Advancing the Care of Women With HER2-Positive Metastatic Breast Cancer

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

HER2 is overexpressed and/or amplified in approximately 20% of breast cancers. It is a clinically aggressive subtype; however, the introduction of targeted therapies has greatly improved survival rates. At JADPRO Live 2022, presenters discussed recent updates to clinical practice for HER2-positive metastatic breast cancer, and how to interpret emerging evidence on HER2-low data. They also highlighted best practices for monitoring and managing side effects for patients on these therapies.

Human epidermal growth factor receptor 2 (HER2) is a receptor on cells that helps promote growth and, in some cases, migration and survival. However, when these receptors are overexpressed and overactive in HER2-overexpressed breast cancer, they cause cells to grow too quickly and metastasize. Approximately 15% to 20% of breast cancers are HER2-overexpressed, which tend to be more aggressive and have a poorer prognosis with increased risk of recurrence if not exposed to HER2/*neu*-directed therapies in early stages (Slamon et al., 1987).

During JADPRO Live 2022, Marcie Beasley, FNP-C, AOCNP®, and Brooke Daniel, MD, of Tennessee Oncology/OneOncology, discussed recent updates to clinical practice guidelines on the treatment of patients with metastatic HER2-positive breast cancer. The presenters also shared best practices for monitoring and managing side effects associated with novel HER2-targeted agents.

DRUG CLASSES

As Dr. Daniel reported, 7% of patients with HER2-overexpressed breast cancer have metastatic disease at the time of diagnosis. HER2-overexpressed breast cancer is also associated with a higher incidence of brain metastasis, with 30% of metastatic patients eventually developing brain metastases (National Cancer Institute, 2022).

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There are four classes of drugs used to treat HER2-overexpressed breast cancer: chemotherapy, monoclonal antibodies, antibody-drug conjugates, and small-molecule tyrosine kinase inhibitors.

Trastuzumab (Herceptin) and pertuzumab (Perjeta) are examples of monoclonal antibodies. Trastuzumab binds to the HER2 receptor at the subdivision four domain, inhibiting the receptor and therefore inhibiting cell growth, while pertuzumab binds to the second domain and inhibits it from binding to the HER2-103 receptors. Margetuximab (Margenza), a monoclonal antibody approved in the third-line setting, has been altered to bind to the HER2 receptor and combine with natural killer cells.

Antibody-drug conjugates such as trastuzumab emtansine (T-DM1; Kadcyla) and trastuzumab deruxtecan (Enhertu) bind the same way as trastuzumab (i.e., inhibiting the HER2 receptor) but also release a cytotoxic chemotherapy agent directly into the cancer cells.

Lastly are small-molecule tyrosine kinase inhibitors. Lapatinib (Tykerb) is a reversible small-molecule inhibitor of both EGFR and HER2. Neratinib (Nerlynx), on the other hand, is an irreversible inhibitor, which inhibits EGFR, HER2, and HER.

FIRST-LINE SETTING

According to Ms. Beasley, first-line standard of care for HER2-positive metastatic breast cancer remains unchanged and consists of a triple regimen of a taxane plus pertuzumab and trastuzumab for six cycles. Patients then proceed to a maintenance trastuzumab and pertuzumab once every 3 weeks. For estrogen receptor (ER)-positive patients, endocrine therapy is added once the maintenance phase of therapy has been reached.

SECOND-LINE SETTING: TRASTUZUMAB DERUXTECAN

As Ms. Beasley explained, trastuzumab deruxtecan is an antibody-drug conjugate designed to target and bind to the HER2 receptor. It consists of a monoclonal antibody (trastuzumab) that binds to the HER2 receptor and a cytotoxic agent (deruxtecan) that is attached to the antibody via a linker. When trastuzumab deruxtecan binds to the HER2 receptor on cancer cells, the cytotoxic agent is released, leading to the destruction of the cancer cells. Trastuzumab deruxtecan has a higher drug-to-antibody ratio than traditional antibody-drug conjugates, which may explain its efficacy in HER2-low tumors.

The DESTINY-Breast03 trial was a phase III, open-label, randomized trial that looked at the use of trastuzumab deruxtecan vs. T-DM1 in the second-line setting for patients with HER2-positive metastatic breast cancer (Cortés et al., 2022). Patients in the trial had to have received trastuzumab and a taxane and could have brain metastases, but they had to be treated and clinically stable. The trial stratified patients based on hormone receptor status, prior treatment, pertuzumab use, and history of visceral disease.

