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KLEPIN:**

All right. Well, thank you very much for the opportunity to be here and to speak to you today. And I'm really going to be talking about the other half of the discussion. Julia, or Dr. Lawrence, raised a lot of important points about a discussion about adjuvant therapy that we have with our patients with respect to who's going to benefit. So that's half of the discussion you're having when you see patients in that adjuvant setting. But the other half is what's the trade off? What risks are you taking on if you go ahead with adjuvant therapy? So what are the side effects? And that's really where this topic of late effects comes into play.

So this is an outline. Very briefly, I'm going to give you a definition. Because actually when I first started hearing the term late effects, I was a little bit off on exactly what it meant. And I'll talk specifically about cardiovascular and cognitive late effects, because it's a huge topic, and I wanted to focus on two specific things and then touch on a couple of future directions. So as I mentioned, when I first came into the field of oncology and heard the term late effects, I just assumed this meant late effects and that there was this other category of early effects and maybe intermediate.

But in fact, the NCI definition, as Dr. Halco pointed out to me several times, is a health problem that occurs months or years after a disease is diagnosed or after treatment has ended. And late effects can be caused by the cancer or the treatment for the cancer, and may include physical, mental, social problems, or second cancers. So this is really-- the clock starts at the time of diagnosis, the time of treatment. So late effects is quite a broad term.

So I'm going to narrow that down and specifically talk about cardiovascular late effects. First-- and when we talk about cardiovascular late effects, the most common chemotherapy-related cardiotoxicity is left ventricular dysfunction or congestive heart failure. So that's really where I'm going to focus on for this first part. And again, I'm really focusing on late effects after chemotherapy. So thinking about the adjuvant setting-- a patient who's going to be getting chemotherapy.

So this is a topic that I think most of you know quite a lot about. The main offenders with respect to systemic therapy, chemotherapies in particular, with the anthracyclines and then trastuzumab, which you all know is the monoclonal antibody to treat HER2 overexpression-- so used in all the regimens for HER2-positive patients. So we'll talk first about anthracycline induced cardiotoxicity. So this has been known for years, and years, and years. So this is a bit of a refresher with a little bit of more recent data on risk factors.

So the majority of cases-- these are truly what I call late effects. They fit my definition, meaning that they typically occur a year or so after the therapy is complete. So congestive heart failure or left ventricular dysfunction that's diagnosed after therapy is completed, often a year or several years later as we'll see from some of the data. And I put here that it may be irreversible. I think that was a little soft. It's generally thought to be irreversible.

So most people who have anthracycline induced cardiotoxicity have that for the rest of their lives as opposed to-- we'll talk later about trastuzumab associated cardiotoxicity, which can be reversible for lots of patients. The biggest risk factor for anthracycline induced cardiotoxicity is cumulative lifetime dose. And so everyone I think knows that. And in medical oncology, we talk about this. What are the thresholds? How much can any one person be exposed to, to really be over the limit with respect to risk of cardiotoxicity?

So a threshold that's commonly used-- and this is based on doxorubicin so the drug typically used in adjuvant breast cancer regimens-- would be 450 to 500 milligrams meter squared-- would be the limit for cumulative lifetime dosing. And this is just to give you an idea of how dose impacts risk with doxorubicin specifically. So this is the dose relationship for anthracyclines and the development of cardiomyopathy. So this is symptomatic congestive heart failure. And I have on the x-axis the cumulative lifetime dose, milligrams meter squared, specific for doxorubicin And these are based on clinical trial data-- pool data essentially. And this is from the *ASCA Clinical Evidence Review*.

And what you can see is that if you keep the dose below 550 milligrams meter squared-- again, lifetime dose-- that your risk of cardiomyopathy is quite low. So these are clinical trial data, so less than 5%. Most of our adjuvant regimens are well below that in your cumulative dosing. If you think about AC times four, that's 240 milligrams meter squared. So we're well within that.

But in the studies-- and this is not just limited to breast cancer-- where higher doses have been used historically, you see a 30% risk with 600 milligrams meter squared. And people who have been exposed to a gram over a lifetime, 50% of those patients develop congestive heart failure. So it's a huge dose relationship. We certainly stay below the 550 milligram meter squared window.

