Understanding the Clinical and Economic Burden of Metastatic HER2+ Breast Cancer

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Disease burden

Despite advances in treatment for breast cancer, 20% to 30% of patients experience relapse with distant metastatic disease. Human epidermal growth factor receptor 2 (HER2)-positive disease is an independent risk factor for relapse and has been associated with increased risk of disease spread to specific sites.[1] The estimated annual U.S. incidence of HER2+ metastatic breast cancer (mBC) is just under 9,000,[2] and up to 14% of patients with breast cancer have HER2+ disease,[3] which tends to be more aggressive and more likely to recur than HER2-negative disease.[1,4]

HER2+ disease also impacts survival, as the five-year survival rate for HER2+ mBC is only about 28%.[2,4] Deaths related to breast cancer are often secondary to the impact of distant metastases, and the most common sites of HER2+ mBC-related metastases are in the brain, bone, lung, and liver.[5,6]

Impact of brain metastases

Brain metastases occur at an increased rate in patients with HER2+ mBC; throughout the course of HER2+ mBC disease, up to 50% of patients will develop brain metastases.[6-9] Brain metastases are associated with poor outcomes and reduced quality of life, including shortened survival, limitations in activity, and cognitive impairment.[4,6]

Brain metastases are difficult to treat because many targeted therapies and cytotoxic chemotherapies do not easily cross the intact blood-brain barrier, thus offering a sanctuary for central nervous system (CNS) metastases and allowing them to develop independently of extracranial disease control.[10,11] Among those with brain metastases, patients are also more likely to die from progression in the CNS compared with extracranial disease progression.[11,12]

In addition, brain metastases are associated with a high economic burden. A retrospective cohort study found that, following diagnosis, total monthly costs were $13,000 to $34,000 higher for patients with HER2+ metastatic disease compared with those without metastatic disease. Costs were primarily related to outpatient visits ($195,162) and HER2-targeted drugs ($177,489).[13] One-year costs for patients with HER2+ mBC with brain metastases are 2.21 times higher compared with patients without brain metastases.[14]

Patients with progressing brain metastases have historically been excluded from clinical trials because of their poor functional status, shortened life expectancy, and increased risk of toxicity. Thus, there is an incomplete understanding of the natural history and management of brain metastases in the real world and an unmet treatment need.[4,15]

Treatment considerations

Within the past year, the U.S. Food and Drug Administration (FDA) approved three therapies for HER2+ mBC. In December 2019, fam-trastuzumab deruxtecan-nxki was approved for patients with unresectable or metastatic HER2+ breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting,[16] based on results of the DESTINY-Breast01 clinical trial.[17] In February 2020, the FDA approved neratinib in combination with capecitabine for adult patients with advanced or metastatic HER2+ breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting, based on the results of the NALA clinical trial.[18] In April 2020, the FDA approved tucatinib in combination with trastuzumab and capecitabine for adults with advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting,[19] based on results of the HER2CLIMB clinical trial.[20]

The National Comprehensive Cancer Network (NCCN) guidelines recommend the following as preferred treatments for recurrent or stage IV HER2+ mBC: pertuzumab plus trastuzumab and docetaxel (category 1) and pertuzumab plus trastuzumab and paclitaxel (category 2A). Other recommended therapies in this setting include:[21]

- Tucatinib plus trastuzumab and capecitabine (category 1)
- Ado-trastuzumab emtansine (T-DM1; category 2A)
- Fam-trastuzumab deruxtecan-nxki (category 2A)
- Trastuzumab plus paclitaxel and carboplatin (category 2A)
- Trastuzumab plus paclitaxel with or without carboplatin (category 2A)
- Trastuzumab plus docetaxel (category 2A)
- Trastuzumab plus vinorelbine (category 2A)
- Trastuzumab plus capecitabine (category 2A)
- Lapatinib plus capecitabine (category 2A)
- Trastuzumab plus lapatinib without cytotoxic therapy (category 2A)
- Trastuzumab plus other agents (category 2A)
- Neratinib plus capecitabine (category 2A)

Of the NCCN-recommended treatments, tucatinib is one of a few breast cancer studies that included patients with active brain metastases.[20] Tucatinib is also the only FDA-approved drug that includes brain metastases in its indication.[22] Clinical trials assessing fam-trastuzumab deruxtecan-nxki and neratinib also

included patients with brain metastases; however, these represented only a small portion of the trial cohort and were restricted to stable brain metastases only, not progressing ones.[23,24]