Results showed that trastuzumab deruxtecan tripled progression-free survival compared with T-DM1, with a median progression-free survival of 25 months in the trastuzumab deruxtecan arm vs. 7.1 months in the T-DM1 arm.

Trastuzumab deruxtecan also led to improved overall survival and response rates, with a high percentage of patients in the trastuzumab deruxtecan arm experiencing a significant reduction in tumor bulk.

All patient subgroups, regardless of hormone receptor status, prior treatment, pertuzumab use, visceral disease, number of prior lines of therapy, or presence of brain metastases, benefited from treatment with trastuzumab deruxtecan, said Ms. Beasley.

The most frequent side effects associated with trastuzumab deruxtecan were nausea, fatigue, vomiting, neutropenia, alopecia, anemia, leukopenia, diarrhea, constipation, and thrombocytopenia. Trastuzumab deruxtecan also has the potential for serious side effects, including interstitial lung disease and pneumonitis. Patients with heart failure were excluded from the study, said Ms. Beasley, who noted that cardiac function should be monitored for all patients on this medication.

"Despite these side effects, treatment with trastuzumab deruxtecan led to a longer treatment duration and a lower discontinuation rate compared with T-DM1," said Ms. Beasley. "The DESTINY-Breast03 study established trastuzumab deruxtecan as the new standard of care for second-line treatment of HER2-positive metastatic breast cancer."

TRASTUZUMAB DERUXTECAN IN HER2-LOW METASTATIC BREAST CANCER

Dr. Daniel and Ms. Beasley also touched on emerging data about HER2-low breast cancer, a subtype of breast cancer that is characterized by low levels of HER2 overexpression and is more common than HER2 overexpressed breast cancer.

The DESTINY-Breast04 study evaluated the effectiveness of trastuzumab deruxtecan in patients with HER2-low (1+ or 2+/fluorescence in situ hybridization negative) metastatic breast cancer who had previously received at least one line of chemotherapy (Modi et al., 2022). Patients were randomized to receive either trastuzumab deruxtecan or chemotherapy chosen by their physician. The primary endpoint was progression-free survival as assessed by a blinded independent center review.

Findings showed trastuzumab deruxtecan significantly improved progression-free survival in both hormone receptor–positive and hormone receptor–negative patients, with an increase of 9.9 months vs. 5.1 months and 8.5 months vs. 2.9 months, respectively.

Overall survival was also significantly improved in both groups, with an increase of 23.9 months vs. 17 months in hormone receptor–positive patients, and 18.2 months vs. 8.3 months in hormone receptor–negative patients. All patients in the trial also experienced an improvement in overall survival, with an increase of 23 months vs. 16.8 months (hazard ratio, 0.64, $p = .0010$).

"These results established trastuzumab deruxtecan as the new standard of care for HER2-low metastatic breast cancer," said Ms. Beasley, who noted that an additional 50% of patients with metastatic breast cancer will likely derive benefit from this therapy.

The most common side effects of trastuzumab deruxtecan were nausea, fatigue, vomiting, neutropenia, alopecia, anemia, leukopenia, diarrhea, constipation, and thrombocytopenia.

As in the DESTINY-Breast03 study, the most serious side effects observed were interstitial lung disease and pneumonitis (Figure 1).

"It is important to monitor patients for any changes in respiratory symptoms and to initiate high-dose corticosteroid treatment, if necessary," Ms. Beasley emphasized. "If the side effect

