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Differentiating Agents in the Expanding HER2-Targeted Arsenal for Metastatic Breast Cancer

Announcer:
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Dr. Anders:
This is CME on ReachMD, and I'm Dr. Carey Anders. Joining me today is Dr. Sarah Sammons, and our discussion today will focus on the various HER2-targeted agents for metastatic breast cancer.

Sarah, can you start us off by describing some of these agents?

Dr. Sammons:
Yes, absolutely, Carey. We have made really incredible strides in the treatment of our patients with metastatic HER2-positive breast cancer, and we are helping women live longer and longer. And I would even go as far to say that potential cure for HER2-positive MBC is not out of reach in our lifetime.

I would say that there's three categories of therapies that we tend to use for these patients. The oldest tried and true HER2-targeted therapies are the monoclonal antibodies. Those are commonly known as trastuzumab and pertuzumab, and those are the agents that we generally give in the first-line setting with induction of a taxane for most of our patients.

The second class of drugs, which has really become a game changer in MBC over the last decade, are called the antibody-drug conjugates. And these are monoclonal antibodies that target HER2 that are attached by a linker to a payload of chemotherapy.

And then next, we have targeted therapies. And before, I would have just said HER2-targeted tyrosine kinase inhibitors. But now, with some recent data, given the PATINA data, I would also add CDK4/6 inhibitors for our hormone receptor-positive HER2-positive patients.

Dr. Anders:
Well, that's fantastic, and I think we've both seen significant progress over the course of both of our careers, that are very helpful about what's to come. I'm also wondering if you can tell us a bit about the ability of these agents to penetrate the blood-brain barrier for our patients who develop brain metastases, which, as we know, are common consequence of metastatic HER2-positive breast cancer.

Dr. Sammons:
Yes. So, brain metastases in HER2-positive of MBC are definitely a problem. We probably, depending on the study, see metastis to the brain in 30 to 50% of patients. Historically, we would think of the brain as kind of a sanctuary site for metastasis to form.And some studies have even shown that when a patient forms a brain metastis from HER-positive disease, most of the time, their disease from the neck down is actually stable because we're doing so well controlling them with the agents that we have. But not all of the agents that we have are good at crossing the brain-blood barrier.

Historically, we did not think that monoclonal antibodies like trastuzumab and pertuzumab crossed the blood-brain barrier very well. I

would say that we have some newer studies showing that maybe high doses of trastuzumab get in a little better. Sometimes, after radiation, when the blood-brain barrier is interrupted, they can get in. But historically, monoclonal antibodies do not reach the brain particularly well.

Over the last few years, we have learned that antibody-drug conjugates, even though they're large bulky compounds that we did not think we'd get into the brain, they do get into the brain quite well. So, we see with TDM1, the oldest HER2 ADC, we've seen an intracranial response rate around 30%.

And now, strikingly, with the newer HER2 ADC, trastuzumab deruxtecan, or T-DXd, we're seeing intracranial response rates between 60 and 70%. So, these antibody-drug conjugates are getting into the brain.

And then, historically, the smallest molecules, which are the tyrosine kinase inhibitors, such as tucatinib, neratinib, lapatinib, they get into the brain quite well because of their small size.

Dr. Anders:
It's been really interesting to watch this evolution. I think kind of back to the beginning, of when we were starting to test agents in brain metastasis, we were largely relying on the small-molecule tyrosine kinase inhibitors. And then it was this wonderful surprise to see that the antibody-drug conjugates were doing such a lovely job in the intracranial space. And I think that really begs the question of the blood tumor barrier in the setting of metastasis.

And there's a whole body of work on this where, in the setting of metastasis, the blood-brain barrier's effectively breached by the tumors themselves and new vasculature. So, I think there's a lot for us to learn here.

Dr. Sammons:
Have we seen any agents actually prevent brain metastasis yet or prevent a subsequent brain metastasis yet? And what agent would you be most excited might allow us to do that?

Dr. Anders:
There are ongoing studies, such as the COMPASS RD study, which are evaluating moving tucatinib to the residual disease space after neoadjuvant therapy to see if we can decrease intracranial recurrence. And that was somewhat modeled in the NALA study and the ExteNET study, where neratinib did see, in the adjuvant space, particular with ExteNET, showed a slight decrease in brain metastasis. The numbers were low. I think it was like 2.8% versus 1.5%, but that is some evidence that maybe bringing in the tyrosine kinase inhibitors earlier could decrease the rate of brain metastasis for patients who are at higher risk.

I think the jury's still out on the antibody-drug conjugates, and we're awaiting some of the earlier phase data and our ADCs, such as T-DXd, but it is interesting to see the intracranial response rate. So is that going to be a situation where the ADC works well in established brain metastasis, or could it also be protecting the naïve brain prior to metastasis? So, the premetastatic stage. So, very interesting data that we're awaiting.

So, each of these classes of compounds, of course, do come with some toxicity, and I'm curious if you can kind of talk about what you see in your clinic. And what toxicity profiles we would want to be considering as we're prescribing an antibody-drug conjugate or a tyrosine kinase inhibitor in this setting?

Dr. Sammons:
Yeah. Absolutely. When I think about the course of HER2-positive metastatic breast cancer, first-line therapy, at least still in 2024, is taxane with trastuzumab, pertuzumab induction followed by trastuzumab, pertuzumab, and then you would add endocrine therapy if the patient was hormone receptor-positive.

I think, in general, the monoclonal antibodies by themselves are tolerated very well. With pertuzumab, you might see a little bit of diarrhea, a little bit of rash. Certainly, with trastuzumab or really any HER2-targeted agent, there's a small risk of developing heart failure that's reversible when you take away the agent, and so we have to monitor the heart.

But the monoclonal antibodies are very well-tolerated, and it's a really nice period in the beginning of treatment for our patients to be off cytotoxic chemotherapy, off continuous antibody-drug conjugate. And some patients do well just on the monoclonal antibodies for years. So, I think that that's a very nice period for our patients.

We get into the second-line: I think, for most patients, trastuzumab deruxtecan is the agent that we're using. I think, for most patients at this point, based on the results of DESTINY-Breast03, T-DXd outperformed T-DM1 very substantially. The progression-free survival was four times T-DM1 with T-DXd. T-DXd does have some side effects that we have to counsel patients on.

I counsel my patients that there will be some nausea that we'll have to manage. There will be some fatigue. And then, I'm also always

telling them about the risk of developing pneumonitis, which is inflammation of the lungs, which can be cough, shortness of breath, those things that we take very seriously.

The TKIs: I think tucatinib, based on HER2CLIMB and HER2CLIMB-02, is the one that we're using the most, probably with capecitabine and trastuzumab. It's pretty well-tolerated: some diarrhea is possible, a little bit of nausea. We have to watch the liver enzymes, but I think with supportive management and open communication with patients I think most of these are pretty manageable.

Dr. Anders:
No, completely agree, and I think this is where the art of medicine comes in and really picking the right agent for the right patient. I recently had a patient in my practice who has a very hard time swallowing pills. And so we actually were moving forward with an IV therapy as opposed to a therapy which requires potentially six pills twice a day. So, I think it's really nice to understand these toxicity profiles and being able to match the patient so that we can maximize their quality of life while we're trying to provide best control of disease.

Well, thank you all for watching, and we hope this discussion will be useful to you and your patients in your practice.

Dr. Sammons:
Thank you.

Announcer:
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