Improving Outcomes for Women With Metastatic HER2-Positive and HER2-Low Breast Cancer

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Abstract

At JADPRO Live 2023, presenters discussed recent updates to clinical practice in metastatic HER2-positive metastatic breast cancer. During the session, they reviewed review recent FDA approvals, the clinical relevance of HER2-low status, and evidence-based practices for managing adverse events associated with novel HER2 agents.

The landscape of metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer is changing rapidly. At JADPRO Live 2023, Stephanie L. Graff, MD, FACP, FASCO, of Legorreta Cancer Center at Brown University and the Lifespan Cancer Institute, Christine McGinn, MSN, APRN, ACNP-BC, of Lifespan Cancer Institute, and Jeanine R. Showalter, MSN, APRN, FNP-BC, AOCNP®, of Sarah Cannon Cancer Center Institute at HCA Midwest Health, discussed recent FDA approvals and research on HER2-low status, along with their clinical implications for oncology advanced practitioners (APs).

CURRENT LANDSCAPE

Dr. Graff began the session with encouraging reports of improving survival rates for patients with HER2-positive metastatic breast cancer, thanks to the advent of new drugs in the HER2-positive metastatic setting. The current standard of care is pertuzumab, trastuzumab, and a taxane for front-line therapy, and the historical second-line standard of care of trastuzumab emtansine (T-DM1), the first antibody-drug conjugate (ADC) approved for the treatment of metastatic breast cancer. The next generation of ADCs was marked by the development of trastuzumab deruxtecan (T-DXd). The drug combines an anti-HER2 monoclonal antibody, trastuzumab, with a topoisomerase I inhibitor payload. With its approval, T-DXd was updated to be the second-line preferred drug of choice (National Comprehensive Cancer Network Category 1 recommendation).

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MANAGING SIDE EFFECTS OF T-DXD

Common side effects of T-DXd that APs should be aware of include fatigue, nausea, and vomiting. Ms. McGinn described the process for a patient who comes to the clinic with these side effects. After basic labs and a physical assessment, as well as ensuring the patient is well hydrated, the AP will review what the patient has been taking for antiemetics.

Ms. McGinn commented on the effectiveness of dexamethasone in the clinic: "In some cases, simply giving 4 mg of IV dexamethasone can really help patients."

Prophylaxis for nausea consists of three drugs: dexamethasone, a 5-HT3 receptor antagonist (ondansetron, palonosetron), and an NK1 receptor antagonist (fosaprepitant). For patients experiencing delayed nausea, between 5 to 10 mg of olanzapine at bedtime is recommended, paired with dexamethasone twice a day (Navari et al., 2016). Fatigue can respond well to dose reduction.

In a pooled analysis of nine phase I and II trastuzumab deruxtecan (T-DXd) monotherapy studies across cancer types, the incidence of interstitial lung disease (ILD)/pneumonitis was 15.4%, with most being low grade and occurring in the first 12 months of treatment (Powell et al., 2022). In the case of a patient presenting asymptomatically with ILD found on imaging incidentally, clinicians should hold the drug and treat with a lower dose of corticosteroids of 0.5 mg/kg a day. After 7 to 14 days, they should begin a slow taper and reassess for symptoms, with the option of restarting once the symptoms are grade 1 (Rugo et al., 2023). If a patient presents with symptoms such as a dry cough or chest tightness, T-DXd should be interrupted. Evaluations include a chest x-ray or high-resolution CT, along with a pulse oximetry and pulmonary function test. Infection should be ruled out. Bronchoscopy and bronchoalveolar lavage are also options if clinically indicated and feasible. Steroids are initiated, generally starting at 1 mg/kg.

"If patients are really symptomatic and struggling, then I usually bring them into clinic 3 days in a row consecutively. I'll use between 500 to 1,000 mg of methylprednisolone in clinic daily, and then put them on a prednisone taper for about 6 to 8 weeks," Ms. McGinn explained.

Prophylaxis for pneumocystis pneumonia should be added with trimethoprim/sulfamethoxazole 3 days a week when patients are on a prolonged steroid taper.

On consulting pulmonology in academic and community settings, Ms. Showalter and Ms. McGinn both agreed that they will often put in a pulmonary consult but won't delay steroid administration and will monitor patients closely in the meantime.

