the force plates move and the picture-- the visual surround moves. And they do those movements in various combinations, and they can test various aspects of your balance. And you get some very granular quantitative measures of postural sway in various planes.

And then the picture on the right is a gait mat. It's an instrumented walkway. It connects to a computer, and it measures gait parameters-- not just velocity, but it also measures things like cadence, the rhythm of your gait. It measures stride and step, width and length, and the variability in those parameters which are highly linked to-- they're highly prognostic of fall risk.

Again, just like the nerve function test, these gold standard physical function tests have some lack of practicality to them. They aren't very accessible. Again, we have, I think, one in the UPMC system. It's at Eye and Ear. Who wants to go to Oakland and park if they don't have to? Certainly, none of us. And certainly, none of our patients who are undergoing cancer treatment. And we actually tried to get patients in one of my pilot study to do this, and they really did not want to do it. And the other thing is, again, access. Rural centers, small community hospitals don't have this kind of equipment.

So again, we can use some more clinical measures. We can use patient-reported outcomes instruments to ask about physical function and impairments. And we can also use some brief objective clinical tests.

In my work, I use the short physical performance battery. There are many others. But the SPPB has been used in other cancer studies. And it's very quick and very easy to do-- doesn't take a lot of space. And it gives you balance, gait, and strength kind of in one test. So it is a great test to use.

However, it also has some drawbacks, as I think many of these physical function tests have. It's a timed test. So individuals are asked to hold various poses for a certain number of seconds. Originally, it was 10 seconds when it was validated with older adults. There's literature out there suggesting modification to holding for 30 seconds in cancer survivors and other populations that aren't quite as ill or frail.

In our pilot study, even asking our patients to hold for 30 seconds, pretty much all of them could hold these positions for 30 seconds, even after six cycles of chemotherapy with a lot of nerve function damage. But we were still getting a ceiling effect. They could all hold for 30 seconds even though we could see that they were having a lot of trouble maintaining their balance. And they were telling us, this is hard. I'm working hard here. Something is not right.

So we started looking for better ways to measure the sort of more sensitive granular changes in balance and gait. I was fortunate to receive a Career Development Award from the Oncology Nursing Society. And I went to learn about how to use the gaming sensors, as Dr. Bender mentioned, to use in the clinic at point-of-care to assess balance and gait changes.

And so, the beauty of these is that you do a simple test, like the SPPB that we've already been doing in the clinic. On the picture on the left, you can see there's a little sort of a sensor on a tripod. This is the same kind of sensor that is in my son's Xbox. And the Wii has it, the PlayStation-- all of them have that.

It's on a tripod. It connects to a computer. The frame in the middle is what the assessor sees on the computer screen. It guides you through administering tests like the SPPB. And at the end of the 30 seconds it calculates postural sway in all the various planes, same as you would get from the NeuroCom machine.

Now, you might be concerned that people don't want to have themselves videotaped. Even though the operator-- the assessor-- sees that actual color video, what is saved in the computer are these shadow pictures. This is the depth image that is saved. And the computer software uses those depth images to calculate the postural sway parameters. That can also be used to do the same kinds of gait things that you would use with an instrumented gait mat. So it can calculate things like cadence and stride, length and width variability, and those kinds of things.

So we're about to start a pilot study where we're actually going to use this in the clinic at Passavant and Magee and see if we can actually use this, use it feasibly, and get information that would be valuable to rehab clinicians to use for treatment planning, so that they don't have to try to get patients to go in for these sophisticated tests.

So the clinical pearl here is that assessment is key. And assessing early and often is key. Assessing nerve function-- ideally, prior to starting chemotherapy-- as well as physical function and frequently throughout chemotherapy is really important.

I'm going to talk a little bit about treatment and management. So let's talk pharmacologic treatments. There are a lot of drugs that we all use out there for treatment of neuropathy symptoms. The really best evidence out there in terms of an effective treatment is duloxetine. It's an anti-depressant-- SSRI or SNRI-- I can't remember. And it's been demonstrated in a very nicely done clinical trial that it does tend to decrease painful CIPN.