You can't, however, say that there's a safe dose. So even if you're below that window, that doesn't mean that your patient isn't going to develop cardiomyopathy as a result later on in life. And we'll go through who's at risk and how you see those patterns develop over time.

So what are the risk factors for anthracycline induced cardiotoxicity? I've divided these into treatment related factors and patient characteristics that have come up repeatedly in clinical trial data when we look at who develops cardiomyopathy. Treatment related-- obviously, dose I've mentioned-- use of other cardiotoxic drugs. And I'll show you some more data on that. The biggest, most relevant offender in that regard these days is trastuzumab-- so combination regimens, and history of chest irradiation has come up in several studies-- not everyone-- but certainly it's logical that that would increase your risk-- and then how the anthracycline is delivered.

So there were studies that have demonstrated that infusional delivery of anthracyclines lowers cardiac risk and cardiotoxicity compared to bolus. So those are really the treatment related factors. I think the most relevant for most of our patients is-- or for our HER2-positive patients and trastuzumab use in that setting, which is standard-- and then, of course, the dosing that we talked about.

With respect to patient characteristics-- and when your patient comes in, characteristics that they come in with that are not related to their breast cancer treatment-- older age, not surprisingly, is the number one risk factor. So the age cutoffs typically where you start to see the increasing risk in most of the studies are around 65 to 70. Although, I'll show you some data for younger age risk in the trastuzumab setting. And then preexisting cardiovascular conditions. So these are all fairly common sense.

The one that jumps out the most-- obviously, history of coronary disease. We take everybody who already has CHF off the table. That's a no-brainer. But hypertension has come out repeatedly in many trials. So women with poorly controlled hypertension are typically at higher risk. So this is some data looking at the risk of cardiomyopathy in older women specifically. So this is your higher risk population. And the reality is that these are the majority of the patients that are going to be coming in with breast cancers now and over the years to come. When we're talking about adjuvant chemotherapies, we still use anthracyclines in certain settings. So they're still relevant.

This is a population based data, so it's from the Surveillance, Epidemiology and End Results database, so not clinical trial data. They looked at thousands of women. This is specifically the figure looking at women who were diagnosed and treated with anthracycline versus other breast cancer treatments between ages 66 and 70. So these are not patients that are seen in my clinics and they're not over 75, but just over that risk threshold of 65 to 70.

And looking at those women, these three lines represent-- the blue line are women who had breast cancer but received no chemotherapy. The yellow line are those that received chemotherapy without an anthracycline. The green line are those that-- everybody OK? It's OK. The green line are those that received anthracycline based chemotherapy. And there's a bug in the back, so don't panic if there's some crawling on your legs. [INAUDIBLE] And what they plotted here is the proportion of women who actually developed symptomatic congestive heart failure-- had a claim for this. So this is based on claims data over the course of 10 years from the time of their treatment. So this is longer term follow up than we typically get in most clinical trials.

And what you can see, there are a couple points here that I think are important to remember. Number one, if you look at women who didn't get any chemotherapy at all-- so that's the blue line-- pretty much the same as those who got chemotherapy without anthracycline. Their risk over 10 years of developing-- having a claim for congestive heart failure-- so presuming those claims mean doctor diagnosed it-- 30%. So 30% of women that you see age 65 to 70 are likely going to have a diagnosis or claim for congestive heart failure within 10 years. That's already a very high rate.

Not surprising, it's a common co-morbid condition. But I don't know that we all think about that at the get go, that that's sort of the baseline risk that our older women in this age group are experiencing or looking at. And then if you add anthracycline, at least from this data, you're adding a risk on top of that. So the risk went up to almost 40% of those women having a claim for congestive heart failure in the next 10 years. So you certainly added something with respect to their risk.

And the other thing to notice is that the divergence of these curves doesn't start right after they got their treatment, but we're seeing the curves continue to diverge over the course of 10 years. So that risk actually continues to increase a little bit over time.

So anthracycline cardiotoxicity-- those are, I think, some of the relevant points. I think the biggest question really nowadays is with respect to trastuzumab and how that influences cardiotoxicity for our patients. Typically-- and this is a different type of cardiotoxicity, thought of more as a stunting a myocardial stunting versus the apoptosis that you see that the cardiac injury and death essentially-- not death of patients, but death of cells-- with the anthracyclines.

