

Joan Kjaer: Welcome to WorldCanvass from International Programs at the University of Iowa. I'm Joan Kjaer and we're coming to you from Merge in downtown Iowa City. Thank you for joining us. We have a focus tonight on research. We're going to be speaking in this segment with two people investigating the effects of chemotherapy on brain function. I'm very pleased to introduce Dr. Sneha Phadke, a clinical assistant professor in the Department of Internal Medicine here at the University of Iowa. Thanks for being here Sneha.

Sneha: Thank you for having me.

Joan Kjaer: Mm-hmm (affirmative) next to her is Dr. Kanchna Ramchandran, an associate research scientist in the UI Department of Internal Medicine. And thank you very much, Kanchna, for being here.

Kanchna : Thank you for inviting us.

Joan Kjaer: You bet. So I'll start with you Sneha. The common name for the condition that I know we're going to be talking about principally tonight, that many cancer patients suffer when undergoing chemotherapy, is chemo brain. Can you explain what it is and how you're trying to both address it and perhaps a relieve those symptoms?

Sneha: So chemo brain is sort of a lay person term for what we as physicians or investigators refer to as cognitive deficits after chemotherapy. And that's a really broad term. So patients will say that they feel that they've just lost some ability to multitask, for example, or maybe they don't have the same ability to concentrate or focus or jump from one sort of cognitive activity to another. They've lost some of what we call cognitive flexibility. And so those are often symptoms that patients describe, but the actual diagnosis is somewhat elusive because there's no criteria for diagnosing this entity. And I think the reason for that is really multifactorial. Probably it wasn't until the last 5 or 10 years that it was even truly recognized as a real thing that happens.

Sneha: And I think the resistance to maybe funding research in this area or really recognizing it as an entity is that there can be underlying conditions that may sort of confound this diagnosis. Obviously after a diagnosis of cancer, it's not uncommon that someone may have anxiety disorder, depression, sleep disturbance, and those things can also contribute to those same symptoms of lack of focus or concentration. And so that's been the challenge, I think, as an oncologist, is being able to even provide patients with an accurate diagnosis of what they have.

Joan Kjaer: Yeah, yeah. And so finding that pool of patients that can serve as sort of a, I don't know, core group or a test group, you have so many variables, it's probably difficult to just focus in on people who may have sort of a more, what should I say, a more similar experience. And I think you have focused mostly on breast cancer patients?

Sneha: So I'm a breast oncologist and actually some of the first reports of chemo brain were from breast cancer patients, because I think women tend to multitask. We do a lot of things at one time and we're often in charge of work responsibilities and home

responsibilities and we're used to being able to do all that. And I think that women after chemotherapy just felt like they weren't able to do that as well anymore. And so I think that breast cancer patients were really the first ones to sort of advocate for this, not only this term as a diagnosis, but also for research funding. And chemo brain, really, it can affect anyone who has cancer, it can affect patients who got all sorts of different types of chemotherapy. So it's not necessarily one type of chemotherapy or one type of cancer or one type of patient. Men can get chemo brain. But the symptoms may be a little bit different, which again, is why the diagnosis can be a little bit elusive.

Sneha: Interestingly, there's even some evidence that patients will start to feel that they have these declines in neurocognitive function before they even get chemotherapy. So whether there's some component of the cancer itself that's causing inflammatory sort of chemicals to be released in the body that's affecting brain function...these are all questions we don't know the answers to yet.

Joan Kjaer: Yeah. So when a patient has concluded chemotherapy, would you say that it seems that the symptoms are relieved after six months or a year? Do people sort of return to the way they thought they were before?

Sneha: So what's interesting is that I, in my experience at least...patients don't tend to realize that they have any symptoms during chemotherapy. It's not until they sort of get back to normal life and then they start to do things that they did before chemotherapy. And that's when they sort of recognize that things just aren't quite the same as they were before.

Sneha: The good news is that even though it's a hard thing to diagnose and an even harder thing to treat, most people do improve with time away from chemotherapy. So the longer time that you go, usually those symptoms do improve. Although there are certainly patients who never feel they completely recover.

Joan Kjaer: Yeah. Well, in a conversation we had prior to the program, you said that chemotherapy can lead to accelerated aging at a cellular level as well as patients reporting feelings of aging? Help explain that.

Sneha: So that's a relatively new field and, just here in the last three to five years, there's been research that's been published looking at certain changes in genes that are associated with aging. And they found that patients who got chemotherapy had those same changes in genes that you would expect to only see in older people.

Sneha: So it was very preliminary research. So it's certainly not anything that has changed practice or changed standards of care, but certainly I think validates the feelings that a lot of patients have that they just feel older after chemotherapy.