There's no-- they didn't actually look at people's function though. So just because their pain was decreased, we're not sure whether it actually helped their physical function. The other thing is we don't know if it helps people who don't have a painful neuropathy presentation. There might-- the numbness-- we're not sure whether duloxetine helps.

Chemo dose reduction is actually another pharmacologic measure. Obviously, that has survival implications. Dose reduction-- my personal soapbox is that that should not be a neuropathy treatment. But we don't have a lot else to offer people right now. So that is still one of those things that we tend to see done.

I have had study participants who have said to me, I don't want to tell my clinical team that I have neuropathy because they're going to cut my chemo. And I need my chemo. So, you know, dose reduction is really just not a fantastic option. So I would encourage people to use some of the management techniques that I'm going to talk about instead of just cutting chemo.

Now, opioids pretty much don't work on neuropathic pain. That's fairly well known. But we are using a lot of things like gabapentin, pregabalin, vitamins, calcium and magnesium infusions, those kinds of things which may work for some people. There's not good evidence.

That doesn't mean they don't work. But what it means is there's not good across-the-board evidence that this is really a well-established treatment. So this is a trial-and-error process. And that's another reason why it's so important to be talking with our patients about what they're feeling, so that we can try all of these different things that might help them.

A couple of words about things like acetyl-L-carnitine and some of these other supplements. There has been some talk in the literature about them being not particularly safe. I'm not a pharmacologist. I can't go there. I can't discuss that. But I would say that those should probably be used with caution until we have some better evidence out there as to their safety, as well as their efficacy.

So then there are some nonpharmacologic things that we can try. There's neuromuscular stimulation like TENS units or functional electric simulation that has been shown to provide some pretty good temporary pain relief. The caveat to that is that it doesn't seem to be particularly long-lasting. So people have to keep getting these TENS treatments repeatedly in order to achieve that sort of symptom reduction.

Balance, gait, and strength training by physical therapy-- this is not going to help the neuropathy per se. But this is going to help people overcome some of the functional impairments that happen as a result of the neuropathy. I was talking to my tablemate earlier, and we were talking about the fact that it's hard to get people referred to these kinds of treatments because insurance doesn't want to pay sometimes. And there's not enough education among the medical community about what these treatments can do. So that's another of my soapbox comments-- refer your folks to PT.

Sensory re-education and fine motor and dexterity rehab can also be quite effective for some people. And those are often provided by occupational therapists. They do things like exercises with Theraputty. They do skills practice. For example, they use dexterity tasks like a grooved pegboard.

Exercise-- well, we have heard from I think probably just about every speaker today that exercise is good for us. And with neuropathy that's no exception. So there's been some early evidence suggesting that Tai Chi and yoga can be effective at helping with balance.

But there's actually been some work that was just published. It was a systematic review of exercise trials-- it was published in 2018-- where the auditors found that a sort of multimodal exercise program that consisted of strengthening, endurance training, and sensorimotor training actually improved symptoms and improved function. And it actually seemed to improve objective nerve function as well.

So that's one systematic review. It looked at five trials. But that's some pretty positive evidence. I think that's much more positive than what we've seen from a lot of other interventions.

Safety and fall prevention-- of course, as clinicians we're all providing that kind of education to our patients. People that have these balance and gait problems from neuropathy are at high risk to fall. And so, you know, we're all used to telling people to take up your throw rugs, and don't have a cluttered environment, and be careful the kind of chairs-- sit in a sturdy chair and those kinds of things. Also, things like putting a thermometer in your bathroom to check the water temperature of your bath water before you get into the tub because of the decreased sensation, using care in the kitchen because of potential burns.

But adherence to this teaching is a real issue. I don't think my grandmother would take away her throw rug just because I told her it might make her fall. And so we tell our patients this. And they nod and they say, OK, sounds good. And then most of them, I don't think, maybe do what we tell them to. I'm not saying don't do the education. But what I'm saying is kind of go into it with eyes wide open-- that this is not the panacea that we might think it is.

And then certainly occupational and vocational modifications can be made. People who use computer for work can get modified keyboards. There are different kinds of trackballs and joysticks to use to help use the computer. And driving rehab-- it is a little scary to me to think that people who can't feel their feet are out driving two-ton pieces of metal.

