

HER2+ Breast Cancer and Brain Metastases: Challenges and Treatments



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At an *Around the Practice*[®] program hosted by CancerNetwork[®], a panel of experts discussed the implications of brain metastasis among patients with HER2-positive breast cancer, as well as optimal treatment strategies in advanced settings. The discussion was led by **Joyce O'Shaughnessy, MD**, the Celebrating Women Chair in Breast Cancer Research at Baylor University Medical Center and director of the Breast Cancer Research Program at Texas Oncology, US Oncology in Dallas.

Panelists included **Virginia Kaklamani, MD**, a professor of medicine at The University of Texas Health Science Center at San Antonio (UT Health San Antonio) and leader of the Breast Cancer Program at UT Health San Antonio MD Anderson Cancer Center; **Andrew J. Brenner, MD, PhD**, a medical oncologist and neuro oncologist at Texas Oncology–Austin Brain Tumor Center; and **Heather McArthur, MD, MPH**, associate professor, Komen Distinguished Chair in Clinical Breast Cancer Research, and clinical director of the Breast Cancer Program at Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center in Dallas, Texas.

Second-Line Treatment Strategies

O'SHAUGHNESSY: How do you typically treat patients in the second-line setting?

KAKLAMANI: Until recently, the standard of care would be giving ado-trastuzumab emtansine [T-DM1; Kadcyla] based on the phase 3 EMILIA trial [NCT00829166].¹ Now we have new data. We have another antibody-drug conjugate, fam-trastuzumab deruxtecan-nxki [T-DXd; Enhertu], based on the phase 3 Destiny-BREAST03 trial [NCT03529110], which would probably be my first option here.² Another option is the phase 2 HER2CLIMB [NCT02614794] regimen: tucatinib [Tukysa], trastuzumab, and capecitabine.³

O'SHAUGHNESSY: When patients are asymptomatic, you always [wonder whether there's any role for endocrine therapy]. Usually if patients are on maintenance trastuzumab and pertuzumab [Perjeta], that's where I might use an endocrine agent because it might prolong progression-free survival. It seems it's the patients with estrogen receptor [ER]–positive disease who eventually experience progression. Some patients stay on trastuzumab and pertuzumab for life—[most often] those

with ER-negative disease rather than ER positive.

MCARTHUR: In the phase 3 CLEOPATRA trial [NCT00567190], hormone therapy was permitted as maintenance therapy, but it wasn't mandated.⁴ As such, there was a lot of variability around practice.

Nonetheless, I agree. I've begun incorporating hormone therapy for patients with hormone receptor [HR]-positive disease who have a good response and whom I maintain on HER2-directed therapy.

BRENNER: In terms of tolerability and [ease of] tailoring to individual patients, trastuzumab seems to be well tolerated. Most patients will follow that [regimen] very well. The response rates look great.

With capecitabine, you do have to worry sometimes about diarrhea, and patients might not be able to tolerate the HER2CLIMB regimen in the second-line setting. As such, you might favor trastuzumab deruxtecan in that setting.

Brain Metastases: Clinical Practices

MCARTHUR: When is the best time to screen for brain metastases?

O'SHAUGHNESSY: This is an interesting question. We don't see many recurrences these days in our practice among patients treated with docetaxel, carboplatin, trastuzumab, and pertuzumab, followed by optimal endocrine therapy. The history of first-line HER2-positive metastatic disease is such that more than half of cases are de novo metastatic these days.

Those patients can do great. These are the patients who can stay on [treatment] for a very long time. We do see recurrences, like in the ER-negative, HER2-positive setting. Often it's a consequence of this hybrid cancer of HER2-positive and basal-like [disease], which isn't as sensitive to HER2-based therapy.

What is your standard first-line treatment in these patients?

MCARTHUR: I've had the rare patient on maintenance trastuzumab plus pertuzumab for years—sometimes even decades—who needs to take a break from

therapy for travel or personal reasons.

Given the risks [surrounding] HR-negative, HER2-positive disease, I've been reluctant to introduce “drug holidays” in that population. I might, in that setting, continue with trastuzumab/pertuzumab, reintroduce a taxane if I was concerned about progression, [and then] move on to second-line therapy if there's an adequate interval since last exposure. This is the artfulness of medicine.