So this is different. It occurs early during the course of treatment, which you all know. The rates of symptomatic congestive heart failure in clinical trials with the use of trastuzumab in combination with chemotherapy-- so this is all in the adjuvant setting-- but 1% to 4% on clinical trials. Keeping in mind who's on a clinical trial-- younger women, middle-aged, healthier, screened, not a lot of co-morbid conditions. The rates of asymptomatic congestive heart failure on clinical trials-- quite a bit higher. So these are women who we picked up a decline in their ejection fraction by routinely assessing their ejection fraction during treatment-- 17% to 20%. So that's pretty high. So these are people who-- they didn't know-- they didn't have symptoms, but we detected a decline.

So these are a couple of points-- lessons from a clinical trial. So I'll show you a little bit of clinical trial data to dig a little deeper here and then some population data. This is data from B-31-- so the National Surgical Adjuvant Breast and Bowel Project. This was one of the landmark clinical trials that demonstrated the benefits of adding trastuzumab for HER2-positive patients to the chemotherapy regimen. Comparing-- the control arm were women who-- these were on node positive women-- HER2-positive who received triple drug chemotherapy including an anthracycline. So it was doxorubicin, cytoxan, and paclitaxel-- that's control arm, which is in yellow here.

And then the experimental arm, which is now standard of care, is with the addition of trastuzumab. So everybody got an anthracycline. And what they're showing here over the course of seven years since the completion of treatment is the incidence of cardiac events, which is symptomatic congestive heart failure. So not those asymptomatic patients, but symptomatic CHF or cardiac death. And it was mostly symptomatic CHF.

And you can see that there's a big difference. So people who had the addition of trastuzumab certainly experienced higher incidence of cardiac events compared to those who only had the anthracycline, so 1% versus 4%. Then keeping in mind, the absolute numbers there are quite small in both arms. So if we scaled this-- this is scaled up to 5% so it looks really impressive. But if you scaled it to 100% you would have little, tiny curves and you would see a little, tiny difference. So it's significant. You're adding risk, but if you look at the absolute numbers, the risks are still quite small.

They then dug a little deeper to say OK, well, on this clinical trial, who really was at risk? What are the risk factors for predicting trastuzumab chemotherapy associated cardiomyopathy? And what they found here was that age, again, comes out. They did see a slightly younger cut off. So with the addition of trastuzumab, women who were 50 to 69 years of age at the time that they started therapy did have a higher risk, but little over two-fold higher risk than those who were younger than 50. And you saw a similar risk for those over 60. Now keeping in mind, there's really no over 75 here. So we're just looking at risk for, again, middle-age to early older age.

Hypertensive medications put patients at higher risk. So just the presence of hypertension-- and then, not surprisingly, their baseline ejection fraction. So this is all based on MUGA testing. But for women who started out with a low normal-- 50% to 54% on their ejection fraction-- they were at significantly higher risk of developing cardiomyopathy during the course of treatment or afterwards.

So when they looked at the multi-vari analysis, and they looked at age, hypertension, and ejection fraction, hypertension actually fell out, and the two independent risk factors were age and baseline ejection fraction. So they used this data and calculated a cardiac risk score to better predict at baseline, what is your individual risk of cardiotoxicity if you take a-- use a trastuzumab anthracycline containing regimen.

So they plotted here, based on their cardiac risk score, two examples. So what they're showing here-- A, which is on the bottom-- that little, tiny bottom marking-- the yellow curve there. The yellow curve is cardiac risk score plotted on the x-axis, and the prediction of cardiac events on the y-axis. And so if you have a woman who's 45 years old who has an ejection fraction of 65% at baseline, using their calculation, which you can actually find in the reference-- so they have it published-- the score was 48, which translated into a 2% incidence of cardiomyopathy for those women, versus a 65-year-old with an EF of 55%, higher cardiac risk score, and a higher incidence of around 13%. So gives you a way of being able to calculate for an individual patient who comes in the door. If I'm going to give you this type of regimen-- so your ACTH type regimen-- what is your risk of cardiomyopathy?