But driving rehab can help with modifications to pedals. It can help with modifications to steering wheels. And it can actually do a detailed assessment of what people's capabilities are and whether they are safe to drive or not. So referrals to that can be very helpful.

A little bit about prevention-- there is almost no evidence of anything that works in terms of a preventive technique for CIPN. But one really promising thing that just came out is cryotherapy. So we've all heard of cooling caps for preventing alopecia-- same idea. It was a really very nicely done study where people were self-controlled.

So they wore the cryotherapy mitten and boot on one side and not the other side. And they controlled their dominant and nondominant hand and all that. And then they started it before patient's chemotherapy induction. And they applied the cryotherapy 15 minutes prior to the infusion beginning, left it on through the infusion, and took it off 15 minutes after the infusion.

And what they found was a whole lot of benefits in terms of preventing nerve dysfunction, but also preventing physical dysfunction. And this is just one of the graphs from the paper. But so, on the y-axis, higher is worse. And as you can see then on the control side, function on the group pegboard test got worse over the course of chemotherapy, whereas on the intervention side it actually got a little bit better.

So that is really promising in terms of a possible preventive. And it's not very complex and certainly not contraindicated like a lot of drugs might be. So that's an exciting development. So another clinical pearl is, again, in assessing, we need to assess both nerve function, but also physical function and really sort of understand how this affects patients' daily lives.

I'm going to bust a couple of myths-- things that we kind of all have accepted as gospel through the years and have often told our patients. And there's a lot of literature coming out to bust those myths. So the first one is that CIPN is purely a dose-dependent phenomenon. So the conventional wisdom is that the more chemo you get, there's a linear relationship. The more chemo you get, the worse your neurofunction is.

And this is some data that we started to analyze from my pilot study that recently concluded. And when we look at symptom ratings on day one of chemo for each chemo cycle-- this is in women with ovarian cancer-- it certainly looks that that's the case. Severity tends to increase over time as the total cumulative dose increases.

But then we decided to start looking at the data a little bit differently. We also captured daily symptom ratings for the entire 126 days that our women are receiving chemotherapy. We asked them about their neuropathy on a daily basis. And rather than try to interpret all that complication, the take-home point from this slide is that you can see there's an incredible amount of variability in days to first report of any numbness and tingling, days to first report of clinically significant numbness and tingling-- that is, greater or equal to a level of three on a zero to 10 scale-- and days to continuous numbness and tingling that's clinically significant.

And so the point of that is that it's not just a dose-dependent phenomenon. Clearly, there are other things involved here. This is a huge open research question. There are a lot of physiologists across the street that are looking at stuff like this. But that's just to say, it's not just a dose-dependent phenomenon.

Another thing that we have often told our patients is that it's temporary. As soon as you stop your chemo it'll go away. This is LIVESTRONG survey data that we looked at. And we are in the process of finishing this analysis right now. This is a sample of over 4,000 people. The mean number of months since they received their most recent chemotherapy is 52. So these are people that are a number of years out from chemo.

And you can see that it's like lung cancer-- 60% of patients still exhibit neuropathy, 63% colorectal cancer, ovarian, 57%-- 57 and 1/2%. So it is not necessarily a temporary phenomenon. These are a couple of other research studies that basically say the same thing. So I'm not going to go into them in any great detail.

And then another myth is that CIPN really has no functional effects. Now, you know it does because I've already talked about them. But we have said to patients, oh, it's uncomfortable. I'm sorry that you have to deal with that. But it really-- it's not going to really impact your daily life. You just kind of have to learn to live with the discomfort.

There are more and more studies being published every day that show that that is not the case. It does have severe functional effects. Everybody knows about balance, gait, and falls. But the thing that I found interesting was that some studies are now showing that things like instrumental activities of daily living are affected by CIPN. So things like using the telephone, doing housework, shopping, meal prep, medication management. And those are pretty important life skills. And then, as we mentioned before, driving.

This is another-- this is some data that came out of a sample of 700 women that had a history of treatment for ovarian cancer. I work in ovarian cancer. That's why I'm talking about it. There are other cancers. I know that.