Joan Kjaer: So you had said that the process of diagnosing this thing we're calling chemo brain is really what you're engaged in now. You're trying to find markers that can be followed or similar symptoms that you can track over time with people. And are you both involved in setting up a protocol here at Iowa that will be used by other physicians as well?

- Sneha: So right now it's very preliminary research. We're doing some pilot studies. Like I said, there's no standard treatment option and the treatments that we have are usually medications indicated for other things like depression or even dementia. And so the research behind them is not robust and they honestly don't usually work very well. So we're trying to find new treatment options and, at the same time, we're trying to provide clinicians with a way to definitively diagnose chemo brain using neuropsychological testing and also MRIs.
- Sneha: So we have one protocol that's open right now and specifically looking at patients who get a certain type of chemotherapy called doxorubicin and we're testing their neurocognitive function before they get chemotherapy. And then again after doxorubicin chemotherapy. And then we're also doing MRIs at both of those time points and then during the time that they're getting chemotherapy, we're going to be asking them about symptoms of anxiety, pain, depression, so that we can factor those things in and see how they play into subjective feelings of chemo brain.
- Joan Kjaer: Mm-hmm (affirmative) Thank you. So Kanchna, you're a research scientist and you're working on this same project with Sneha. Tell us what you're looking at in your own research.
- Kanchna : So as we age, our metabolism slows down perhaps. And so metabolism around energy available for both brain and bodily function as well as part of the metabolic changes is that with age the amount of free ion concentration seems to increase in the brain and the body. And these free ion concentrations disrupt other metabolic processes down the line. And there seems to be some evidence, at least with the body that the chemotherapy agents that Sneha talked about, they seem to actually increase the free ion concentrations in the body. And so we think it may be increasing in the brain as well.
- Kanchna : And so recently, a few years ago, the Magnetic Resonance Research Center at the University of Iowa, we acquired a 7-Tesla scanner. So it's a high resolution scanner and using a particular form of noninvasive imaging, we hope to be able to track increased levels of ion concentration in the brain. And therefore we are hoping to catch them at two time points before and after chemotherapy and see if those ion concentrations increase. And then the extent to which that correlates with their cognitive impairments. If they're experiencing any. Then we know that this could be a biomarker for chemo brain.
- Kanchna : The other thing that we're hoping to do is to look at the degeneration of connections between different parts of the brain, what's known as white matter connectivity. So again, with both the neurotoxicity due to chemotherapy, cells connecting different parts of the brain may begin to die. And so we would want to see how that connectivity is affected with the iron concentrations along those connectivity lines.
- Kanchna : The third thing that we're able to do again is because this is a high resolution scanner, we were actually able to see the concentrations of large molecules in the brain that are involved with energy transmission between different areas of the brain. And we already know some of the locations in the brain that are involved with the higher order

cognitive functions like planning and decision making. So if we zoom into particular areas of the brain that are involved with things like multitasking and flexibility and then we start looking for concentrations of these large molecules that are involved with transmitting information between the energy and information between different parts of the brain. Then it gives us a good sense of how those concentrations reduce after chemotherapy.

Joan Kjaer: This sounds like really painstaking and slow investigative work.

Kanchna : The goal I think over here is to have different forms of investigation come together. So it's really multimodal imaging that we're trying to get at. And additionally we're also trying to explore and examine what might be the changes in genetic expression before and after chemotherapy. So the genes that express themselves with aging or with inflammation that may be associated with cancer. So we are then able to track to see if there are some changes in genetic expression.

Joan Kjaer: Well, as we all know, a cancer diagnosis is obviously going to upset someone. It may cause depression or anxiety. All of these kinds of things. How do researchers break it down so that you can try to separate out these various potential influences with any individual patient, let alone looking at a larger group and try to find ways to sort of really learn something for a population?

Kanchna : So I think that's the reason why we do some neuropsychological testing so to speak, that just measures their functions on issues like decision making and planning and all of that. But we also separately try and track their anxiety and depression and lifestyle changes and changes in sleep for instance, over a period of time that they are enrolled in the study. So that we have measurements of all these variables that we can then control for while doing our analysis.

Joan Kjaer: And then presumably with the Holden Comprehensive Cancer Center where so many different teams are working on so many different issues and problems, you interweave with other doctors and other research teams and perhaps will find a way to relieve this issue for individual people or it will help inform which chemotherapy drugs appear to be the most problematic? Are you looking at individual drugs in this portion of the study?

Sneha: Well, so for this study we're mainly looking at this chemotherapy called doxorubicin, which in breast cancer is very commonly used. But if you look at the literature on chemo brain, it's been reported that almost any of the chemotherapies can result in patients feeling like they have some neurocognitive decline. So it's likely that there may be more than one mechanism by which chemotherapy causes these problems. And that's what makes this somewhat more difficult in that there may not be one way to prevent this or one way to treat this. We may have to use a multimodal assessment to diagnose it and to treat it.

