Brain Metastases in Patients with HER2+ Metastatic Breast Cancer:

Incidence, Diagnosis, and Treatment Options

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Incidence and impact of brain metastases

Breast cancer incidence is increasing slightly in the U.S. (by about 0.5% per year), but, at the same time, breast cancer death rates are decreasing (by about 1.5% per year).[1] The National Cancer Institute estimates there will be 281,550 new breast cancer diagnoses and 43,600 deaths in the U.S. in 2021.[2] Of these new cases, about 15%-20% will be found to have human epidermal growth factor receptor 2-neu–positive (HER2+) disease.

HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth and differentiation. HER2+ status is an independent risk factor for relapse, metastasis, and death.[3,4,5] Historical data indicate that between 10% and 16% of patients with breast cancer develop brain metastases, but in HER2+ metastatic breast cancer (mBC), up to 50% of patients with will develop brain metastases during the course of their disease.[6-9] With distant spread, five-year survival in HER2+ mBC drops from greater than 95% (with localized disease) to as low as 38%.[4]

The development of central nervous system (CNS) metastases in breast cancer patients represents a challenging clinical scenario. Despite improvements in treatment, prognosis has traditionally been poor, with median survival ranging from two to 25.3 months.[10] Brain involvement is associated with progressive neurologic deficits, increased morbidity, and substantially reduced quality of life.

Currently, the American Society of Clinical Oncology (ASCO) does not recommend routine magnetic resonance imaging (MRI) screening for brain metastases in mBC patients without a history of brain involvement or symptoms.[11] However, based on the evidence — and expert consensus opinion where there is a lack of evidence — the society recommends that clinicians should "have a low threshold for magnetic resonance imaging of the brain because of the high incidence of brain metastases among patients with HER2-positive advanced breast cancer."

ASCO recommendations also state that patients found to have brain metastases should receive "appropriate local therapy, including surgery, whole brain radiotherapy, and stereotactic radiosurgery, dependent on patient prognosis, presence of symptoms, resectability, number and size of metastases, prior therapy, and whether metastases are diffuse." Systemic therapy can be used, if indicated, along with best supportive care, enrollment in a clinical trial, and/or palliative care.[11]

Treatment Options for HER2+ mBC

HER2-targeted therapies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine have improved overall survival (OS) in patients with HER2+ mBC.[12,13] However, the standard therapy to treat disease progression after these agents is not well defined. In 2020, the FDA approved two new drugs for HER2+ mBC: neratinib and tucatinib.

In February 2020, neratinib, an irreversible pan-HER (HER1, HER2, and HER4) tyrosine kinase inhibitor (TKI), was approved in combination with capecitabine for patients with advanced or metastatic HER2+ breast cancer who have received two or more prior anti-HER2–based regimens in the metastatic setting. This approval was based on the NALA clinical trial, in which neratinib plus capecitabine improved progression-free survival (PFS) by 2.2 months compared to lapatinib, a reversible dual TKI, plus capecitabine in patients with HER2+ mBC who had received two or more anti-HER2–directed regimens in the metastatic setting.[14] Although a numerical difference favoring neratinib was observed for OS, statistical significance was not reached (hazard ratio [HR] = 0.88; stratified log-rank P=0.2086).

Patients with asymptomatic or stable CNS brain metastases (treated or untreated) were eligible for NALA. Baseline scans were not mandated, but 16% of included patients had known brain involvement at baseline. The overall cumulative incidence of intervention for CNS disease was 22.8% in the neratinib arm and 29.2% in the lapatinib arm (P=0.043).

Tucatinib received FDA approval in April 2020. Tucatinib is a third-generation HER2-directed TKI. The approved indication was for tucatinib plus trastuzumab and capecitabine for adults with advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases or those who have received one or more prior anti-HER2–based regimens in the metastatic setting.

Tucatinib is a highly selective inhibitor of HER2 with minimal inhibition of estimated glomerular filtration rate (eGFR), resulting

in less eGFR-related gastrointestinal toxicity (diarrhea and rash) as compared to older TKIs.[12,15]

The HER2CLIMB trial enrolled heavily pretreated patients who were randomized to receive trastuzumab plus capecitabine with or without tucatinib. Initial results were published in the *New England Journal of Medicine* in early 2020 and showed that the addition of tucatinib statistically significantly prolonged PFS (7.8 vs. 5.6 months; HR=0.54; P<0.001) and OS (21.9 vs. 17.4 months; P=0.005).[16] PFS at one year was 33.1% and 12.3% for tucatinib and placebo, respectively (HR=0.54; P<0.001).

