CLINICAL VIGNETTE

Antibody-Drug Conjugate Treatment of HER2 Positive Metastatic Breast Cancer with Intracranial Disease

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Case Presentation

A 66-year-old woman presented with de novo metastatic breast cancer involving the left breast with multiple lesions in the lung, liver, and bone on her initial staging PET-CT scan. Pathology from breast biopsy revealed invasive ductal carcinoma which was ER positive and PR negative. HER2 status was positive demonstrating immunohistochemistry of 3+ and HER2 fluorescence in-situ hybridization with an average HER2/centromere ratio of 8.8 and HER2 copy number per cell of 27.85. She was initially treated with four cycles of docetaxel, carboplatin and trastuzumab (THP) with partial response and continued with an additional cycle of carboplatin and trastuzumab. Unfortunately, brain MRI at that time showed metastases, and she received one fraction of 18 Gy to three intracranial lesions. She subsequently started tucatinib, capecitabine, and trastuzumab per the HER2CLIMB clinical trial, which is a systemic regimen that crosses the blood brain barrier and included patients with treated as well as active brain metastases.[1] Follow-up PET-CT had no active disease, but brain MRI continued to demonstrate progression in several small intracranial lesions.

At this point, options for treatment included use of an antibody-drug conjugate such as trastuzumab-deruxtecan (T-DXd) with or without stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT), or a clinical trial involving an experimental HER2-directed tyrosine kinase inhibitor.[2] Risks, benefits and alternatives were discussed with the patient, and she elected to initiate therapy with T-DXd. Notably in consideration of her concern for side effects of neurocognitive decline, she chose to forego further brain radiation. Surgery was not an option as the numerous lesions were too diffuse and poor candidates for resection. Remarkably after treatment with T-DXd, subsequent MRIs of her brain showed a decrease in size of all brain metastases (Figure 1).

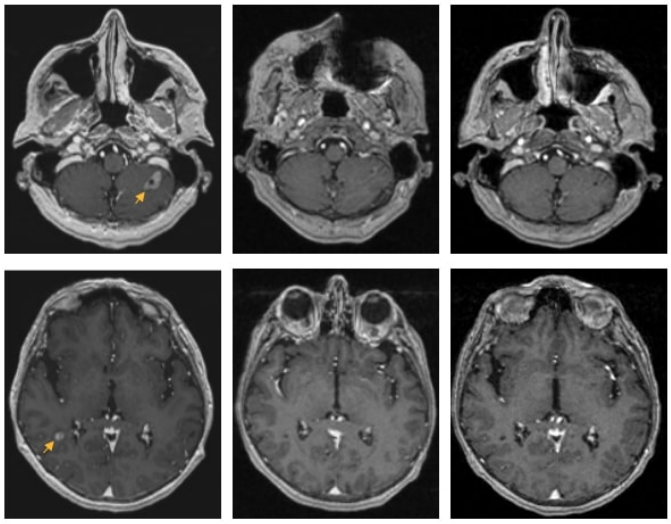

Figure 1. *Top row*: Cerebellar lesion measuring 0.99 cm x 1.91 cm prior to treatment (left) with trastuzumab-deruxtecan, with only residual linear disease after one dose (middle), and complete response after two doses (right) *Bottom row*: cerebral lesion measuring 0.89 cm prior to treatment with complete response after one/two doses (middle, right)

Discussion

Brain metastases are a common occurrence in patients with breast cancer, reported in up to 10-16% of patients and portend a poor prognosis with shorter overall survival and reduced quality of life.[3] Up to half of patients with HER2-positive breast cancer will develop brain metastases.[4] Treatment for brain metastases from breast cancer includes surgery, stereotactic radiosurgery, whole-brain radiation therapy, chemotherapy, and other targeted therapies. One of the first classes of targeted therapies to show penetration of the blood-brain barrier were tyrosine kinase inhibitors (TKIs). Tucatinib is an oral tyrosine kinase inhibitor that is selective for the kinase domain of HER2, given in combination with capecitabine and trastuzumab. This regimen was approved following results of the HER2CLIMB trial, which was a randomized controlled trial of patients with previously treated HER2-positive breast cancer comparing the addition of tucatinib or control to a regimen of trastuzumab and capecitabine. Patients treated with tucatinib had reduced risk of 68% for intracranial progression or death (HR 0.32, $p<.0001$);

these results show that targeted therapies had efficacy with brain metastases in HER2 positive breast cancer.[1]