Sneha: So the goal is really for this project is really to see if these tests that we're doing with the MRI and the neuropsychological testing will provide some sort of framework that we can then use and maybe even spread through our research and dissemination to other

physicians that can use this as a way to try to distinguish between things like anxiety and depression versus chemo brain.

Joan Kjaer: Right, right. And so are the folks you're studying, are they all people coming to this particular university for help with their illness?

Sneha: Mm-hmm (affirmative).

Kanchna : That's right. We are trying to work with the physicians and the clinics, the best breast cancer clinics and the breast surgery clinics, to be able to recruit patients so that we have a fairly really good profile of what chemotherapy drugs they are on as well as is what their genetic profiles are as well. And so that we can have some tight controls in the study.

Joan Kjaer: Yeah. Well and you had said earlier that it could be really any kind of cancer and it seems that just about any kind of drug could have this effect on people. For a long time one heard that funding for research into cancers that are more prevalent with women lagged behind. But I think breast cancer is one of those areas where there has been more funding available for research in the last decade or two decades. Does that make this a little bit easier in terms of funding your research?

Sneha: I think so. In some ways. I mean, like you said, and like I said earlier, this is not something that's specific to any one type of person or any one type of cancer. But because we're specifically looking at it in breast cancer, there are certainly a lot of funding opportunities available. One thing I think that is more specific to breast cancer is that fortunately because of a lot of the research funding that has been provided over really the last three or four decades at this point, the outcomes from breast cancer are largely very good. Most women that get breast cancer don't die of breast cancer. They actually live a normal lifespan.

Sneha: And so I think we got to a point where now we do a pretty good job for the most part at treating breast cancer. We're not perfect, but we've definitely improved. But now we really need to make sure that we're not just increasing years of life, but we're making sure those are good quality years of life. Otherwise we're not really doing our job.

Joan Kjaer: Well, and then I imagine.... you've mentioned aging a couple of times, but there are other things that happen particularly to women and women who may have breast cancer. You go through that change of life period, which has its own set of reported symptoms and all of these things kind of complicate finding one answer, right?

Sneha: Definitely. I mean I certainly see women around the age of menopause and, regardless of whether they took chemotherapy or not, they feel that their neurocognitive function declines or changes in some way. Maybe they feel they are a little bit more scatterbrained or something like that. So there are many things that can confound this diagnosis.

Joan Kjaer: What are you hoping will come out of your next few years of research Kanchna?

Kanchna : We're hoping that our small sample of pilot studies will give us a couple of signals that'll further and help us refine our research designs to actually identify those biomarkers. And if we find some good effects in this small sample, then we hope to be able to then go out and broaden our study and collect data on several more patients. So that we can have a really solid protocol with good research controls that we can then try and unearth some biomarkers. But not to put the cart before the horse. Even without a diagnosis we now have FDA approved treatments for treatment resistant depression by noninvasive brain stimulation.

Kanchna : And so that's one of the grand start pilot grants that was funded by the Holden Comprehensive Cancer Research Center by which we're hoping again to stimulate some of those areas that we know are involved with those cognitive symptoms that patients come complain of. And so we're hoping that by stimulating those areas, really just sending a magnetic pulse from the top of the head down to those areas, just beneath the surface. If patient's can experienced some relief from these cognitive symptoms, then that again gives us a signal that we're onto something. That will again help us expand our study. So while the Fraternal Order of Eagles funded our initial imaging grants, our imaging program, the SCC has enabled us to try this particular clinical trial of stimulation, brain stimulation.

Joan Kjaer: And a clinical trial, is there a predetermined length for clinical trial? The usually a couple of years running before you feel you have enough information?

Sneha: So it really, yeah, it really depends on the trial, depends on how fast we're able to accrue patients. And it depends on how long the protocol is, whether it's a diagnostic or treatment protocol. Because this is a pilot study and we have a relatively small number of patients that we're trying to accrue. We're hopeful that we would be able to have some results relatively quickly. But clinical trials can definitely, you're in it for the long haul. It's not a short process.

Joan Kjaer: Yeah, I guess that's true. Well, boy, I've want to say thank you so much to Kanchna Ramchandran and to Sneha Phadke for joining us this afternoon and boy, what good work you're doing and it's so, so important. And all of us who've been touched in some way personally or with friends and family with cancer, we're just all hoping that you can find the best possible results. So thank you for being here and thank you for joining us for this portion of WorldCanvass. I'm Joan Kjaer and we'll be back with the third part in just a moment.