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HER2-Positive Breast Cancer and the Challenge of Brain Metastases

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the treatment of brain metastases in HER2-positive metastatic breast cancer is Dr. Heather Parsons. She's an Associate Professor in the Clinical Research Division at Fred Hutch Cancer Center in Seattle, where she's also an Endowed Chair in Breast Cancer Oncology Research and Program Head of the Breast Oncology Program. Dr. Parsons, it's great to have you here today.

Dr. Parsons:
Great to be here. Thank you.

Dr. Turck:
Well, starting off with some background, Dr. Parsons, how has our understanding of HER2-positive metastatic breast cancer with central nervous system involvement evolved in recent years?

Dr. Parsons:
So I think when people hear about breast cancer with brain metastases, or brain metastases generally, it's sort of terrifying. But really, in HER2-positive breast cancer, we know that it's actually very common. Somewhere around up to half of patients with metastatic HER2-positive breast cancer will develop brain metastases over the course of their disease, and it really has become, for many patients in that situation, the critical problem. The brain metastases and progression of disease is a thing that we worry most about and struggle most to deal with and treat.

Our therapies now, for HER2-positive breast cancer, are very effective. They're, I would say, some of the most effective therapies we have, but because the disease has a tendency to go to the brain, and because the brain is a sanctuary site, it makes the treatment of brain metastases very important and different from treatment of other systemic metastatic disease. But very encouragingly, recently, some of our systemic therapies have shown strong efficacy in treating brain metastases, and this gives us other options in addition to the local therapy that we always have used, such as radiation therapy and surgery in some cases. So I think it is a field and an area in evolution, but in a positive direction.

Dr. Turck:
Well, I was going to ask, what are the treatment goals when managing brain metastases in this patient population, and how exactly do they differ from those related to management of the primary cancer?

Dr. Parsons:
So, with breast cancer brain metastases, our goals are the same, in that we want to control the disease. But because it has become a sanctuary site, we focus on local therapy, which is different than our treatment of systemic disease in other spots in the body. And so we do use radiation as well as surgery, which differs significantly from what we might do if we had a liver metastases with breast cancer metastatic disease, for example. Our disease control still remains the long-term goal, and we use different tools and have different people involved in the care of patients with breast cancer brain metastases, all with the goal of controlling disease.

Dr. Turck:
I was wondering if you would walk us through the standards of care for patients with HER2-positive metastatic breast cancer who have

brain metastases, particularly the role of newer agents, like tucatinib or trastuzumab deruxtecan.

Dr. Parsons:
Sure. So local therapy still remains a critical part of treatment of HER2-positive breast cancer brain metastases—so surgery for bulkier disease, but more often, radiation therapy. Because of our awareness of breast cancer brain metastases, patients are often getting brain MRIs, and disease is discovered sooner than it might have been previously. And so those local therapies are important, but our systemic therapies, again, have become more effective.

Historically, therapies—monoclonal antibody therapies like trastuzumab and pertuzumab—were not very effective against this brain disease, but we've seen it really dramatically in the HER2 CLIMB study looking at tucatinib in metastatic HER2-positive breast cancer. This study included patients with untreated breast cancer brain metastases, so patients could have had progressive disease and/or no prior, local therapy to their disease, and could have been included in this study. And we saw that patients had a significant improvement in their outcomes compared to the standard therapy arm. And then with trastuzumab deruxtecan, though the initial studies in metastatic disease did not include patients with active brain metastases, subsequent studies and retrospective reviews of other real-world data have been really encouraging. And we do see efficacy of trastuzumab deruxtecan in this setting too.

Those are sort of the two most effective therapies we have. There's some efficacy from older agents like T-DM1, but all of these give us promise, hope, and the inclusion of patients with breast cancer brain metastases in our clinical trials going forward, given the importance of this problem and also these wins in terms of efficacy for these patients.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Heather Parsons about strategies for managing brain metastases in patients with HER2-positive metastatic breast cancer.

So, Dr. Parsons, let's continue our discussion on management in this population. What are some of the key factors you consider when making treatment decisions for patients with brain metastases?

Dr. Parsons:
So if someone has a recently diagnosed breast cancer brain metastasis, we would think first, is that person symptomatic from the disease? What is the size of the metastasis? Is it more amenable to surgical intervention versus radiation? Is the brain met causing structural changes? Is it compressing other areas of the brain? All of those are things that we might think about initially when someone's diagnosed with a brain met.

We also want to think about what and whether someone's had, in terms of prior treatment systemically. And for patients who have had prior local therapy, that factors into our decision as well. And finally—it's always important in all of our oncologic decisions—what are the patient goals and what's the patient's condition from the perspective of the systemic disease as well as the brain met? Many patients with brain metastases, though—again, they sound, very scary—can be very much asymptomatic and otherwise, doing very well with this disease. And so all of those factor into our discussion of management in this population.

Dr. Turck:
And taking a broader view now, how are collaborative models and multidisciplinary approaches changing how we coordinate care for these patients?

Dr. Parsons:
Breast cancer brain metastases in HER2-positive disease are very complicated, collaborative conversations and models, in terms of care. They involve everyone from surgeons to radiation oncologists, medical oncologists, radiology, and supportive care, among others. And so it's particularly important that we work carefully with our colleagues to decide on the best plan. If you meet a patient with a new brain metastases, we don't necessarily go straight toward local therapy, which would have historically been the most often route. And so it's an important discussion between colleagues about what the best plan is for a particular patient in front of us.

Dr. Turck:
Now, before we wrap up our discussion today, Dr. Parsons, are there any promising strategies or ongoing trials that you're watching closely that you're particularly excited about?

Dr. Parsons:
Yes. I think this space is really an exciting area of developing research and addressing this important problem in breast cancer. In particular, because of our knowledge that many patients with HER2-positive disease will develop brain metastases, there's an emphasis on exploring whether a maintenance-type strategy with drugs like tucatinib or others might be important for preventing breast cancer brain metastases.

We're actually running a curative intent study in patients with newly diagnosed stage IV breast cancer that's HER2-positive and using a curative intent approach that includes maintenance systemic therapy for patients with the intention of preventing metastatic spread to the brain.

There are other agents in development as well: small molecule inhibitors that, I think, have promised that they may be effective in this setting. And then the efficacy of trastuzumab deruxtecan, which is not a small molecule but an antibody drug conjugate, has been very promising and influential in terms of how we think about this problem, opening up the possibility of other ADCs having efficacy in this setting. So I think there's a lot of promise for the future. It's still very much an important problem to address and remains the critical problem for patients with HER2-positive metastatic disease, but I'm optimistic for the future.

Dr. Turck:
Such great reflections for us to consider as we come to the end of today's program. And I want to thank my guest, Dr. Heather Parsons, for joining me to discuss how we can optimize care for patients with HER2-positive metastatic breast cancer and brain metastases. Dr. Parsons, thanks for being here today.

Dr. Parsons:
Thank you so much for the invitation.

Announcer:
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