The American Society of Clinical Oncology (ASCO) practice guidelines recommend surgery with postoperative radiation, whole-brain radiotherapy, and stereotactic radiosurgery depending on metastasis size, resectability, and symptoms for HER2+ mBC with brain metastases. For patients without a known history or symptoms of brain metastases, the ASCO guidelines do not recommend magnetic resonance imaging (MRI) to screen for brain metastases.[25]

Carey K. Anders, MD, medical director of the Duke Brain and Spine Metastases Program, a member of the neuro-oncology (primary) and breast cancer (secondary) programs within the Duke Cancer Institute, and a Translating Duke Health Scholar, discussed the treatment landscape for patients with HER2+ mBC and brain metastasis and how the new treatment options may fit into the paradigm.


Carey K. Anders, MD

Q: What are the key unmet needs for the HER2+ mBC population that you see in your practice?

A: My practice in breast oncology spans stages I-IV, including patients with brain metastasis. I also have a special interest in young women diagnosed with breast cancer and those who have CNS recurrence. With the latter as an interest, a large majority of my patients are stage IV. I think we have fantastic therapies that were not available when I was in training, particularly in the neoadjuvant and adjuvant settings.

Unfortunately, we still see recurrences, even in patients who have a pathologic complete response to systemic therapy prior to surgery. Many times, that recurrence is in the CNS, so that can be a real challenge. We think that's multifactorial, but largely due to the fact that the monoclonal antibodies, like trastuzumab or pertuzumab, don't cross the blood-brain barrier, allowing for a sanctuary site. Preclinical studies have shown that HER2 can enhance recurrence in the CNS.

Another challenge in the stage IV setting is that patients' tumors acquire resistance to their current therapy. Women can go many months, sometimes years, on the same therapy, and ultimately, the tumors start to acquire resistance mechanisms—then we come in with the next line of systemic therapy to circumvent those resistance mechanisms.

The therapies come with toxicity, and each has their own unique toxicity profile—anything from mucositis and diarrhea to myelosuppression and alopecia. In addition to managing the disease itself and resistance mechanisms that can emerge, we need to help the patient through their experience, so they are able to enjoy their time of stability and not be fraught with side effects.

Q: How common are brain metastases in patients with HER2+ mBC? How common are asymptomatic patients, and how do you identify them?

A: Unfortunately, it's very common. In the advanced setting, we see that about one-third of patients who have advanced HER2+ breast cancer will eventually develop brain metastases during the course of their disease. The number of patients who present with CNS metastasis as their first site of disease is lower, approximately 10% to 15%. If you look across all patients with HER2+ breast cancer, across all stages, the number of patients who will develop CNS metastasis is definitely less than 10%. But for those who are already at stage IV, the rate can be as high as one in three.[8,26]

Many times, these women will present with a spectrum of neurologic conditions. We also see the diagnosis of brain metastasis in patients who were asymptomatic, and many times that occurs when we're screening for a clinical trial. Luckily, now many of the clinical trial protocols are allowing for local therapy to the brain and proceeding onto the planned systemic therapy for the trial.

There's really no guideline to include brain MRI as part of staging in asymptomatic patients. That is a bit different from what we see in lung cancer, where patients with advanced lung cancer undergo a brain MRI as part of their initial staging. There are studies prospectively looking at this to determine if we could diagnose brain metastasis earlier in an asymptomatic state, and perhaps decrease the need for therapy that might later cause side effects; this could not only improve patient outcomes, but also quality of life.

Q: What are the key differences caused by brain metastases for your patients?

A: Many patients with brain metastasis present with symptoms, and those symptoms can be life-altering—difficulty with memory and function, upper or lower extremity control, and disease in the posterior cranial fossa can also present with balance difficulties and vertigo. Many patients will have headaches. The symptom burden is problematic in terms of quality of life.

Many of the initial HER2-directed or antibody-based therapies (larger, bulkier monoclonal antibodies) inherently do not cross an intact blood-brain barrier. You can envision that larger molecules might be able to traverse a region within the blood-brain barrier that is disrupted by tumor, but globally, antibodies have a harder time accessing the CNS. When we're thinking about a treatment trajectory for patients with advanced disease and brain metastasis, we're trying to control extracranial disease in the liver, lung, or bone, but we're also trying to think about therapies that will get into the CNS, such as the smaller tyrosine kinase inhibitors (TKIs) that may have better access to the CNS.

Q: What is your opinion on the ASCO guidelines about maintaining systemic therapy in the case of isolated brain progression?

