Transcript Details

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HER2-Directed ADCs in Breast Cancer

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum and is titled “HER2-Directed ADCs in Breast Cancer”.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Hurvitz:
This is CME on ReachMD, and I'm Dr. Sara Hurvitz, Professor of Medicine and Medical Oncologist at UCLA.

The treatment of HER2 positive breast cancer has been revolutionized by the development of HER2-targeted therapies, including HER2-directed antibodies, tyrosine kinase inhibitors, and most recently antibody-drug conjugates [ADCs], which selectively deliver chemotherapy to HER2-overexpressing cancer cells. While these drugs have demonstrated significant antitumor efficacy, there are unique side effects to be aware of.

The first ADC to be approved for HER2-positive breast cancer was trastuzumab emtansine, or T-DM1. Until very recently, this therapy was the standard second-line treatment for metastatic disease and also is now standard adjuvant treatment for patients who have residual disease after standard neoadjuvant chemotherapy and HER2-directed therapy.

The efficacy of T-DM1 is highly dependent on high expression of HER2 on the tumor cell. This ADC has a fairly good therapeutic index, meaning its toxicity is relatively low compared to standard chemotherapy, as off-target toxicity is limited.

Patients may experience thrombocytopenia with this agent, especially in the first several cycles, as well as transaminase elevations. Thus, patients should have bloodwork done at the time of infusion to monitor for these toxicities.

Rarely, nodular regenerative hyperplasia may occur for which T-DM1 should be permanently discontinued, and evaluation by a hepatologist is certainly warranted.

Neuropathy may also develop over time, though uncommonly is this severe.

Rarely, patients may experience interstitial lung disease or cardiomyopathy. Thus, monitoring patients for symptoms and periodic cardiac function monitoring is called for. Referral to a pulmonologist or cardiologist may be warranted if one of these side effects were to develop.

Trastuzumab deruxtecan, or T-DXd, was the second ADC to be approved for metastatic HER2-positive breast cancer. It was approved in the third-line setting and beyond based on the single-arm phase 2 DESTINY-Breast01 clinical trial in 2019 and more recently, in the fall of 2021, was demonstrated significant benefits compared to T-DM1 in the second-line setting in the DESTINY-Breast03 trial. This drug has stunning antitumor efficacy for breast cancer but is associated with important side effects.

In contrast to T-DM1, the cytotoxic payload of T-DXd is membrane permeable, leading to bystander effects and a broader toxicity profile more similar to chemotherapy.

Patients may experience significant nausea, which is usually manageable with pre-medication and PRN [pro re nata/as-needed] medications. Patients may also have neutropenia, febrile neutropenia, diarrhea, fatigue, and alopecia with this drug.

One potentially life-threatening toxicity is interstitial lung disease [ILD]. The management of this side effect often requires the

involvement of a pulmonologist to evaluate and co-manage patients who develop symptomatic ILD. Any patient with symptomatic ILD should permanently discontinue T-DXd, initiate steroids, and see a pulmonologist. For those patients with asymptomatic grade 1 ILD seen only on imaging, T-DXd should be held and, in my opinion, patients should be considered for a pulmonology evaluation.

Please note a presentation relating to this topic was presented at ASCO 2022, titled Monitoring and Management of ILD Pneumonitis Among Patients with Metastatic Breast Cancer Treated with Trastuzumab Deruxtecan.

Unfortunately, that's all the time we have today. To summarize, ADCs have shown significant benefits for patients with HER2-positive breast cancer, but they are associated with unique side effects, some of which may call for a multidisciplinary collaboration with hepatology, pulmonology, or cardiology to optimally manage.

Thank you so much. I hope this has been helpful.

Announcer:
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