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Managing ADC-Related Pulmonary and Cardiac AEs in NSCLC

Announcer:
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Dr. Smit:
This is CME on ReachMD, and I am Dr. Egbert Smit from Leiden University Medical Center in the Netherlands. Today, I'll give you an overview of the cardiac and pulmonary adverse events related to antibody-drug conjugates, or ADCs, therapy as reported in clinical trials for non-small cell lung cancer

Now, let's start with T-DXd, or trastuzumab deruxtecan, which is currently the only approved ADC for non-small cell lung cancer with HER2 mutations.

What do we know about the safety profile of T-DXd? Well, these drugs are actually very well tolerated in the clinic. And the main toxicities are pulmonary AEs, in the sense of interstitial lung disease [ILD]. And as one might expect of trastuzumab-containing ADCs, cardiac toxicities may also be prevalent. However, the latter was not true in clinical trials. You only have to follow the ECG [electrocardiogram] for a couple of times in the first year, and the guidelines suggest that that should be done every 3 months.

However, interstitial lung disease or lung toxicity was a problem in the early clinical trials with T-DXd. In the phase 2 study where patients were treated with the 6.4-mg/kg dose administered every 3 weeks as an IV infusion, the rate of interstitial lung disease actually was 26.5%. That was of concern because the drug was a very active drug against tumors with HER2 mutations.

In order to minimize this pulmonary toxicity, a lower dose of trastuzumab deruxtecan was tested in the same population in patients with HER mutations in a randomized phase 2 study. With respect to efficacy, the results were quite similar in terms of objective response rate and overall survival as well as progression-free survival. But there was a marked advantage of the lower dose of trastuzumab deruxtecan with respect to the interstitial lung disease. The median time of onset to ILD or pneumonitis was very variable, and the median time was 88 days.

Many of these patients in the context of clinical trials were treated with steroids, in which most of the patients have recovered. In the lower-dose regimen it was 11 of 13 patients who had steroids administered, and 8 of these patients recovered; whereas, 3 at the time of cutoff of the study did not. Of note, none of the patients with grade 1 ILD were re-treated with T-DXd. In fact, we have very little information on whether it is possible to re-treat patients with trastuzumab deruxtecan once they have recovered from an event of pneumonitis or ILD.

So let's turn now to the investigational ADCs that are currently tested in non-small cell lung cancer. I think it's sufficient to say that these agents, including datopotamab deruxtecan and patritumab deruxtecan, which are currently investigated in phase 3 trials, are associated with low incidence of cardiotoxicity and, remarkably, also with low incidence of pulmonary toxicity.

How do we manage these toxicities so that patients can stay on treatment safely, in particular for ILD? I think the first thing we should think of is that we have to optimize the dose or we have to use the lower doses of trastuzumab deruxtecan to ensure the most favorable

safety profile, identify risk factors for pulmonary AEs, which actually are not quite well known, and follow the guidelines on baseline assessments and monitoring to ensure early detection of ILD. And for ILD, this is a baseline CT, and at least 9 to 12 weeks during treatment, a follow-up CT, which is necessary not only for response assessment, but also for the detection of, in particular, low-grade pulmonary AEs including ILD and pneumonitis.

And I think equally important is a close collaboration in this regard with your consulting pulmonologist because a main differential diagnosis when these abnormalities are seen on a chest CT scan would include not only ILD, but also infection or progression of disease.

And with that, my time is up, and thanks for listening.

Announcer:
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