They also showed us some data on trajectory. So what happens if your ejection fraction declines, what happens over time? Does it stay low as we see typically in anthracycline therapy, or do we actually see improvement? And there have been multiple studies that have looked at this on clinical trials, such as this one, and in some observational data looking at older patients. And you tend to see a reversibility component. So not everyone gets back to their baseline, but most people do have improvement from their nadir and often go from a low symptomatic ejection fraction into the normal range, or at least better than where they were, if you stop the trastuzumab at the time that they're having symptoms or you notice a decline.

And here they just plotted for the-- the yellow line are the folks who received the combination regimen with trastuzumab, and the blue line are those who just got anthracycline chemotherapy. They plotted the ejection fraction over time from the time of therapy, actually 18 months out. And you can see the decline. These are the women who declined in the first six months. And then obviously those who declined, therapy was stopped as far as the trastuzumab.

You can see a leveling off in the anthracycline arm, the blue arm. And then actually a leveling off-- and you can see an early improvement in the yellow line, which are those who have trastuzumab therapy on board. And if you were to follow this out, there have been other studies that show that that improvement tends to continue a little bit. So there is a reversible component.

The other thing I just wanted to point out is that when we quote these numbers to our patients, and we say, well, clinical trial data says that the risk of cardiomyopathy is around 4%, that's-- but a lot of times you hear [INAUDIBLE], or you might hear that in tumor board. Again, that's based on clinical trial data. If you look at population based data, which is looking at applying our clinical trial paradigms into a less selective patient population, we tend to get different numbers and usually higher risk of side effects when you're applying it in this setting. And that's the real world setting. So there are a lot of biases in here in observational studies that we see in population based data. But it's important to have both pieces of information when you're talking to your patients, especially if your patient isn't quite the person who would have made it on that clinical trial.

So this is some data from population-based registry looking at over 12,000 women. And again, plotting cardiomyopathy-- the incidence of cardiomyopathy over time. And I've showed you two different age groups. They looked at women less than 65 years of age who received different types of regimens, either no chemotherapy, just anthracycline, non-anthracycline. And in the top line is the combination of anthracycline and trastuzumab. So these are the combination-- HER2-positive women nowadays might be getting a regimen like this. And you can see that really that's where you see the difference in risk of cardiotoxicity or cardiomyopathy is with the combination regimen, both for the younger women-- that's the top line-- and for the older women.

You can also see that the risk is much higher for the older women. And if you plot this out, this is, I think, six years-- can't even read it. It's tiny-- have to go to the source. But it's five to six years out from treatment, and the absolute numbers are a little bit higher even for the younger women. They're getting about 8% to 9% risk of cardiotoxicity for the women less than 55, and much higher than that in the older women. So population based data, again, it has its biases. But I think what it tells us is that 4% risk that we quote is probably a little bit low for the average person we see, and that the risk is somewhere in between, likely what we're seeing here and what we see in the clinical trials.

So a couple of recommendations from the standpoint of cardiotoxicity-- obviously, I think the main thing that we can do is more carefully select our patient and select the regimen for that patient. So we know what some of the risk factors are. A lot of our patients are going to be older women who have hypertension. If they're HER2-positive, consideration of a non-anthracycline regimen is a good one for most of those patients. Obviously, monitoring of left ventricular function is standard of care with herceptin or trastuzumab therapy. There are no recommendations for monitoring ejection fraction after you finish your therapies.

So once you're done with trastuzumab, once you're done with your anthracycline, when you're off therapy, there are no guideline recommendations that you keep following. And that's something that does come up when we talk to patients. The only indication to obtain additional monitoring with MUGA or an echo is if the patient has symptoms.

So now I'm going to change gears slightly and talk about neurocognitive late effects. And this is an area where there's a lot of data but not a lot of consensus yet. This is a really, I think, very important-- it's a hot topic. It's on everybody's mind. That's a joke. But it's a field in its infancy. So when patients come in, especially my patients, probably a lot of your patients, this is one of the side effects that they want to know about. And especially the older patients say, am I going to get demented if you give me chemotherapy? This is one of their number one concerns with respect to side effects.