BRENNER: It depends also on a patient's disease burden. I sometimes see patients who start off with minimal disease burden who do very well [on treatment] for a long period of time, who can take a break from trastuzumab/pertuzumab and continue on an aromatase inhibitor. Again, you have to base [the decision] on the individual patient, and that's the art of medicine.

O'SHAUGHNESSY: What are the options for second-line therapy in these patients?

KAKLAMANI: I don't [perform brain imaging] unless a patient has symptomatic disease. If a patient does develop symptomatic disease, we have options to treat them and improve their symptoms. Many of my colleagues will perform brain imaging at first or second progression, which is perfectly fine, but I differentiate between active and inactive brain metastases. HER2CLIMB was the only randomized phase 3 trial to include patients with active brain metastases. In that case, I would favor tucatinib, but for those without brain metastases or with treated brain metastases, T-DXd is my go-to agent.

O'SHAUGHNESSY: When and how should clinicians perform surveillance imaging?

BRENNER: The recommendations regarding surveillance imaging for brain metastases have changed slightly; it's no longer discouraged, [but it's not] recommended either. The data are indeterminate.

[However,] there are some data suggesting what changes with early detection. There was one study from around 10 years ago in which investigators screened patients with HER2-positive disease from the beginning.⁵ They treated some of those patients with asymptomatic brain

metastases that were incidentally found at staging and compared them with other patients who were only treated at the time they became symptomatic. There was no difference in terms of survival outcome, but there were differences in terms of progression, which you would expect.

Now that there are data on a tucatinib-based combination from HER2CLIMB and on T-DXd from the phase 2 TUXEDO-1 trial [NCT04752059], you have to wonder [whether] it's time to revisit those studies.⁶ As of right now, however, the data [are] not convincing that we can change outcomes by performing early imaging to detect asymptomatic brain metastases.

O'SHAUGHNESSY: What is your approach in your practice?

BRENNER: There are several important points to consider when talking about brain imaging.

Firstly, 50% of the HER2 metastatic population will develop brain metastases. That's a large number. Moreover, the time to development of brain metastases is relatively short; it's about 12 months from the diagnosis of metastatic disease. About 60% of these patients will develop brain metastases prior to their second-line regimen. So it tends to happen early.

I'm always vigilant when looking for neurologic symptoms. Sometimes it could be something as simple as a patient not feeling cognitively well or having an increased level of fatigue. Sometimes it could be something more specific—some neurologic symptoms that clearly indicate brain metastases. Clinicians should have a very low threshold for concern. That's the best way to go.

MCARTHUR: This is a bit of a moving target. As has been mentioned, we don't have much data to inform when we should be looking for brain metastases and whether early surveillance impacts the course of the disease. In a recent update from the phase 3 KATHERINE trial [NCT01772472], there was a surprising number of patients who presented with brain metastasis who had residual disease,

which probably heightened my awareness.⁷ [Nowadays we have] treatment options that are effective in patients with brain metastases, which has historically been an area of unmet need, but again, there are no data.

I can't say I'm performing brain imaging up front at metastatic diagnosis, but I am watching [for brain metastases] earlier on than I have historically. Whereas before I've looked only when patients had symptoms, now I might look when transitioning to second-line therapy.

KAKLAMANI: If I perform imaging, it'll be an MRI, but I don't typically perform it unless a patient has a symptomatic manifestation. [Of course], you can't ignore little symptoms because they might end up being important. You don't want a patient going into the hospital with a seizure. If you're able to capture that symptom before it manifests itself with a seizure, that can be critical.

O'SHAUGHNESSY: What is the role of the neuro-oncologist in the treatment of HER2-positive patients?

BRENNER: It varies from practice to practice, but there are a couple different pivotal roles. One is to help with symptom management for patients experiencing premetastasis. You're often dealing with seizures, edema, and even the consequences of prior treatments, such as stereotactic radiosurgery [SRS]. It's often difficult to discriminate between progression and pseudoprogression from prior treatment. We have some ways we can help with that [as neuro-oncologists, such as] perfusion imaging, which we may be a little more familiar with than the general medical oncologist.

