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HER2-Directed ADCs in Gastric Cancer

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

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Dr. Ajani:
In the past several years, there has been tremendous development in technology that has resulted in a multitude of chemotherapeutic molecules that have provided tremendous advantages to our patients. One of the technologies is called antibody-drug conjugate [ADC]. And basically, what that is, is you have 3 components. One is the antibody that targets a particular molecule on the cancer cell. Then you have a linker, which will attach on the other side of the antibody with a cytotoxic moiety, which is like a chemotherapy.

So you have these 3 components integrated into 1 therapeutic agent, and that is called ADC. And several ADCs have been approved recently for treatment of multiple tumors. Today, we are really interested in talking about ADC in gastric cancer. One of the molecules that is of great interest is trastuzumab deruxtecan.

This is the CME program on ReachMD, and I am Jaffer Ajani. I'm a GI [gastrointestinal] medical oncologist, and I'm really happy to talk to you today.

The primary topic of discussion today is HER2-directed ADCs and the best practices related to identifying ADC-related AEs, which is adverse events, but more importantly, using multidisciplinary approaches. We’re going to focus on trastuzumab deruxtecan. It's also called T-DXd. And as we mentioned before, this is a combination of trastuzumab and deruxtecan which is a Topo-1 inhibitor. Very potent drug. But it can cause some AEs [adverse events]. And the most important one is called interstitial lung disease, or ILD. And the frequency of ILD is really related to a previously existing pulmonary condition.

So for example, in the data from lung cancer study with T-DXd, the rate of ILD was about 23%. So that is a little concerning, but you can understand these are lung cancer patients; they already have lung disease. But the rate in breast cancer was about 10%. In gastric cancer, about 10%. Majority of the ILDs are grade 2 or less, but it can be severe, and sometimes it can be fatal.

So ILD is already graded; it is based on 2 major parameters. One is the radiographic appearance of the lungs. So there is a defined criteria for that. And then the second one is oxygenation on room air. And you can also go by other criteria such as symptoms that a patient may have. They may relay to you that they have shortness of breath with minimum exertion.

When ILD is diagnosed, it is better to consult a pulmonary physician. So that's what I do. And the good thing is that many patients are getting treated by T-DXd, and some patients are getting ILD. And so our pulmonary experts are becoming very familiar with ILD. So when I send a patient to them, they feel very comfortable about grading the ILD and guiding me as to what to do next.

But if we look at the guidelines that are already established, once you diagnose ILD, the first thing to do is stop T-DXd. You really have to stop. And if it is grade 1 or 2, then they may or may not need steroids, for example. But they may need some time to recover. And you can resume T-DXd at a lower dose, for example. But if a patient develops grade 3 or 4 ILD, then I think it's a significant concern.

You may not want to resume T-DXd in that patient. It is kind of unfortunate, but there is a possibility that you resume T-DXd at a lower dose and the ILD gets worse, and we cannot reverse it.

The next one is a cardiac AE. And as you well know that trastuzumab can cause congestive heart failure in very low frequency in some patients, like 1% to 2%. Same thing with T-DXd, you can document cardiac AE but in very few patients. So it's not particularly higher because you have an ADC.

The other important one is the hematologic toxicity. Particularly, neutropenia occurs in almost 30% of patients, and there is no special way of handling it. It's like any other neutropenia that you are used to managing, only we have to be aware that it is occurring. And then you can use either Neupogen or Neulasta or similar biosimilar drugs, just based on the ASCO guidelines.

Somebody with liver dysfunction, you don't want to use T-DXd on that patient. So there can be a low risk of liver function abnormalities in these patients. In fact, I haven't seen too many that could be attributed to T-DXd, but it certainly has been documented. So we just have to be aware. So check the liver functions regularly. And then the way to manage is to let it cool off. In other words, you stop T-DXd for a little while and just follow the liver function. Exclude all other causes of abnormal liver functions. For example, addition of a new drug that patient may have begun, or their PCP may have started another drug and you didn't know about that and their liver function is abnormal. And so there may be another reason for abnormal liver function rather than T-DXd.

Neurologic toxicities have been described. The patient population I treat, for example, gastric cancer, neuropathy occurs from the first-line treatment by the use of oxaliplatin and sometimes paclitaxel, but it is not exacerbated by T-DXd.

And the last one of importance is ocular toxicity. So this is also a rare phenomenon. And I would say be cognizant of ocular toxicity. We have to make sure that we listen carefully to patients' symptoms such as dry eye or pain or blurry vision. Then in that circumstance, what I would do is consult my ophthalmology colleague. And as we said before, all these experts are becoming better and better because we are treating more and more patients with T-DXd. It's a team approach to management of AEs. And the more patients we see, the more comfortable we get. And not only that, we treat them better. We can prevent severity of all these toxicities.

So unfortunately, that is all the time we have today. And I hope that what we discussed today is going to help you with the management of T-DXd, which is, by the way, a very active drug. Especially in the gastric space, we haven't seen anything like that. So active drug with a frequency of AEs. And what is important is patient selection and identification of AEs early and management of AEs with your colleagues. Depending on what the AE is, call upon an expert who is familiar with the side effects and manage the patient properly with them. So with that, I say goodbye to you and all the best.

Announcer:
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