And right now, we don't have a lot that we can tell them conclusively, here's your risk of x and y with respect to this. But I'll walk you through some of the big picture points and then let you know where I think the field is going. So the evidence is mixed as far as whether or not adjuvant chemotherapy results in cognitive dysfunction. And the magnitude of the dysfunction that's showing up in some of the studies is really unclear but looks to be fairly small. There are significant differences in self-report and objective testing, and I'll go into that a little bit. Data on trajectory-- does it last? Does it go away-- not really clear yet.

And the reason is that there are a lot of confounding variables. So a lot of the well done studies aren't out there yet, so what we have are studies that give us little snapshots, where it's not clear if it's the cancer diagnosed through the treatment that's resulting in the side effect that they're picking out. What are the influences of the stress, depression, anxiety, which we know affects cognition in the short term and the long term. So it's hard to tease those out.

And trial designs are very different. So the data out there, there's a lot of difference. It's hard to compare apples to apples. So you might compare a group of systemic therapy patients to a group of healthy controls, versus breast cancer controls, different time points. So there's a lot of information coming out, but it's hard to put it into very neat packages.

So a couple of things that we all know. So what do patients report? They typically report these symptoms pretty consistently. A subset of our patients report problems with memory, concentration, speed of thought processing, clarity of thought. I mean I hear this a lot. I'm sure a lot of you hear this from friends that you know have gone through therapies or from your patients. And that has a lot of negative consequences. So we hear a lot-- I have trouble with my job now. I just can't perform my job the way I used to, or I'm having trouble learning new things. It impairs education, impacts relationships. Obviously, there's a tie-in with quality of life as all of these things relate-- and depressed mood. So these go together. So it's a really, really important topic for our patients.

I'm going to walk you through a little bit of what's out there-- just giving you snapshots of the data. So how commonly do patients report cognitive symptoms? Well, it depends. It's a little bit all over the map. If you pick out-- this is where the research started. It started with surveying breast cancer survivors, so women who've been through treatment for many years out and they're asked questionnaires-- do you have problems with memory concentration, etc. And in those studies, anywhere from 17%, so close to 20% of women to 75%, depending on the patient population asked, reported some problems with something related to cognition.

And I'll give you an example. This is one of the early studies that was published in 1999, and they interviewed and actually did some cognitive testing on women who had chemotherapies-- so 39 of those women-- and breast cancer controls two years out from their treatment. So these are-- later survivors not in the throes of their therapy. And they ask them questions about concentration and memory. And you can see a big difference in reporting of problems in these areas compared to those who had chemotherapy-- so that's the brown bars-- and those who had breast cancer diagnosed, had surgery, but didn't have any chemotherapy.

So big differences, up to 30% had trouble with concentration, reported at least. In this study, if they had had chemotherapy compared to about 5% in the controls. However, if you look at a different study, you get a little bit of a different answer-- so another cross-sectional study. So cross-sectional means they just looked at one point in time and asked patients now-- and tried to make comparisons between risk factors and outcomes, but only in one slice of time. This is not longitudinal data.

And in this study, they looked at six months after treatment-- so this is a shorter time interval-- again, women who received chemotherapy versus those who had cancer but had radiation only-- and asked them if they had problems with, again, self-report, problems with language, memory attention, et cetera-- showing a little bit of the data, and they asked this in a different way. They said, rank how often you have trouble with these things. One-- almost never. Five-- almost always. So it's a game of scale.

So there really were no differences between women who had chemotherapy and those who didn't. So now you have a differing result in the comparison. Is it the chemotherapy? Is it the breast cancer? These two studies say different things. What they both show, however, is that both sets of women reported a lot of problems, so that the average score here was around 4. That's on the almost always side of things. So we're consistently seeing complaints in both of these groups of women.

If you look at longitudinal studies-- a lot of studies out there. There's a nice systematic review-- I left the data off here-- this is from 2010-- that looked at 27 studies. So again, we see this a lot when we don't have really good randomized control trial data. We take all the data that's out there and try to bring it all together in some systematic way to look for threads, to look for themes.

