Transcript Details

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Optimal Standards of Care for Second-Line HER2-Positive Advanced Gastric and GEJ Cancers

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Optimal Standards of Care for Second-Line HER2-Positive Advanced Gastric and Gastroesophageal Junction Cancers” is provided by Prova Education.

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Dr. Smyth:
HER2 expression is a critical biomarker for treatment selection for patients with advanced gastric and GEJ [gastroesophageal junction] cancers. Until recently, HER2-directed strategies had not been successful in improving survival in second line. However, new treatments are available for patients with HER2-positive gastric and GEJ cancers. Are you sure that you’re selecting the right treatment for your patients in the second-line setting?

This is CME on ReachMD, and I am Dr. Lizzy Smyth.

Dr. Ajani:
And, hi, I’m Dr. Jaffer Ajani.

Dr. Smyth:
Thanks, Jaffer. Initial treatment for our patients with HER2-positive gastric or GEJ cancer is a trastuzumab-containing regimen. Until recently, there were limited options available for patients who progressed. Jaffer, can you take us through a patient case that demonstrates how you select an appropriate second-line option?

Dr. Ajani:
This is a 62-year-old gentleman diagnosed with HER2-positive, 3+ by IHC [immunohistochemistry] gastroesophageal adenocarcinoma that was metastatic at the time of diagnosis to the liver and lymph nodes. Its microsatellite status was stable. PDL-1, CPS [combined positive score] was more than 1. He was treated in an outside hospital with a regimen containing oxaliplatin, fluorouracil, and trastuzumab. He received treatment for a total of 15 months. He had a dramatic response to therapy initially with a, at least, progression-free interval for at least 10 months. And following that, he had cancer progression, as we see in majority of our patients.

He was then referred for second-line therapy. I particularly emphasize that he had no pulmonary disease history and no other significant comorbidities. And on the left, you can see there is CT [computed tomography] cut of his chest showing lungs are pretty clear. And on the right, you can see liver metastases as well as the primary. We recommended trastuzumab deruxtecan for his treatment.

Dr. Smyth:
Thanks, Jaffer. Do you think that there’s any value in rebiopsying before trastuzumab deruxtecan? There are data to show that around 1/3 of patients lose HER2 expression after trastuzumab. So if you didn’t do a biopsy, do you think that you will do one in future?

Dr. Ajani:
We are doing this, rebiopsying, in clinical trials, but it is really not very clear at the moment whether we need to do rebiopsy and whether

you rebiopsy primary or should we biopsy metastases. And because of heterogeneity of HER2 expression, I know of many cases and there are many studies showing that if you biopsy on, for example, left side, it can be positive, and the right side can be negative.

So it's not absolutely clear. I think it's better to rebiopsy, but then your rebiopsy may not tell you the truth. So that's my concern.

Dr. Smyth:
I agree. It's a difficult situation. And we can gain more information from liquid biopsy. I know that there is translational work from some of the trastuzumab deruxtecan studies that show that although ctDNA [circulating tumor DNA]-positive and -negative patients benefit, the patients with the highest level of HER2 amplification on liquid biopsy are those who benefit the most.

Dr. Ajani:
He had a good response to trastuzumab deruxtecan, or T-DXd, as you can see from the before and after photographs of his CT scan. And we continued to monitor his lungs on a periodic basis. Here, you see his lungs after 6 doses, and they look very clear. Patient was asymptomatic. But after receiving 10 doses of T-DXd, he started having progressive pulmonary symptoms, and his chest CT became very abnormal as you can see.

So we were aware of potential ILD [interstitial lung disease], as we should be in every patient. T-DXd was immediately stopped. And this was in the midst of SARS–CoV-2 infections. That was excluded by 2 different testing methods. And ILD due to T-DXd was considered the most likely cause of the pulmonary abnormalities. So we consulted our pulmonary team. The patient was admitted because of requirement of oxygen and the symptoms, and it was predominantly managed by our pulmonary team. And that is because some of the pulmonary experts have become very familiar with T-DXd-induced ILD because it's being also used in breast cancer in a very large number of patients.

Dr. Smyth:
This patient had ILD, and it's important for us to have an awareness of this. But rates of ILD were quite low in the DESTINY-Gastric01 and 02 studies, which looked at T-DXd in gastric cancer, so less than 10%. I've had a couple of patients with ILD, one grade 1, one grade 2, which have resolved with steroids. But I would say that involving the pulmonologist early is critical. We do need to have these patients examined by the pulmonologist, relevant negatives excluded. We need to consider COVID; we need to consider other forms of infection. For example, PCP [pneumocystis pneumonia] could mimic ILD as well. So I think that our multidisciplinary approach is really important to the management of this condition. Would you agree?

Dr. Ajani:
Yes, I certainly do. In lung cancer study of T-DXd, there was 23% rate of ILD in that paper that was published in New England Journal of Medicine. So I think preexisting pulmonary condition lung cancer patients, for example, they are at higher risk. But the majority of gastric cancer patient or breast cancer patients, as you outlined very clearly, that the rate is low.