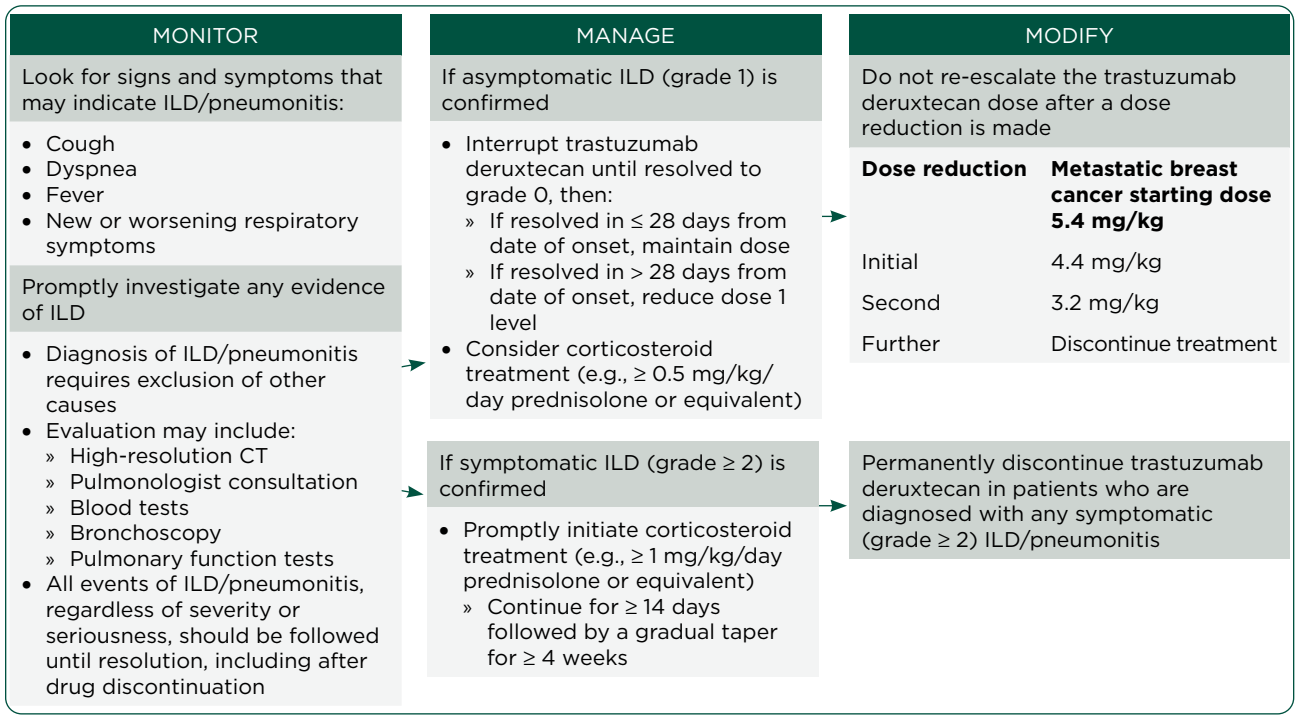

Figure 1. Early identification is key to pneumonitis management. Note that a higher incidence of grade 1 and 2 interstitial lung disease (ILD)/pneumonitis has been observed in patients with moderate renal impairment.

is grade 2 or above, it is recommended to discontinue the drug."

Trastuzumab deruxtecan was approved by the US Food and Drug Administration for the treatment of metastatic breast cancer in the newly defined "HER2-low" subtype in August 2022.

TUCATINIB

Tucatinib (Tukysa), a tyrosine kinase inhibitor, is another drug that has shown promising results in the treatment of HER2-positive metastatic breast cancer, particularly in patients with brain metastases.

The HER2CLIMB trial was a phase III clinical trial that compared the use of tucatinib, trastuzumab, and capecitabine with placebo, trastuzumab, and capecitabine in patients with HER2-positive metastatic breast cancer who had previously received trastuzumab, pertuzumab, and T-DM1, and had an Eastern Cooperative Oncology Group performance status of 0 to 1 (Curigliano et al., 2022). The primary endpoint of the trial was progression-free survival, and results showed that the addition of tucatinib reduced the risk of progression or death by 46%.

Overall survival was also improved, with the risk of death being reduced by 34%.

"In patients with brain metastases, the risk of central nervous system (CNS) progression or death was reduced by 68%, and the risk of CNS progression or death was reduced by 64% in patients with active brain metastases," said Dr. Daniel, who noted that tucatinib also showed improvement in overall survival in patients with brain metastases.

"These are really hopeful results," Dr. Daniel added. "We've finally found something that appears to cross the blood-brain barrier."

Reported adverse events were consistent with those seen in other trials of HER2-targeted therapies, including diarrhea, hand-foot syndrome, and nausea.

"We have found that dose reduction helps," said Dr. Daniel. "We start with 300 mg twice a day, but you can dose reduce down to 250, 200, or even 150 mg twice a day." ●

Disclosure

Dr. Daniel had no relevant financial relationships to report. Ms. Beasley has served on speakers bureaus for Daiichi-Sankyo/AstraZeneca and has received consulting fees from Seattle Genetics.

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