A: The ASCO guidelines[25] for the management of patients with HER2+ breast cancer with brain metastasis essentially say that if a patient is eligible for a local therapy to the brain, either neurosurgical resection followed by radiation or radiation therapy as the primary modality of local control, and if their extracranial disease is stable, the recommendation is to maintain the same systemic therapy—their anti-HER2-directed therapy. As an example, if a patient was on trastuzumab/pertuzumab, they have stereotactic radiosurgery to isolated lesions in the brain, and their extracranial disease is stable, we would then resume trastuzumab/pertuzumab post-treatment to the brain.

I think we have all practiced that way for years, but it is a bit disconcerting to the physician and patient, most importantly, because they have had a progression event in the brain. We know that the tumor cells were able to find their way to the CNS and proliferate within the CNS, and yet we're not changing their systemic therapy to prevent that from happening again in the future. We're certainly treating the disease in the brain with local therapy, but I think what we're all keen to develop is tactics to prevent or delay the time to that next CNS progression.

Q: Can you discuss the treatment approach for patients with HER2+ mBC as disease severity and symptoms progress? What are patients' options?

A: Guided by the phase III, randomized, controlled studies in the literature, we have a very nice algorithm for the treatment of patients with HER2+ mBC. The first-line option is traditionally a taxane with trastuzumab and pertuzumab, based on the CLEOPATRA data,[27] which illustrated both progression-free survival (PFS) and overall survival (OS) advantage for the addition of pertuzumab to trastuzumab. Then, eventually resistance mechanisms evolve, and we need to try to treat with therapy in a different manner. Our traditional second-line therapy is T-DM1, which is an antibody drug conjugate, which conjugates trastuzumab to a microtubule inhibitor, emtansine, and delivers the microtubule inhibitor directly to the HER2 over-expressing cells. That has traditionally been our second-line therapy based on the EMILIA study,[28] which showed the superiority of T-DM1 over lapatinib and capecitabine. The first- and the second-line settings, at least to date, are pretty well-established.

The third-line setting is where things become a lot more challenging, and the good news is we now have a lot of options. In the past, we have largely relied on HER2-directed TKIs, either lapatinib or neratinib, concurrent with capecitabine. In the past, I have also given vinorelbine with trastuzumab or have partnered a chemotherapeutic with trastuzumab to maintain HER2-directed therapy. This year, we had three new additional FDA approvals. We have combination tucatinib, capecitabine, and trastuzumab, which showed both PFS and OS advantage for the addition of tucatinib to the capecitabine/trastuzumab regimen in patients with advanced disease with or without brain metastasis. We also saw the approval of an antibody drug conjugate fam-trastuzumab deruxtecan, with a PFS of nearly 16 months. In that study, there were a handful of patients with stable brain metastasis at study entry. We also saw neratinib in combination with capecitabine be approved for adults with advanced or metastatic HER2+ breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Q: Are there limitations with current therapies for HER2+ mBC?

A: Financial toxicity is always an issue, but that is really across the board in oncology. The presence or absence of brain metastasis is a real consideration when we're trying to decide on therapies to control both intracranial and extracranial breast cancer. We've seen success with TKIs, but over the past decade those have also been fraught with toxicity, largely due to cross-reactivity with epithelial growth factor receptor (EGFR) also known as HER1. The lapatinib compound targets both HER1 and HER2, as does neratinib. Lapatinib is a reversible TKI, and neratinib is an irreversible TKI, so in both of those settings, we see toxicity related to inhibition of EGFR, including rash and diarrhea.

With the advent of tucatinib, one of the benefits is that it is a largely HER2-selective TKI, so there isn't the inhibitory aspect of EGFR; therefore, there is a much lower incidence of diarrhea and very little incidence of rash. We do see mild elevation in liver function tests with tucatinib that needs to be monitored and dose-adjusted over time.

In terms of other side effects, of course, with the taxane and trastuzumab combination, patients develop alopecia, which can be a quality of life issue. However, with the antibody drug conjugate T-DM1, we don't see alopecia, nor do we see alopecia with the TKIs, unless the patient has received other therapies that induced alopecia prior to their administration.

Q: Can you share your thoughts on the recently approved HER2+ mBC therapies?

A: It has been a very exciting time for drug development for patients with HER2+ mBC. I have loved being able to educate my patients on the new options we have. This has happened over the course of the past six to nine months. Globally, it has been a very positive time for this disease. I do think there are some key points about the different compounds and FDA approvals, in terms of how to position these therapies in our practice.

