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HER2-Directed ADCs in Lung Cancer

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

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Dr. Gainor
This is CME on ReachMD, and I'm Dr. Justin Gainor, director of the Center for Thoracic Cancers at the Massachusetts General Hospital and an associate professor of medicine at Harvard Medical School.

Today, we'll be discussing HER2-directed antibody-drug conjugates [ADCs]. HER2 ADCs are really being explored in HER2-mutant non-small cell lung cancer. As a reminder, HER2 mutations are found in approximately 2% of patients with non-small cell lung cancer. These tend to occur in exon 20 and are most commonly insertion mutations. The reason why we think about HER2 ADCs in this patient population is that the presence of these mutations really leads to increased cycling of HER2 from the cell surface. And this is really something that can sensitize these tumors to antibody-drug conjugates.

Recently, we've seen exciting data with trastuzumab deruxtecan or T-DXd from the DESTINY-Lung01 study. In this study, we saw response rates of over 60% [54.9%] among patients with HER2-mutant non-small cell lung cancer. Given this promising activity, it's important to have a sense of what the safety profile of this agent is, particularly in non-small cell lung cancer. In general, about 50% of patients experienced a drug-related adverse event in the DESTINY-Lung study, the most common of which were nausea, fatigue, alopecia, and vomiting. I should add that, you know, a particularly important adverse event in this patient population was interstitial lung disease [ILD]. In DESTINY-Lung, 26% of patients had centrally adjudicated interstitial lung disease on this study. 75% of these events were grade 1 or grade 2, but 4 patients had grade 3 pulmonary events and 2 patients had grade 5 events; thus, prompt recognition of interstitial lung disease is critically important when using this agent.

So it's important to be able to recognize the adverse events associated with this agent, particularly as it has recently received breakthrough therapy designation by the United States FDA for treatment of EGFR-mutant non-small cell lung cancer.

When encountering interstitial lung disease in patients receiving T-DXd, generally, we want to be quite conservative. This agent currently is not FDA-approved in non-small cell lung cancer. It has breakthrough therapy designation, but I think we can take some of the lessons in areas where it is FDA-approved, such as in the setting of HER2-mutant breast cancer. When ILD is observed, according to the current FDA label, usually for grade 2 or higher ILD, we’re discontinuing therapy, and grade 2 implies patients are symptomatic. And so we should be coordinating with our pulmonary colleagues and considering initiation of corticosteroids to help manage the ILD.

Questions as we move to the future are what are the risk factors for ILD as well as whether the dose used in non-small cell lung cancer may be playing a role. The dose used in non-small cell lung cancer is higher than the FDA-approved dose of breast cancer. And so we really need additional data to explore that further.

T-DXd is not the only antibody-drug conjugate that's been explored in HER2-mutant non-small cell lung cancer. The earliest data that we

saw was with T-DM1. And this was being explored in a phase 2 study led by investigators at Memorial Sloan Kettering, Bob Li and others. In that study, the most common adverse events that were drug related included elevated AST and ALT, thrombocytopenia, fatigue, infusion reactions, and nausea. Of course, when using any trastuzumab-based agent, we also have to be mindful of monitoring for cardiotoxicity and reductions in left ventricular ejection fraction. And so therefore, periodic echocardiograms are part of the ongoing management for these patients.

When encountering other adverse events such as cytopenias, generally, I would apply the same principles that I use towards chemotherapy-based side effects. That is, if I were seeing cytopenias, I would just dose interrupt and consider a dose reduction with subsequent cycles of therapy. Obviously, we want to discuss with our patients throughout to have a good understanding of what they're experiencing with respect to nausea, vomiting, and use standard antiemetics, just as we would with cytotoxic chemotherapy.

I think one misperception among clinicians is that with an antibody-drug conjugate, that we are eliminating some of the side effects that we see with traditional chemotherapies, be mindful that patients still can have nausea, vomiting, and using antiemetics as we normally would.

Ultimately, for both T-DXd and T-DM1, when you do encounter adverse events, particularly things like ILD as well as cardiotoxicity, it is critical to engage a multidisciplinary care team to help give patients the best management as well as to try to ensure that we're able to treat them with the most effective therapy. So I think we'll be seeing more of antibody-drug conjugates, particularly in the HER2 space based upon this success.

Announcer:
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