Additionally, neuro-oncologists can help determine how to treat a patient with local therapy. [For example, they can help with] neurosurgery for a craniotomy to remove a symptomatic solitary large lesion, followed by SRS, switching to whole-brain radiation with hippocampal avoidance [while] ensuring that patients are on memantine to preserve cognitive function.

So [neuro-oncologists help] with both decision-making and management of morbidity. Given that 50% of patients with HER2-positive metastatic breast cancer will have brain metastases, management of morbidity is important.

O'SHAUGHNESSY: What are your practices regarding third-line treatment?

MCARTHUR: I think about the location of metastasis. I think about the burden of disease. I think about intervals, about prior exposure to therapy. In the first-line setting, I might reintroduce a taxane if there has been a sufficient interval. I think about timelines since last exposure, and brain metastasis is a critical consideration.

I also think about patient preference because now we have options, and patient input is critical. I'm struggling a bit with T-DM1. Where do I fold it into the treatment? Is it a third-line treatment? Is it fourth line or beyond? Those are becoming very nuanced discussions.

O'SHAUGHNESSY: How can clinicians control systemic disease and also try to prevent the clinical manifestation of brain metastases?

BRENNER: Generally speaking, if a patient has untreated brain metastases and progresses intracranially but has good extracranial control, I don't switch to a systemic regimen. We treat locally first to manage the brain metastases and [then] continue the systemic regimen. That's very important: If you have local treatment options, you don't abandon therapy.

Once a patient does not have local treatment options available anymore and if they have recurrence at the site of prior treatment, they're not a candidate for either craniotomy or radiation. At that point, I look toward which [treatments] have the best central nervous system [CNS] activity, and tucatinib has the best [supporting] evidence, with 50% of patients in HER2CLIMB having an intracranial response. Those patients tend to do very well on the tucatinib regimen.

Other treatment options include T-DXd, supported by data from TUXEDO-1, which is a very small study, but it showed a

high level of activity. There are other soon-to-be-published studies showing the CNS activity of T-DXd. We also have salvage regimens such as lapatinib [Tykerb], but that becomes a questionable option after tucatinib.

O'SHAUGHNESSY: Can any agents forestall the development of brain metastases?

KAKLAMANI: Margetuximab-cmkb [Margenza] is the most recent drug to be approved in the HER2 space.⁸ We don't have the CNS data, but we know it's an active agent and we can combine it with several chemotherapeutic options to benefit the right patient.

Otherwise, regarding neratinib [Nerlynx], I draw from the phase 3 ExteNET trial [NCT00878709], in which neratinib prevented the development of brain metastasis in an early-stage setting.⁹ We know that neratinib is active. Will it work after tucatinib? We don't know. We don't know if tucatinib will work after T-DXd either.

All these trials are evolving so quickly that we have a lot of questions without answers, but we've always done this in oncology. At some point, we have to work with the data we have.

O'SHAUGHNESSY: In the third line, I tend to treat everyone with tucatinib, capecitabine, and trastuzumab. This is because of the evidence [supporting them] but also because of the subset analysis of patients who hadn't yet had brain metastases, in whom [this regimen] decreased the incidence of these metastases.¹⁰ We don't know if it prevents these metastases, but it reduces the risk.

Hopefully the phase 3 CompassHER2 RD trial [NCT04457596] will finally show some impact on brain metastases. Given that more than 60% of patients will develop these metastases, it's best to delay them for as long as possible.

BRENNER: Most of the available data on T-DM1 [shows that it] prevents progression of CNS metastasis in patients with stable disease or responses in stable disease, [but it doesn't prevent] brain metastasis [altogether]. You need to differentiate

[between] stable vs active brain metastasis. I'm less comfortable using T-DM1 for patients with active brain metastases because we don't have solid data.

KAKLAMANI: The one important thing is for patients to be compliant. We've talked about the benefits of oral agents, but if a patient doesn't take them—or doesn't take them correctly—they won't work.