The trial included 291 patients, nearly half of the overall cohort of 612 patients, with brain metastases at baseline. An innovative feature of the study was that 174 (59.8%) of those with brain metastases had active brain disease, meaning either newly diagnosed, untreated with surgical resection or radiation, or progressed after prior local therapy.

A second paper described the impact of tucatinib on the 291 patients with BM.[17] The risk of intracranial progression or death was reduced by 68% with tucatinib (HR=0.32; P<0.0001) and median CNS-PFS increased from 4.2 months in the control arm to 9.9 months in the tucatinib arm. OS also favored the addition of tucatinib (median OS = 18.1 vs. 12.0 months; HR=0.58; P=0.005).

Tucatinib is the only TKI tested specifically in a population with brain metastases and the only FDA-approved drug that includes brain metastases in its indication.[18]

Insights from an oncologist

Gregory Vidal, MD, PhD

Gregory Vidal, MD, PhD, is a medical oncologist at West Cancer Center in Memphis, Tennessee and an associate professor at the University of Tennessee Health Science Center in Memphis. His PhD thesis contributed to the understanding of how the EGFR/HER family of proteins influences breast cancer cells, and his research is focused on bridging the gap between the laboratory and the clinic to develop safe and effective treatments for breast cancer.

How common are brain metastases in patients with HER2+ mBC, and how well does what you see in your practice match the literature?

It is pretty close. The literature suggests that up to 50% of HER2+ patients will have brain involvement, and we saw in our data that also about 50% of HER2+ patients had metastatic disease in the brain and beyond. *(Manuscript under review.)* Their treatment can differ, but 50% or more have CNS involvement at some point in their disease.

How do brain metastases impact quality of life outcomes or survival in these patients?

It is probably the CNS involvement that most affects their quality of life and survival. The brain is housed in a boney skull, so anything growing in the brain doesn't have room to expand. Also, because the brain affects all body functions, any alteration to the neural network causes symptoms — headaches, weakness, loss of sensation, visual changes — all of which can be significantly disabling to patients. The treatments associated with brain metastases can also markedly impact quality of life.

When are most patients with HER2+ mBC diagnosed with brain metastases?

It varies according to the line of therapy. In our recent manuscript under review, we saw that about 38% of our patients developed brain metastases during first-line treatment. We generally think that the further patients are along with their disease, the more likely they are to have brain metastases; however, we saw that even first-line metastatic patients have this high risk of brain involvement.

What can be done to improve earlier diagnosis of brain metastases in these patients? How might earlier detection impact outcomes and/or survival?

Theoretically, if we screened every patient with HER2+ breast cancer for brain involvement, we might find brain metastases earlier, but this strategy has not been proven to impact survival, so it is currently not recommended. Given the high incidence of brain involvement, some clinicians will order MRIs, but again, guidelines do not include brain MRI routinely in staging asymptomatic patients.

It makes sense that earlier diagnosis could positively impact a patient's quality of life because they are more likely to be asymptomatic and the lesions smaller, making treatments potentially more effective. This currently is a "data-free" zone. I have not yet seen any study that conclusively shows that routine MRI screening impacts survival or quality of life. In the HER2CLIMB trial, a small percentage of asymptomatic patients were noted to have CNS involvement, but whether this strategy impacted quality of life or overall survival for that group of patients has not been shown. This would be an important piece of information.

What are the treatment options available for HER2+ patients with brain metastases?

Broadly speaking, we use local treatment with surgery and/or radiation, systemic therapies that may cross the blood-brain barrier and intrathecal treatments. Most of our systemic treatments do not cross the blood-brain barrier and, therefore, do not have activity in the CNS. We now have tucatinib which, combined with trastuzumab and capecitabine, showed very nice efficacy for the treatment and control of brain metastases. This is revolutionary as we hadn't had previous randomized

data that were prospectively focused on brain metastasis outcomes. Neratinib is another oral TKI that should help control these metastases when given systemically, but data are limited.

Surgery is invasive and radiation therapy has side effects and downstream effects. For these patients, do you think there is an unmet treatment need?
There is definitely an unmet need. When more therapies like tucatinib that prove beneficial and effective at crossing the blood-brain barrier are discovered, then we'll need to rely less on surgical procedures and radiation. Radiation and surgery has been the mainstay of treatment for these patients for a long time and remains an excellent treatment option; but it is associated with a lot of side effects, such as memory loss, headaches, and edema of the brain — things that obviously adversely impact quality of life.

