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Updates in Treatment of HER2-Positive Breast Cancer and Brain Metastases



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At an *Around the Practice*® event hosted by CancerNetwork®, experts spoke about updates in the treatment of patients with HER2-positive breast cancer. The discussion was led by **Sara A. Hurvitz, MD**, medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit, codirector of the Santa Monica-University of California, Los Angeles (UCLA) Outpatient Oncology Practices, director of the Breast Cancer Clinical Trials Program at UCLA, and an associate professor at the David Geffen School of Medicine at UCLA.

Additional experts included **Stefania Maraka, MD**, assistant professor in the Department of Neurology and Rehabilitation at the University of Illinois College of Medicine at Chicago in Illinois, and **Ruta Rao, MD**, director of Coleman Foundation Comprehensive Breast Cancer Clinic, medical director at Rush University Cancer Center, and assistant professor in the Department of Internal Medicine, Division of Hematology, Oncology, and Cell Therapy at Rush Medical College in Chicago.

CASE 1

- A 30-year-old woman presented with a right breast mass in April 2016.
- Biopsies were taken on April 7, 2016.
 - The right breast had a poorly differentiated invasive ductal carcinoma (IDC), grade 3 disease, estrogen receptor (ER) expression of 100%, progesterone receptor (PR) expression of 95%, and HER2 immunohistochemistry (IHC) of 3+.
 - The right axillary lymph node had poorly differentiated adenocarcinoma with metastases to the lymph node.
 - The tumor was retested, with ER less than 90%, PR at 70%, and HER2 amplification of 3+ with a ratio of 13.5.
- A bone scan on April 24, 2016, showed widespread skeletal metastases. CT of the chest, abdomen, and pelvis showed many hepatic masses.
- Treatments received:
 - Between May 2016 and August 30, 2016, trastuzumab (Herceptin) plus pertuzumab (Perjeta) plus abraxane was given and liver function tests normalized.
 - Trastuzumab plus pertuzumab was given from September 2016 to May 2019.
 - On December 11, 2018, a bilateral salpingo-oophorectomy took place, with ER at 90%, PR at 5%, and HER2 IHC 3+.
 - IDC grade 2 was found in the left breast in April 2019, and ER was 75%, PR was negative, and HER2 IHC was 3+.
 - From April 14, 2020, to June 9, 2020, fulvestrant plus

trastuzumab plus pertuzumab was given.

- Restaging:
 - On August 2, 2020, a PET scan was done and found progression of disease in the lymph nodes and well-healed osseous lesions, with an increase of standardized uptake volume in left breast lesion.
 - August 6, 2020:
 - Breast ultrasound showed a slightly decreased size of the left breast mass and the right breast was stable.
 - CT of the chest, abdomen, and pelvis showed a small increase in lymph nodes.
 - Brain MRI showed progression.
 - Treatment for brain metastases
 - Brain radiation was complete on September 2, 2020.
 - On September 8, 2020, trastuzumab was given and tucatinib (Tukysa) plus capecitabine was started.
 - Follow-up
 - Capecitabine dose was reduced on September 9, 2020, and held until January 14, 2021, with continued treatment of tucatinib plus trastuzumab.
 - An MRI of the brain on January 10, 2022, found favorable and expected temporal evolution of post-radiation changes.
 - PET/CT was given February 18, 2022, and was stable compared with one given January 10, 2022.

HURVITZ: Can you briefly review the up-front standard-of-care treatment options for a patient with metastatic

HER2-positive breast cancer and how you are incorporating endocrine therapy into the regimen?

RAO: For first-line therapy, it's well established that using the dual antibody therapy trastuzumab plus pertuzumab plus taxane is our standard first-line regimen. We saw [the data supporting this regimen] many years ago in the [phase 3] CLEOPATRA trial [NCT00567190], in which the median overall survival [OS] for these patients had improved significantly with the use of the combination [vs trastuzumab/chemotherapy]. The median OS at last reporting was 57.1 months for the group of patients who received the dual antibody therapy [HR, 0.69; 95% CI, 0.58-0.82].¹

Thinking about when to add hormone therapy, we are hopeful that these patients will be on treatment for a long time. It behooves us to give them not only the best treatment for their disease but also something that they can continue to tolerate in terms of [adverse] effects. That's why I stopped her chemotherapy after she had shown a very nice response, not only with the breast exam but also on PET-scan imaging. Because her tumor was so strongly positive for ER and PR [expression], we had decided to go down the route of pursuing endocrine therapy and our first treatment was actually to do the oophorectomy, not really expecting that we would find metastatic disease in her ovaries.