We have nurses and pharmacists call patients to ensure they receive the drug and that they're compliant with their appointments because [otherwise] they may not come every 3 weeks for chemotherapy. Assuming all this is in place, the HER2CLIMB regimen is my go-to [in the third line].

These antibody-drug conjugates that are large molecules somehow do treat brain metastases. Especially if you've treated one of these metastases, the blood-brain barrier we all love to discuss probably doesn't exist anymore, right?

BRENNER: Yes, this is a very active area of research. There's the blood-brain barrier and what we call the blood-tumor barrier, which is usually denuded of the structures [that] help prevent things from crossing through, such as astrocytes and parasites. There are some studies of radiolabeled antibodies showing that the concentration within brain metastases is much higher than in normal brain [tissue]. So they do get across.

The question is: to what extent do they get across? It's obviously not going to be the same as in other parts of the body where the larger molecules can pass through. It is disrupted. The amount that gets across is different than the rest of the body, and [this amount] may not be sufficient to result in activity.

O'SHAUGHNESSY: How often should clinicians perform brain MRIs once a patient has developed a brain metastasis?

BRENNER: For a patient who is clinically asymptomatic after treatment, the guidelines recommend every 2 to 3 months. That's what I do in my practice. I perform one every 2 months. I prefer the shorter interval because it gives me a little

more time to be proactive. Sometimes you can monitor lesions to obtain more clinical data.

O'SHAUGHNESSY: Let's imagine a patient who receives T-DXd and a brain MRI every couple months and [that] she develops a couple of brain metastases but remains systematically stable on her regimen. How would you manage this?

MCARTHUR: This is why multidisciplinary collaboration is so critical. Typically, it depends on what's possible locally, whether that be additional SRS, whole-brain radiation, or neurosurgery. Afterward, I would continue the systemic therapy, assuming the non-CNS disease is controlled. Local strategies are important for controlling active brain metastasis.

O'SHAUGHNESSY: As a neuro-oncologist, is this what you would recommend?

BRENNER: Yes, that's what the data currently [show]. For patients with endocranial progression, you give a local therapy first, and you continue with the systemic agent; you maximize its use.

If the patient has new lesions that are recurrent in an already-treated area, it becomes more complicated. You need to consider what your salvage regimens are. [You need to consider] if the patient is a candidate for whole-brain radiation with hippocampal avoidance, for example, if they've already received SRS.

There's also this concept of brain metastasis velocity. One thing we need to decide is: Should you give SRS to a patient if they have 1 or 2 brain metastases? What was the timeline since their prior brain metastasis?

Some of the studies examining salvage therapy suggest that if a patient has more than 4 brain metastases per year, you probably need to move from a stereotactic approach to a whole-brain treatment or at least consider whole-brain with hippocampal avoidance for these patients with a higher brain metastasis velocity.

O'SHAUGHNESSY: Many guidelines are around relying on local therapy for the brain and staying the course on a successful systemic therapy. If somebody keeps developing these metastases or if they develop

multiple or large [metastases], isn't it time to think about a treatment that might do a better job for the brain?

BRENNER: How HER2CLIMB was conducted, and how I conduct my practice, is thus: Patients with an active brain metastasis had to be clinically stable, and there must be time for systemic therapy to work. [When treating] patients with very large tumors causing a lot of mass effects or patients who have disease in a very eloquent area, you might not have time to wait for a systemic regimen.

As such, you also need to consider, as was done in the study, whether the symptoms derive from the metastasis when choosing [between] an active, systematic CNS regimen and local therapy.

Halting Treatment, Switching Therapies

O'SHAUGHNESSY: When and how do you make the decision to halt a treatment?

MCARTHUR: These are luxurious challenges because we have options now. We haven't yet talked about toxicity monitoring [regarding] T-DXd and interstitial lung disease [ILD] and how it coincides with monitoring for brain metastasis. I would consider switching [treatments if a patient had] recurrent brain metastasis.

O'SHAUGHNESSY: If a treatment is beginning to show red flags, [such as with] life-limiting sites of metastasis, then we have to [respond].

BRENNER: That's a great point. For patients who develop brain metastases from HER2-positive disease, 70% will die from CNS progression. It's important to continue treating them systemically if you feel their local options are running out.