With therapies moving into the adjuvant setting, how has that influenced when certain treatments are used in each treatment line?
What will hopefully happen is that the drugs that are moving up into the adjuvant setting will lower the number of patients we see in the metastatic setting, meaning we are curing more patients. That would be one of the most compelling reasons for moving those drugs up. Otherwise, there isn't much of a reason to use them early. We run the risk of developing more highly resistant, less responsive tumor in patients who did not receive that "cure." This has been demonstrated, for example, in patients previously exposed to aromatase inhibitors who are at risk of developing ESR1 mutations, making some available metastatic regimens less effective. Additionally, and depending on the disease-free intervals, these drugs may no longer be therapeutic options. This has yet to be proven in the HER2 space, but we may potentially lose treatment options in the metastatic setting because we used them in an earlier line of treatment. Don't get me wrong: The goal is cure, and if these drugs are proven capable of increasing the cure rates, I will definitely use them in the earlier setting.

I generally follow the guideline recommendations, which is pertuzumab plus trastuzumab plus a taxane as first-line therapy. And, depending on the treatment interval between completion of adjuvant therapy and metastatic disease, I use TDM-1 in second line. Again, my first- and second-line treatments can be influenced by whether that patient has CNS involvement and the extent of CNS involvement because I then want to choose a drug that can penetrate the blood-brain barrier, so tucatinib might move up in the treatment line if there is CNS involvement.

Then, in the third line, tucatinib is probably the drug of choice given its PFS and OS benefit. I may also use TDxD depending on my need for response and patient's preference. After that, we have chemotherapy with trastuzumab or margetuximab.

For patients having systemic disease control with one or two primary lesions, my preference is to surgically remove and irradiate the tumor bed using stereotactic radiosurgery while continuing systemic treatment, then follow for progression. For patients with multiple brain metastases I have leaned on my radiation colleagues in directing me when there are too many brain lesions for stereotactic radiosurgery. Whole brain irradiation has become my last resort. Evidence suggests that radiosurgery may be as effective as whole brain irradiation in terms of survival, but with a reduction in adverse effects. In general, however, if my patient has extensive brain involvement and surgery is not an option, I will also try to add a drug like tucatinib that crosses the blood-brain barrier to achieve better disease control.

The 2021 NCCN CNS guidelines recommendations contain five treatment recommendations for breast cancer–related brain metastases, while the NCCN breast cancer guidelines recommend 12 treatment options for HER2+ recurrent resectable or stage IV mBC. How do the treatment options between those two guidelines compare, and what do you take away from those guidelines?
This disparity is related to the difficulty of finding agents that cross the blood-brain barrier. There will always be more options for systemic treatment than for CNS treatment. This underlines the unmet treatment need in these patient population.

The ASCO practice guidelines for patients with HER2+ mBC with brain metastases recommend surgery and radiation, depending on the metastases size, resectability, and symptoms. Do you typically follow this guideline? What are your thoughts on this recommendation?
Yes. I usually follow that guideline because I think they also appropriately reflect the available data, but I should mention that I'm on the ASCO guideline advisory board. I think the recommendations provides physician with enough leeway to make the most appropriate treatment option based on that individual's presenting features. For example, it allows for patient with one or two lesions to get surgery and/or radiation, as opposed to recommending whole brain irradiation or radiation only for every patient.

Are there any studies that you would like to see done or that are underway that might help improve options or outcomes for patients with HER2+ mBC with brain involvement?
The theory that we can manipulate the blood-brain barrier to make it more permeable and get better penetration of systemic drugs is something I'd like to see better investigated in larger studies. In general, we need more CNS-focused studies, more combination studies, and more targeted therapies, or even treatment options that protect the CNS from tumor invasion in

patients who do not yet have CNS involvement.

Going further, I look forward to finding ways to improve radiation treatments and minimize its toxicities. Can we better protect the normal adjacent neurons while zapping the tumor cells? Can we get away with less radiation, at lower doses, and still get the efficacy without the side effects? Anything that improves survival, minimizes adverse reactions, and has less impact on quality of life is an area I'd like to see better investigated.

Dr. Vidal received compensation for his contribution to this initiative.

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