HURVITZ: How do you think about which chemotherapy to pair with trastuzumab and pertuzumab?

RAO: This is a personal preference. I am more comfortable with weekly paclitaxel. I usually give it [every] 2 weeks—1 [week on], 1 week off—more for tolerability reasons. That's what I had started with in this patient. When she reacted to the paclitaxel, that's how she moved to abraxane in its place. For a patient who is not able to come in for the second

week of weekly paclitaxel, docetaxel is a good option. That was the drug that was used in the CLEOPATRA study, so that would be also following the exact CLEOPATRA protocol.

HURVITZ: What are some of the various treatment options available for this patient now and how do you choose among the second- and third-line regimens available?

MARAKA: For patients with HER2-positive breast cancer, our team of neuro-oncologists and breast oncologists work in collaboration. The main decisions come from breast oncologists, and we are helping with this decision. The first question we are trying to answer is if this patient will get systemic treatment plus or minus local therapy with radiation or surgery, then what is the most appropriate systemic treatment as well? For surgery itself, we know for single lesions—assuming that they are also symptomatic—we want to do resection followed by SRS [stereotactic radiosurgery]. We know radiation improves survival and local control and if it is multiple lesions, especially if they are symptomatic, then we are doing whole-brain radiation.

When it comes to systemic treatment, the last few years we have been getting away from radiation to use more of the systemic treatment. There are now accumulated data that show, especially for asymptomatic brain metastatic lesions, that tucatinib can produce a good response and we can avoid radiation to use it later. Traditionally in the past, we were using lapatinib [Tykerb]; but it was found that neratinib [Nerlynx] was more beneficial in the [phase 3] NALA trial [NCT01808573].² Now with the new [phase 2] HER2CLIMB study [NCT02614794], tucatinib in combination with capecitabine is the systemic treatment that we are using mostly in the presence of brain metastases.³

When we have progression on tucatinib and capecitabine, then the next systemic treatment that we are considering with breast oncologists is trastuzumab deruxtecan [Enhertu; T-DXd]. Now, there are newer data that show some benefits after progression with tucatinib. Mostly those are the options that we are considering with breast oncologists, radiation oncologists, neurosurgery, and tumor boards to make a decision.

HURVITZ: Can you describe your process for deciding to use tucatinib. In doing so, take us through the available data relating to its benefits in the brain for a patient such as this?

RAO: We had the multidisciplinary team involved here, but the patient developed initial brain metastasis about 2 years into her metastatic treatment. About a year later, she developed some additional small brain metastases and had SRS. About another year later, she was noted to have an increase in the size of 2 of these masses, and at that time she underwent whole-brain radiation therapy. We were switching her systemic therapy as well and because I knew that over time she had progression of her brain metastasis, I wanted to choose a therapy that would be effective systemically as well as in her brain.

With the help of our neuro-oncologist, we decided to treat her with the triplet regimen of tucatinib, capecitabine, and trastuzumab. This was based on the HER2CLIMB data. I think we are all familiar with these data showing that adding tucatinib to the capecitabine trastuzumab combination improves not only the progression-free survival but also OS for these patients. Specifically, the unique thing about this trial was that it allowed for patients with brain metastasis. We have seen that the addition of tucatinib has been able to reduce

the risk of intracranial progression or death by 68% with a hazard ratio of 0.32 [95% CI, 0.22-0.48; $P < .0001$] and reduce the risk of death for these patients with the addition of tucatinib. We also saw an increase in the intracranial overall response. These data were behind my decision to start her on this specific triplet regimen.⁴

HURVITZ: How do neuro-oncologists fit in the management of HER2-positive breast cancer?

MARAKA: We have a very close collaboration with our breast oncology team. We are deciding together what's the best systemic treatment for these patients. We are also doing surveillance MRIs in the brain. In my clinic, we will see the patients and the brain MRI at the same time and give our interpretation together with the neuro-radiologist regarding progression, radiation necrosis, and if we need to do more specialized imaging like perfusion studies or spectroscopy. Those are studies that help us understand if the patient is experiencing progression or radiation changes. That's a very common question that we have to answer. We are helping with the neurological examination, so we understand if specific symptoms and findings on the exam are consistent with the progression of these patients or [adverse] effects from medications. Many times, our patients will be on steroids and they will present with weakness and we'll have to understand if this is clinical progression or if it is steroid-induced myopathy. For our patients who have CNS [central nervous system] involvement with a lymph-immune arterial disease, we have established a clinic with intrathecal treatments, and neuro-oncology is leading the decision to administer intrathecal drugs. That's the environment between neuro-oncology and breast oncology collaboration.