So this sample of 700 women from across the country, we looked at what predicted walking disability. This was self-reported disability-- difficulty with walking. And what we found was that-- and so block two is what we want to look at.

And certainly, currently receiving chemotherapy does impact neuropathy. But the average length of time of these women being off of chemo, again, like the LIVESTRONG sample, is about five years. And so we still had people with significant amounts of difficulty with walking. And numbness, tingling, fatigue, and pain were the three symptoms that were most highly associated with that.

And numbness and tingling and pain could be neuropathic. And fatigue could also be neuropathic because some of the autonomic neuropathy. So it's almost like a little neuropathy symptom cluster. So the other clinical pearl is that as we've been talking, it's not temporary. And it needs some in-depth assessment when we see these patients in clinic.

Now, this word cloud is generated from some qualitative data that my colleague Heidi Donovan has at the School of Nursing. She did a web-based symptom management trial. And we took the qualitative data from people that complained of neuropathy and generated this word cloud, which I just think is pretty neat. But it's really kind of interesting to see what people talk about.

But I have a couple of quotes from some of our patients that were in that study to give you in their own words what it felt like to them. One of them said, "As the neuropathy has gotten worse, I've found that if I walk in the morning I have more difficulty moving around for the rest of the day. Initially I continued walking, hoping that exercise would improve the condition. But lately, I've been walking less because it seems I pay for it later." So yes, we all need to exercise, but it's just so debilitating for people that adherence is going to be a real problem.

This one I find particularly poignant. "I wondered if this aching in my hands and feet would affect me for the rest of my life, and would I need to go to a nursing home?" So people are really-- these are some pretty big sort of existential concerns that people have related to this.

This is Susan Gubar. She's an author and a professor of, I think, women's studies and women's literature. She writes a regular column in *The New York Times.* She's part of their Well Blog series. And she is eloquent at describing her experiences with ovarian cancer and its treatment. She wrote this book, *Memoir of a Debulked Woman.* It is not an easy or a pleasant read, but I highly recommend it.

And it talks about her experiences with all of her treatment. She's had several recurrences. She's had-- I think it's been about six years since her initial diagnosis. And she's had several recurrences, but she is still plugging away and writing. But she talks about how she can't stand to stand. And she talks about that her dead soles and paralyzed toes keep her from doing a lot of the things that she wants to do.

So lest we-- you know, lest we think that everybody is just-- that it's doom and gloom, I do have some really nice quotes from this web-based symptom management study that talk about living in spite of neuropathy. Let me read a couple of those. "So when the symptoms are less I resume my craft-- beading. This gives me a great deal of pleasure." So people are looking for those opportunities to do what they like when they feel up to it.

One woman says, "I concentrate on each step. I use a cane to help stabilize my walking. I go slowly, and I try to perform as many of my daily tasks sitting as possible." So people are really good at sort of figuring out compensatory strategies. One woman actually talked about scooting herself around her kitchen on a wheeled stool. And the rehab nurse in me about died when I read that because that's not exactly safe. But, you know, people are-- they're problem-solving. They're figuring out how to do it and to get along in their lives.

And this one involves this woman's work. She says, "Because I'm right-handed, I have started using my left hand more. I'm a cashier, and I've had to learn to do things with my left hand. At home when I have to open a can, I bought a can opener that automatically will open the cans." And occupational therapy can help figure out kitchen mods too. "I also use more caution when I'm baking so as not to burn myself because I can't feel it if I do put my hand on a hot rack." So people are-- despite this incredible debilitation that people can feel and this terrible symptom burden, people are managing to push through despite this.

So I feel like I have gone 90 miles an hour and barely scratched the surface. But I want to bring it home and wrap it up just to summarize to say that CIPN, as we've seen, is not simply a function of cumulative dose. There are many other factors as yet to be discovered in who gets it and how bad it gets. CIPN is not temporary or short-term. And it has numerous functional effects.

Whoops. I did have a final clinical pearl slide. I don't know what happened to it. But, OK. Anyway, so that's my last slide. And you know what the clinical pearls were. I called them out when we were talking.