HER2-POSITIVE BREAST CANCER WITH BRAIN METASTASES

The HER2CLIMB trial found that in heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival (PFS) and overall survival (OS) outcomes than adding placebo (Murthy et al., 2020). HER2CLIMB randomized patients with HER2-positive metastatic breast cancer that had previously been treated with trastuzumab, pertuzumab, and T-DM1; therefore, mostly third-line patients.

"HER2CLIMB was an innovative trial because it allowed patients with previously untreated or progressing brain metastasis that didn't need urgent intervention to enroll in the study," Dr. Graff remarked.

Progression-free survival at 1 year was 33.1% in the tucatinib-combination group and 12.3% in the placebo-combination group. Median OS was 21.9 months and 17.4 months, respectively (Murthy et al., 2020). When looking at the group of patients that had active brain metastasis, there was again a benefit with the addition of tucatinib, which is thought to be due to its ability to penetrate the central nervous system. Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases (Lin et al., 2023). There have been some data from the DESTINY breast trials that T-DXd potentially benefits patients with brain metastasis as well.

With this option now on the table, the presenters discussed factors to consider when choosing between stereotactic radiosurgery or tucatinib, trastuzumab, and capecitabine, or a combination of these approaches for patients with

brain metastases. In some cases, the oral tucatinib combination can be appealing for patients whose insurance coverage for stereotactic radiosurgery is limited. If there is no evidence of systemic progression, a patient who is receiving trastuzumab deruxtecan could be kept on the drug and then receive stereotactic radiosurgery. Another important factor to keep in mind is a recent study by Lebow and colleagues (2023) that showed that patients who receive radiation concurrently with T-DXd have a significant increase in their risk of radiation necrosis, and therefore T-DXd should be held for 4 weeks. In all cases, the presenters emphasized shared decision-making and engaging the patients in the discussion.

MANAGING PALMAR-PLANTAR ERYTHRODYSESTHESIA

Palmar-plantar erythrodysesthesia (PPE), or hand-foot syndrome, is a common side effect of capecitabine. Educating patients on prevention with urea-based cream is paramount. Advanced practitioners should assess for redness, dark discoloration, skin cracking, tenderness, or inflammation, and if these turn into blisters. The degree will determine if a dose reduction or hold is needed.

"Another preventative option that is a newer recommendation is using topical diclofenac gel topically on the hands and feet twice a day at the start of taking capecitabine, which can help lower the risk of hand-foot syndrome," said Ms. Showalter.

1 g 1% on hands and feet for the first four cycles of capecitabine significantly reduced the incidence of all grades of HFS in breast cancer patients receiving capecitabine and led to less frequent capecitabine dose reductions (Santhosh et al., 2023). It is now also available over the counter.

HER2-LOW

DESTINY-Breast04 was the first randomized clinical trial to show that targeting HER2 provides clinically meaningful benefits for patients with HER2-low metastatic breast cancer. Low expression of HER2 was defined as a score of 1+ on immunohistochemical (IHC) analysis or an IHC score of 2+ and negative results on in situ hybridization. Most patients (89%) had hormone-receptor positive disease. Patients were randomized to receive trastuzumab deruxtecan or physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). In the hormone receptor-positive cohort, the median PFS was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice group, and OS was 23.9 months and 17.5 months, respectively. Among all patients, the median PFS was 9.9 months in the trastuzumab deruxtecan group and 5.1 months in the physician's choice group, and OS was 23.4 months and 16.8 months, respectively (Modi et al., 2022).

Sacituzumab govitecan, another ADC containing a topoisomerase I inhibitor payload, is approved for both metastatic triple-negative and hormone receptor (HR)-positive and HER2-negative breast cancer after two lines of therapy; however, the two drugs have not been compared head-to-head or studied in sequence.

Presenters emphasized that pathology is important when considering T-DXd for lines of therapy and hormone receptor status. Often pathology review, rebiopsying, or biopsying a new site of disease could reveal that patients have HER2-low, which opens the door to T-DXd. ●

Disclosure

Stephanie L. Graff has served on the advisory board for SeaGen, Novartis, Pfizer, Lilly, Daiichi Sankyo, AstraZeneca, Genentech, and Stemline; and owns stock in HCA Healthcare. Christine McGinn and Jeanine R. Showalter have no relevant financial relationships to disclose.

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