In addition to TKIs, there has been growing interest in the potential of a relatively new class of drugs, called antibody-drug conjugates, in the treatment of HER2 positive metastatic breast cancer with brain involvement. One of the first trials to prove efficacy was KAMILLA, a phase IIIb study of trastuzumab-emtansine (T-DM1) in patients with HER2-positive locally advanced or metastatic breast cancer. Within this study, a sub-group of 126 patients with measurable brain metastases was analyzed, with a best overall response rate of 21.4% in patients treated with T-DM1. Roughly 43% of these 126 patients had a reduction ≥30% in the sum of the major diameters of their brain metastases. This included 49.3% of 67 patients who did not receive any prior radiotherapy to their brain metastases.[5] This was one of the largest cohorts to show intracranial response using anti-HER2 antibody-drug conjugates.

This clinical case contributes to the growing body of evidence that antibody-drug conjugates have the potential to cross the blood brain barrier and treat metastatic intracranial disease in HER2 positive breast cancer. Therapies that target HER2 improve survival in patients with HER2-positive metastatic breast cancer and are often included in the first line setting as well as when there is further disease progression.[6] Trastuzumab-deruxtecan is an antibody-drug conjugate composed of trastuzumab (a humanized monoclonal antibody that binds the extracellular domain of HER2) covalently linked to deruxtecan (a topoisomerase I inhibitor). This drug binds to and blocks signaling through epidermal growth factor receptor 2 (HER2/neu) on cancer cells and stops growth and induces DNA damage. The primary treatment reported for trastuzumab-deruxtecan is interstitial lung disease and pneumonitis, which can occur in up to 10.5% of patients.[6]

Trastuzumab-deruxtecan is currently approved for metastatic breast cancer that cannot be treated with surgery, or in patients who have received HER2-targeted therapy before or after surgery for early-stage breast cancer with progression of disease within six months of completing treatment.[7] This approval followed the results of a large phase III randomized trial (DESTINY-Breast 03) which focused on patients whose disease progressed after treatment with a combination of anti-HER2 therapy and a taxane. In this trial, T-DXd showed improved overall response (79.7%) compared to the current standard treatment with trastuzumab-emtansine (34.2%).

Additional data from DESTINY-Breast03 presented at the 2021 San Antonio Breast Cancer Symposium which focused on patients with stable brain metastases at baseline, showed that treatment with T-DXd resulted in higher progression free survival with a median of 15 months compared to 3 months for T-DM1.[8] Additionally, one small study of 15 patients showed success of this drug in patients with active brain metastases with HER2-positive metastatic breast cancer. The single-center phase II TUXEDO-1 trial showed that treatment with T-DXd yielded intracranial responses in 73.3% of the study population and a median progression free survival of 14 months.[9] Among these patients, 40% had brain metastases that were untreated, and 60% had progressed after local therapy.

In the case we present, the consideration of cognitive function was of paramount importance in the decisions for treatment. Given the presence of multiple intracranial lesions, she was offered whole brain radiotherapy treatment (WRBT) but ultimately elected against this due to her concern for cognitive decline. This decision highlights one of the most common challenges physicians face, where alterations in treatment are made either due to patient preference or in light of other known comorbidities. There are reports of treatment of brain metastases from different cancers, that demonstrate patients with one to four lesions treated with SRS alone had similar survival and improved neurocognition compared to patients who received both SRS and WBRT, however local disease control was inferior with SRS alone.[10] While WBRT is still considered a standard of care to treat metastatic disease in which there are multiple brain lesions, there are well-known risks for worsening cognitive decline.[11] In this patient, we were able to achieve a promising treatment response while using treatment consistent with the patient's values and preferences. We were aided by new cancer therapies and emerging data from active clinical trials. This nuance of guiding patients through careful risk/benefit analysis is an important element of patient-centered clinical decision making, which is essential not only in oncology but in all fields where treatment options carry great potential for toxicity and morbidity.

Conclusion

New targeted therapies for HER2-positive metastatic breast cancer are on the horizon, with promising results in recent trials such as KAMILLA and DESTINY-Breast03. Drugs such as HER2-directed tyrosine kinase inhibitors and antibody-drug conjugates are now increasingly perceived to be able to cross the blood brain barrier. The advent of these novel drugs broadens options for the treatment of metastatic breast cancer, even with intracranial metastases, allowing clinicians to offer treatments alongside or in replace of traditional chemotherapy, radiation, and surgery.

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