KAKLAMANI: You get the gut feeling [on when to switch treatments]. Every time you do a scan, you're starting to see the brain disease taking on a life of its own. Regardless of how much we love our systemic agents, at some point, we realize that they're not controlling this disease. Though I [may] try to continue it for as long as possible, I know deep down that I'm not [treating the disease in] the brain.

I might be able to use SRS, but at some point, if you use enough SRS, it's like doing whole-brain radiotherapy.

O'SHAUGHNESSY: Could you avoid SRS and just treat with the tucatinib triplet?

BRENNER: If a patient isn't terribly symptomatic, has active brain metastases, and you're worried about administering more local therapy, you can. I have and will do this. I will switch patients to a CNS-active regimen like the tucatinib triplet, and I've seen great results.

The question becomes: When do you drop the capecitabine? [At a certain point you achieve] good control intracranially, and if the patient has been on capecitabine for a while, they [tend to experience] hand-foot syndrome [or] some level of diarrhea.

O'SHAUGHNESSY: How do you manage the toxicity?

BRENNER: I drop the capecitabine once they start to develop these toxicities, and I keep them on tucatinib and trastuzumab. Sometimes I [can achieve] excellent ongoing control with that [approach].

MCARTHUR: I have to be honest. I've been administering the capecitabine backbone in a 1-week-on, 1-week-off fashion based on the dose-dense modeling by Larry Norton, MD, and colleagues.¹¹ I find it's much better tolerated than a 2-weeks-on, 1-week-off [schedule].

KAKLAMANI: I will bring patients back quickly to ensure they're taking the regimen correctly and that their adverse events [AEs] are manageable. I typically continue administering capecitabine until I begin to see fatigue. Importantly, fatigue is not necessarily just from the drug.

Especially with HER2-positive disease, patients [can] live for more than 5 years with metastatic disease. This is a marathon, not a sprint. They're going to receive a lot of chemotherapy in their lifetime, so we have to pace ourselves. The minute I see that they're running out of patience, I halt it.

If I do have to give capecitabine and the patient has had a lot of toxicity, I switch to the 1-week-on, 1-week-off approach. There [are] some data from the

gastrointestinal world suggesting it may be as efficacious [as the alternative], which is great, but I will start with the original 2-weeks-on, 1-week-off regimen.

O'SHAUGHNESSY: I always start with full-dose tucatinib to ensure I get the best outcomes for the brain, and I start a little lower on the capecitabine. I don't start at the HER2CLIMB dosage of 1000 mg per meter twice a day [because] you don't want to have too much at once. [However], I push [the dosage] up as much as I can.

It sounds like the consensus is to modulate the capecitabine dosage and schedule and to try to keep the tucatinib dosage as high as possible. I haven't had many problems doing this. The diarrheal toxicities from tucatinib don't seem intolerable. It seems that the capecitabine and tucatinib combination is more of the challenge.

Future Perspectives

O'SHAUGHNESSY: How do you hope this field develops in the next 5 to 10 years?

MCARTHUR: The most exciting space is moving strategies from the metastatic setting into the curative-intent setting. I love to see [research into] escalation strategies for patients at higher risk of recurrence to optimize their chance of curability [and research into] de-escalation strategies for patients who could experience good outcomes with less therapy.

BRENNER: I want to see more CNS trials. I was excited to see HER2CLIMB because they included patients with active brain metastases, and it's a shame we don't include more patients with active brain metastases in phase 3 trials. There are ways to do it safely. There are ongoing studies like phase 3 DESTINY-B12 [NCT04739761] [that] are almost like phase 4 trials [in terms of] brain metastasis. We'll see what happens there.

KAKLAMANI: We know that T-DXd has a 10% to 15% incidence of ILD, which can be fatal. We know that it can induce nausea and vomiting. We know tucatinib can induce diarrhea. It's important that we maximize our treatments and minimize

AEs for these patients at the same time. These are patients who are likely to live for a long time, and we want to improve their quality of life when treating them with active therapy. There are also new agents emerging that will hopefully provide even more options for these patients. ■

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