So what there is, is some strong evidence that says that there's an increase in complaints, cognitive complaints, after chemotherapy compared to before. So that seems to be consistent in the small studies that have been done. There's been conclusive evidence, however, with respect to the magnitude of these symptoms for individual patients and the trajectory over time. Does it get better, or does it stay the same?

So the next-- when I first thought about this field several years ago, I thought, well, self-report-- really important-- but we need to have some objective data. We don't know what to do about this if we don't actually know-- if we don't test and have numbers. We all want to have numbers, so. We do. Our patients just want to not have these complaints.

So objective testing-- so now there are several studies that have looked at testing women during the course of their treatment afterwards with cognitive, neuropsychological tests. And what they found pretty consistently-- and there are a couple of meta-analyses looking at this-- that there's really no good correlation between the objective testing and the complaints that patients have, which tells us that maybe we're not measuring the right thing. Maybe our tools aren't matching up with what the deficits are. But they don't correlate, and so that makes things a little more complicated.

And this is, again, going back to that original study where I showed you complaints among women with chemotherapy and controls, and concentration, and memory-- in this same study, when they did the neuropsychological tests, about 28% of chemotherapy patients had objective deficits in some of their testing, versus 12% of controls, which is high actually in both settings. But there was no relationship. They weren't the same people. So the people who reported the complaints weren't necessarily the ones who were testing poorly.

So the second lesson when you look at objective data is that there are objective changes after chemotherapy that seem to be consistently picked up in studies. So when they first started reporting, oh, there's no correlation here. People said, well, then there's really nothing happening. And that doesn't appear to be the case. In most of these studies looking at neuropsychological testing are picking up on something after chemotherapy.

And these are two meta-analyses that were recently published. One, the one on the left hand side, looking at 13 studies included tumors other than breast cancer. The one on the right hand side-- sorry-- checking right, left-- 17 studies are of breast cancer. And both of them, when they combined the data, it looked at the highest quality studies. They said, well, there are deficits that are coming out pretty consistently-- that's the executive functioning and visual ability, visual spatial ability.

I think one of the problems is you're picking up-- they're very specific domains that are categorized under a psychological testing-- what does that mean to a patient? What is verbal-- at least to me. It means I talk a lot, which I do. But visual spatial-- one doesn't come in and say, I'm having trouble with my visual spatial abilities. So we have trouble with matching our testing domains and what people are saying.

One of the factors that comes out is a no-brainer, I think-- is duration of treatment. So the longer you're on treatment, the more likely you're going to pick up something on your testing. Interestingly, both of these meta-analyses came up with the same conclusion about age. So that increase in age didn't seem to result in an increased risk, or wasn't associated with any of these findings, which they both put in their abstracts and in their conclusions.



I think-- to me that's interesting, because I look at my patients and I say, it's got to matter. And I think one of the things that we have to be careful about is that these studies are all looking at, again, younger and middle-aged women. So in that span, maybe increasing age doesn't matter. But they're not studying the 75-year-old or the 80-year-old.

The other, I think, third lesson is that objective testing tells us that only a subset of women appear to be affected. So this is one of the studies that showed that. They looked at a hundred women who received neoadjuvant chemotherapy-- tested them beforehand-- tested them right afterwards with neuropsych testing. And what they found was that about a third of patients had a decline-- measurable decline in their neuropsychological functioning. A third had an improvement-- so that's sort of the testing effect-- I remember this test, I'm going to be better on it now-- and a third it didn't matter. So not everybody's going in the same direction.

The other thing that comes up consistently is that everybody at baseline, in all the studies, seems to be testing on average a little bit lower than age based norms. So there's something about the cancer diagnosis itself. It's already affecting function.

So the last couple of slides-- I think the next step here in the field-- obviously we need better studies-- longitudinal studies with good comparisons. But there's a lot of interest in trying to figure out who are the subsets of people who really are affected. And so a couple of things just to mention, and these are not ready for prime time, but one of the areas of investigation is genetic risk. So are there people where you could actually test their particular allele. For example, the apolipoprotein E genotype E4 allele is a risk factor, if it's present, for Alzheimer's dementia. So there's an interest in saying well, this might be a vulnerable population who might be more at risk-- some pilot studies looking at that.

