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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Systemic Management of Brain Metastases in HER2+ BC: Emerging Strategies and Treatment Approaches

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Anders:
This is CME on ReachMD, and I'm Dr. Carey Anders. In this brief lecture, I'll be reviewing the emerging systemic treatment approaches for managing our patients with brain metastasis arising from HER2-positive breast cancer.

The mainstay of our care for patients with brain metastasis, historically, has been local therapy. And in this case, we have the options of neurosurgical resection of large solitary lesions, particularly when the diagnosis is in question.

We also have radiation, and that comes in two main categories: we have whole brain radiation therapy, which had historically been the mainstay. However, that is quickly moving out of the spotlight as we have more focused radiation therapy approaches that decrease the risk of longer-term neurocognitive sequelae of whole brain.

When we do have patients with multiple lesions or diffuse disease, and whole brain is an option, many times our radiation oncologists are considering strategies to improve longer-term neurocognition with hippocampal sparing techniques and the addition of memantine.

But I would say, in the current era, most of our patients are receiving stereotactic radiosurgery, which is really high doses of radiation delivered directly to the CNS lesions: 2 or greater. This can be given in one fraction or up to five fractions over the course of 5 days. And that really improves local control to the rates of 90%, but it does leave the remainder of the brain at risk for future metastasis. And that's really where our systemic therapies come in.

In the past, we had very few options for patients with HER2-positive breast cancer brain metastasis, with the first therapy in this space being the tyrosine kinase inhibitor lapatinib. But luckily, over the past decade, we've added many new compounds to the toolkit, and I'll review some of those here today.

Most patients in the HER2-positive space are going to start treatment with the CLEOPATRA regimen of a taxane, trastuzumab, and pertuzumab. And if they develop a CNS event on antibody therapy, they can go to radiosurgery or other local therapies. And then maintain their systemic therapy as long as the extracranial disease is stable as per the ASCO guidelines.

If we were to see continued progression in the brain or also concurrent extracranial progression, we really have two main options here. Two classes of drugs: one would be that of the antibody-drug conjugates, and the other would be the tyrosine kinase inhibitors targeting HER2 specifically.

So, starting with the antibody-drug conjugate, this would be the trastuzumab deruxtecan compound, which includes a deruxtecan payload to the HER2 antibody and a high drug-to-antibody ratio of approximately 8. And we've seen efficacy in the CNS, surprisingly.

We didn't expect for a large, bulky, antibody-drug conjugate to have intracranial activity.

But in fact, we've seen many PRs as well as complete responses in the brain across the DESTINY-Breast01, 02, 03, and now 12 studies. Intracranial response rates can be as high as 60% with this compound, and they are quite durable: anywhere from 12 to 18 months, depending on the study.

We also have the option of tyrosine kinase inhibitors, and the most specific HER2-directed tyrosine kinase inhibitor that we currently have FDA-approved is tucatinib. And this compound, in combination with capecitabine and trastuzumab, was FDA-approved in the setting of metastatic HER2-positive breast cancer, including brain metastasis, based on the original HER2CLIMB study.

There was also a follow-up study, HER2CLIMB-02, that combined tucatinib with TDM1. But I will say, in clinical practice, the large majority of physicians will prescribe the HER2CLIMB-01 with capecitabine, trastuzumab, and tucatinib at present. Whether or not to start with a tyrosine kinase inhibitor or the antibody-drug conjugate in this space is somewhat up to the investigator and the patient. In the ASCO guidelines, in the metastatic setting, T-DXd is the clear second-line regimen, but in — in the setting of brain metastasis, we did give some leniency to bring HER2CLIMB up to the second-line as well.

And this may depend on the patient's preference as to whether or not they were comfortable with an oral-based therapy: whether or not they had pre-existing pulmonary disease that might place them at higher risk for T-DXd.

I think we do have some equipoise at this point in time between the trastuzumab deruxtecan versus tucatinib-based regimens in second-line.

When you move beyond tucatinib and trastuzumab, at this point, we're starting to think about other combinations, such as the TDM1/neratinib combination as per the TBCRC 022 study. And neratinib, as a reminder, is an irreversible inhibitor of both HER1 and HER2 or EGFR and HER2. And in combination with TDM1, we saw about a 30% intracranial overall response rate, inclusive of patients who had already received monotherapy with TDM1.

It is important to note, however, that in this combination strategy, we do lower the dose of neratinib from the standard 240 with capecitabine as per the NALA study. In combination with TDM1, we dose neratinib at 160 mg.

They're also many other studies that support the use of trastuzumab deruxtecan in the setting of progressive brain metastasis. Those that are notable include the DEBRA study and the TUXEDO study. And there are also some emerging evidence of activity of both tucatinib and T-DXd in the setting of the challenging space of HER2-positive leptomeningeal disease, which many times can be a late event for our patients with HER2-positive breast cancer.

So, with that, our time is up. And I thank you for your attention.

Announcer:
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