Dr. Smyth:
I agree. So for grade 1, if it's resolved within 28 days, we can resume. That's a really important fact. I would say in terms of catching it early, one interesting aspect that I've noticed is that both my patients who had pneumonitis had developed weight loss despite the fact that their cancer was responding. So they had weight loss and fatigue before they developed respiratory symptoms. Something to watch out for in future, I think.

For those of you just tuning in, you are listening to CME on ReachMD. I'm Dr. Lizzy Smyth and here with me today is Dr. Jaffer Ajani. We're discussing the role of HER2 directed therapies in advanced gastric and GEJ cancers in the second line setting.

Dr. Ajani:
So, Lizzy, over the past few years, there have been significant advances in treatment of HER2-positive gastric or GE junction cancer patients. I think this is a phenomenal period for research. But I think we want to focus on the drug that is immediately available to a lot of us. So would you give us some understanding of the recent trials, including the FDA approval in the US?

Dr. Smyth:
We have 2 trials which have examined T-DXd in second line or beyond HER2-positive gastric cancer. The first was DESTINY-Gastric01. This was an Asian study in which patients with previously treated HER2-positive gastric cancer, around 200 patients, were randomized to either T-DXd or to chemotherapy. And this study was published in New England Journal of Medicine because it was a landmark study showing efficacy of HER2-directed treatment in the second-line setting for gastric cancer. So in DESTINY-Gastric01, patients who received T-DXd had response rates over 50%, which compared very favorably to chemotherapy, which had a response rate of around 14%. And accordingly, overall survival was also improved. Patients who were treated with T-DXd had a median overall survival of more than 1 year. So that was compared to about 8 months with chemotherapy.

So as a result of this, there is an FDA approval for trastuzumab deruxtecan in previously treated HER2-positive gastric and GEJ cancer in the United States and Asia but not yet in Europe. DESTINY-Gastric02, unlike DESTINY-Gastric01, actually did require a repeat biopsy to show retained HER2 expression before study entry. And this was a study of just under 80 patients, non-randomized, all patients treated with T-DXd, presented at ESMO 2021 last year. And what we saw was response rates of about 40%, which is almost equivalent to what we saw in the Asian study and, importantly, a median duration of response of about 8 months.

So the next steps, I think, will be very important.

Maybe, Jaffer, you could tell us about other emerging trials in this patient population?

Dr. Ajani:
The 2 trials that we want to focus on today, one is called DESTINY-Gastric04. And this is ex-US. This is a second-line trial for HER2-positive tumor patients who have received HER2-directed therapy previously, and HER2 positivity is reconfirmed with a new biopsy. And patients are randomized to T-DXd or ramucirumab paclitaxel. This is a large enough trial that there is the likelihood that it will establish a new global standard.

The other trial is focusing on tucatinib which had shown tremendous benefit in breast cancer population. And tucatinib is a tyrosine kinase inhibitor in the HER2 signaling. So this is an interesting but also complicated study. So it is called MOUNTAINEER-02 trial. And this is a phase 2/phase 3 trial in which patients will receive the standard second-line therapy which is ramucirumab paclitaxel. But in addition to that, one group will receive trastuzumab and tucatinib, and the other group will receive placebo for both trastuzumab and tucatinib.

Dr. Smyth:
One interesting aspect to MOUNTAINEER goes back to what we were talking about regarding liquid biopsies. So patients can be recruited to MOUNTAINEER-02 using a positive ctDNA assay and without a biopsy. And I do think that's an approach that's likely to be useful in future.

Well, I would say that this has been a fantastic conversation and before we wrap it up, Dr. Ajani, would you like to share any one take-home message with the audience today?

Dr. Ajani:
Yes, Lizzy. I think we have an active drug in second-line setting for HER2 tumor positive patients. The remarkable thing is that the duration of response and the rate of response is, as you mentioned, we never see that with chemotherapy. So we have a drug that has high response rate, durable response, but is associated with AEs, so we have to select patients very carefully and manage them very carefully. And I think it's a true advance in the management of these patients that we have treated, but now, I think, we are entering a sort of a new dimension.

Dr. Smyth:
I couldn't agree with you more. I think that this is a time of great excitement for oncologists who treat gastric cancer. And what we can expect to see over the next couple of years is moving these treatments, and in particular T-DXd, into earlier stages of disease, combining with chemotherapy and perhaps immunotherapy, and hopefully result in long-term better outcomes for our patients.

Unfortunately, that's all we have time for today, so I want to thank our audience for tuning in and thank you, Dr. Jaffer Ajani, for joining me today and sharing all your valuable insights. It was really great speaking with you today.

Dr. Ajani:
Thank you, Lizzy, and I want to thank the audience for participating. And we hope you have learned something from our discussions today. Goodbye.

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