There's nothing conclusive yet with respect to chemotherapy. There's another-- the COMT genotype-- looking at a specific allele in that setting. So there are some studies that are ongoing. I just mentioned this to say that you may be hearing about this down the road. None of this is ready for prime time. I think the area where we're seeing a little more traction is trying to understand mechanisms a little bit with respect to how would systemic therapy be causing cognitive dysfunction. And one of the steps in that is to really get a look at what's going on in the brain. So all those changes in the brain that we can see, we have a lot of new imaging techniques that correlate with the changes we see in our testing. And does that help then move the field forward with respect to the mechanisms underlying this?

So there are several studies. I just presented one here looking at using specific types of MRI imaging. And this was a study where they looked at three populations of women; young women, either breast cancer who received chemotherapy, those with breast cancer who were not getting chemotherapy, and healthy controls. And they did a pre-battery of neuropsychological tests before chemotherapy and after. They also did these MRI imaging before and after looking for white matter changes. And this is about a three to four month span, so very short term changes. And they did the same three to four months span for these tests with their control groups.

And they did find that there were differences between the chemotherapy treated patients and the control groups with respect to seeing declines in objective testing in the short interval, and correlating that with changes in white matter that they saw on their MRI. So there were white matter changes in the frontal, parietal, and occipital lobes that correlated with the same women who were having trouble with their testing.

There are several studies like this. We have some studies ongoing actually at Wake Forest looking at things like this to try and tie together what's actually happening in the brain with what we're seeing, and then hopefully tying that back to what our patients are experiencing to help us come up with ways to prevent, or at least target, who is at risk and who's not. And I'll make one plug for a study that's finishing up here at Wake Forest now. It's more of Dr. Lawrence's studies.

And this is a really important line of research. So she's looking with Dr. Hunley here, who's a cardiovascular imaging expert, at vascular mechanisms of neurocognitive dysfunction associated with chemotherapy. So their hypothesis is that some of the changes in the vasculature that happened when you're exposed to chemotherapy are one of the direct results of cognitive dysfunction. So it's a vascular mechanism-- the vasculature changes are injuring the brain.

And so they're actually-- they did a pilot study looking at vascular measures; transcranial Doppler, cardiac MRI, several other things, and cognitive measures pre- and post chemotherapy in a small population of women. And I think this is going to be important pilot data to start moving forward to say, what's happening in your body that's resulting in these changes in the brain cells in your body. And that will help us hopefully start to think about not only who's at risk, but what do we do about it. Are there things that we could do that would modify your risk?

So conclusions-- if I can read these-- left ventricular dysfunction-- mostly associated with anthracyclines and trastuzumab. The risk can be minimized mostly by identifying who's at risk and tailoring your regimens. And the neurocognitive late effects-- I think the key points are that symptoms are commonly reported. They don't correlate well with what we're picking up on our testing, yet. But there are objective changes that are being consistently picked up. So this is a real phenomenon, and ongoing research is really, I think, going to be important in identifying who's at risk, what's the mechanism, and what do we do about it.

So I think in the next couple years, you're going to be hearing a lot more, because there's a lot of interest now-- a lot of money going into this line of research. And I think ultimately in the next five years probably, maybe 10, we're going to be using more biomarkers-- so identifying who's at risk using biomarkers that we can actually assay in clinic. We'll probably be a lot more in the way of identifying genetic risk-- so subsets based on that. I think our imaging techniques are going to get better with respect to both who's at risk and monitoring patients during therapies. We'll be able to tailor our interventions more closely based on some of these risk assessments.

And then I think you're going to see more in the way of interventions. There are a lot of intervention studies now that-- pilot studies in particular, with cognitive dysfunction and chemotherapy. It's a bit, in my opinion, cart-- horse-- cart-- one is ahead of the other and it shouldn't be. We don't really know what's going on, and yet people are coming up with, I think, interesting but maybe not mechanistically based ways of trying to prevent cognitive dysfunction. Everybody wants an intervention, so you're going to see more of that. There have been some studies already have come out. None of them have been terribly promising yet, but I think you're going to see pharmacologic therapy, and you're going to see behavioral therapy as well.