CASE 2

- A 53-year-old woman with metastatic ER/PR-positive, HER2-positive breast cancer who has osseous and lung metastases at diagnosis in 2017.
- Weekly paclitaxel plus trastuzumab plus pertuzumab was started and a good response occurred.
- Brain metastases developed with spinal cord parenchymal metastases and potentially leptomeningeal disease in 2019.
- Treatment
 - Whole-brain radiation therapy was started in 2019 at 30 Gy.
 - Neratinib by mouth was administered followed by capecitabine at 750 mg/m² twice a day every 14 days in a 21-day cycle.
 - In 2020, intrathecal trastuzumab was given.
 - In July 2020, the patient progressed and switched from neratinib to tucatinib.

HURVITZ: How might you have treated this patient in your practice?

RAO: In general, the principles are the same. I would give the TKI [tyrosine kinase inhibitor] therapy because we know that that can cross the blood-brain barrier. Now with the availability of tucatinib, and like you said with the larger data set that we see from HER2CLIMB, I would choose tucatinib with capecitabine and trastuzumab. But given the time that this patient was diagnosed, I would have agreed to use the TKI available.

HURVITZ: Are you prescribing neratinib? Are you managing the [adverse] effects with this drug?

MARAKA: No, the breast oncology team is prescribing the systemic treatment and they are following toxicity.

For this specific patient, she did have diarrhea when she was on neratinib and capecitabine. When we switched to tucatinib, her diarrhea was less prominent and she had fewer [adverse] effects. As we know, tucatinib is a selective drug that has [fewer adverse] effects.

HURVITZ: How are you managing or trying to mitigate the adverse effects that go along with neratinib in your practice?

RAO: As you know there is also an extended adjuvant indication for neratinib in patients who have finished a year of [intravenous] trastuzumab. In that setting, we tend to do the dose-escalation method of starting with a lower dose and increasing as tolerated. The other thing that's important for any patient that's starting neratinib, whether it's in the early adjuvant or metastatic setting, is to have all team members on board. The patients have to be well educated to call with any signs of diarrhea. This is not something they should try to wait out. It's upon us to educate them, with nurses and pharmacists who also follow up with the patients regularly outside of clinic visits to see how they're doing with this.

HURVITZ: Can you talk about the prevalence of leptomeningeal metastases in HER2-positive breast cancer and why is it so difficult to treat? What is your preferred regimen for treating this?

MARAKA: Leptomeningeal disease is highly prevalent in my clinic because [we] have selection bias, but it's a rare disease. In [patients with] breast cancer, it accounts for less than 5% of cases. Now the incidence of [leptomeningeal disease] is increasing and this is multifactorial. We now have better systemic treatments so patients are surviving longer. Now we start seeing more and more leptomeningeal diseases based on improved survival of our patients. The MRI technology is advancing, so we can also identify smaller leptomeningeal enhancement that we may have

missed before by using low magnets on our MRIs.

The collaboration with the neuro-oncology and breast oncology teams is advancing the field to identify patients with leptomeningeal disease [earlier] because we have higher clinical suspicion when we're examining these patients. It's a hard-to-treat disease because we do have a very protected environment for our brain. We have the blood-brain barrier and the cerebral spinal fluid that doesn't allow drugs to [penetrate]. That's the main difficulty we are facing in having successful treatments to this tumor. With leptomeningeal disease, it creates a bulky disease and large lesions that are in the leptomeningeal layer both on the brain and the spinal cord. It doesn't allow both systemic and intrathecal treatments to get into those bulky areas. The treatment that we have for leptomeningeal disease is very different.

You do want to have systemic treatment for those bulkier lesions because the local intrathecal treatment will have a penetration success of maybe 1 mm, so you will not be covered. Also, it would make sense to use radiation treatment for larger lesions that are creating symptoms. ■

References

1. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530. doi:10.1016/S1470-2045(19)30863-0
2. Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38(27):3138-3149. doi:10.1200/JCO.20.00147
3. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619. doi:10.1200/JCO.20.00775
4. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-1154. doi:10.1056/NEJMoa2115022