The HER2CLIMB study[20] was unique in that it enrolled more than 600 women to either the triplet therapy tucatinib, capecitabine, and trastuzumab or placebo, capecitabine, and trastuzumab. One of the paradigm-shifting aspects of this study is that close to 45% of the patients had metastatic disease to the brain. I think that really speaks to the overall incidence of patients with metastatic disease also experiencing a CNS metastasis. These patients enrolled beautifully into the clinical trial, so I think that was just a very noble effort that is going to set the stage in a different manner moving forward for our patients with brain metastasis.

In the HER2CLIMB study,[20] the inclusion criteria were extremely similar to "real life" practice. Women could be stable in the brain at the time of enrollment having recently undergone local therapy and were now ready for their next systemic therapy—a very common scenario in our practices. Another scenario, although it was much rarer, was the patients who had asymptomatic untreated brain metastasis. Those patients were actually allowed to move forward with systemic therapy on the clinical trial, and the brain was monitored for response. The third scenario was patients who had already had radiation to the brain and were now progressing in the brain at the time of enrollment—again, a very common scenario in our clinic. The way that study was designed was extremely applicable to the way we practice and the decisions we make on a daily basis in our clinics.

I consider the triplet combination now for my patients who have advanced HER2+ breast cancer who have received antibody-directed therapy if they have no brain metastasis, if they have stable brain metastasis, or if they progressive brain metastasis. I think we have level one evidence now to tell us that is a very attractive and viable option. The other thing that is very nice about the triplet therapy is the toxicity profile, which is quite tolerable. A lot of the toxicity we saw was related to the duration of the capecitabine, because the patients on the investigational arm were on therapy longer

than those who were on the placebo arm.

For fam-trastuzumab deruxtecan, these patients had also received T-DM1 in the DESTINY-01 study. The number of patients with brain metastasis was 24; a smaller number of patients were enrolled with CNS metastasis, and they were required to be stable in the brain at time of entry. There was really an unprecedented PFS interval of 16 months globally and 18 months for the 24 patients with brain metastasis. I think in that setting, fam-trastuzumab deruxtecan is a fantastic option for patients with stable brain metastasis who have already received antibody-directed therapy with T-DM1 in the past.[17]

Now the challenge is learning how to sequence these drugs and whether there are predictors that might allow one patient to respond better to an antibody drug conjugate as opposed to TKI therapy.

Q: What does an NCCN category 1 guideline mean to you for your patients?

A: Oncology is such a rapidly evolving field, and so many of us use the NCCN guidelines[21] on a regular basis to ensure that we're following the appropriate algorithms and applying therapies in sequence for our patients based on their stage and prior therapy. It is a very well-respected roadmap to ensure we are all in compliance. The level of evidence is also very helpful in terms of understanding the amount and quality of data that has been generated to support that recommendation.

Q: What does the recent tucatinib data around brain metastases mean for patients and the management of mBC? What sequencing do you see for tucatinib with your patients?

A: The HER2CLIMB data[19] has really been paradigm-shifting and put a group of patients who traditionally were excluded from clinical trials in the limelight. We have seen the efficacy and tolerability improvement with the addition of tucatinib to our standard chemotherapy-trastuzumab backbone.[20]

Tucatinib is a fantastic addition to our toolkit, but I hope it has also shaped the way the clinical trials are designed in the future for our patients with brain metastasis. HER2CLIMB included patients who had previously received trastuzumab/pertuzumab as well as T-DM1 in the metastatic setting.[20] There are multiple ongoing clinical trials assessing tucatinib earlier in the disease process. For instance, a study at my institution is currently enrolling patients to assess T-DM1 with or without tucatinib.

Presently, HER2CLIMB provides a fantastic option for our patients with brain metastasis. In the trial, patients were enrolled in the third-line setting; however, as per the FDA approval, only one prior HER2-directed therapy was required. I'm hopeful that the randomized trials moving forward will continue to move tucatinib up earlier in a patient's disease trajectory, with the goal of improving disease progression but also preventing or prolonging the time before a patient develops metastasis or improve the time between CNS progression.

Dr. Anders is the medical director of the Duke Brain and Spine Metastases Program, a member of the neuro-oncology (primary) and breast cancer (secondary) programs within the Duke Cancer Institute, and a Translating Duke Health Scholar. In this role, she is expanding her clinical and research focus to brain metastases arising from solid tumors, more globally, alongside a state-of-the-art multidisciplinary team.

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