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Clinical Case Challenge: Navigating the HER2 Treatment Paradigm for Gastric Cancer

Announcer:
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Dr. Ilson:
Hello and welcome to this clinical case challenge on *Navigating the HER2 Treatment Paradigm for Gastric Cancer.* I'm Dr. David Ilson, Professor of Medicine at Weill Medical College of Cornell and a Medical Oncologist at the Memorial Sloan Kettering Cancer Center in New York City. Today we're going to look at a patient case that, while common in the clinical setting, can be very challenging. Along the way, I'll provide relevant information regarding the patient and their condition and at key intervals ask you what you would do next in caring for this patient. After each decision point, I'll provide feedback on the course of action taken.

OK. Let's get started. So, this is a case of a 72-year-old woman who presented with reflux, dysphagia, belching, and early satiety. Past history was notable for, uh, smoking history, asthma, and hypertension. Upper endoscopy revealed an obstructing circumferential mass of the GE junction in the setting of Barrett's esophagus and a biopsy was positive for adenocarcinoma. Her CT and PET scan, which I'll show images of showed metastatic disease with upper paratracheal, paraesophageal, and gastrohepatic lymph nodes, the primary tumor, and small hepatic metastases, and I indicate these on the accompanying CT scan and PET scan images.

So, now we come to a question. Which biomarkers should be tested for in this patient's tissue? Should we test for EGFR? Should we test for HER2? Should we test for PD-L1 and mismatch repair proteins? Or should we test for both B and C? So, the correct answer is D. We would, uh, as initial testing for immunoche- histochemistry in metastatic disease, we would do HER2 testing, PD-L1 testing, and mismatch repair protein expression. All of the biomarkers will help direct therapy. I will say, however, that for, uh, esophageal cancer, less than 1% are mismatch repair protein positive, about 60% are PD-L1 positive, and 20 to 30% are going to be HER2 positive. Minimum testing in a newly diagnosed esophagogastric cancer again should, uh, include upfront IHC for HER2, DNA mismatch repair proteins and PD-L1. It's more important that we use the combined score of the tumor and, uh, macrophages and lymphocytes, rather than the tumor, uh, positive score only. If we have enough tissue, then we can proceed with next-generation sequencing, which will also cover HER2 amplification, identify microsatellite instability and test for rare, but targetable genes, such as NTRK gene fusion, and will t- assess for tumor mutational burden.

So, the patient's tumor tissue tests positive for HER2, with IHC strongly positive at 3+ and PD-L1 positive as CPS 1% and genomic profiling is pending. I'll also mention that the patient tested DNA mismatch repair protein, uh, intact. So, what's the next step? Should we wait for FISH confirmation of HER2 testing? Should we initiate chemotherapy with FOLFOX trastuzumab? Should we start FOLFOX trastuzumab and pembrolizumab? Should we treat the patient with FLOT and trastuzumab? Or should we wait for genomic profiling for the MSI status? So, the correct answer, uh, as of, uh, recent regulatory approval is to b- combine pembrolizumab will FOLFOX and trastuzumab in HER2 positive patients. So, why is this the best course of action? Well, the KEYNOTE 811 trial was a randomized trial of chemotherapy plus trastuzumab with or without pembrolizumab. And in the first 260 patients analyzed in this trial, response rate was

substantially improved from 50 to nearly 75% with the addition of pembrolizumab. And based on that, conditional approval is now given to combine pembrolizumab with first line chemotherapy and typically we would now do FOLFOX trastuzumab and pembrolizumab.

So, this patient was actually treated on the original phase 2 trial that led to the phase 3 trial 811 and she received 5-FU oxaliplatin, trastuzumab, and pembrolizumab. While on treatment, her genomic profiling showed a microsatellite stable tumor, which we, we knew from the DNA mismatch repair proteins being intact. She had a val- validated amplification of HER2 and other mutations including P53. While on treatment with 5-FU oxaliplatin, trastuzumab, and pembro, we reduced her 5-FU due to mucositis and almost immediately her symptoms improved with resolution of reflux and dysphagia and serial imaging showed ongoing response at all sites of disease. And, um, uh, ultimately oxaliplatin and 5-FU were discontinued due to toxicity and the protocol permitted maintenance therapy with, uh, pembrolizumab and trastuzumab.

I show her imaging here and I think most impressive is the response in the primary tumor in the left lower part of the tri- slide, where we can see substantial reduction in the primary and resolution of the small liver metastases. So, her imaging shows ongoing response at 8 months. We continue maintenance trastuzumab and pembrolizumab, but she unfortunately develops nephritis, requiring steroids. So, we had to stop the pembrolizumab, this resolved eventually and she now continued 17 months into therapy on, now on maintenance, uh, trastuzumab and she develops nausea, fevers, and a possible seizure. Her MRI shows at least two brain metastases in the temporooccipital and cerebellar, uh, areas. Here, her imaging shows the two isolated brain metastases.

So, what do we do? Should we resect the brain metastases? Should we change to lapatinib? Lapatinib may have some CNS penetration and be active in, uh, uh, breast cancer brain metastases. Should we refer her for Hospice care given the presence of brain metastases? Or should we do radiation therapy alone?

So, the correct answer here is, uh, with limited brain metastases, and control of systemic disease, we would consider surgery as the, uh, main part of treatment. Um, and we actually opted to do stereotactic radiosurgery on the smaller tumor and we resected the larger tumor. Genomic profiling was repeated. On the brain lesion and she actually retained HER2 amplification 50 in fold, but remember that chemotherapy drugs done penetrate into the brain. With ongoing controlled systemic disease, we continued trastuzumab maintenance and her CNS imaging showed resolution and control of brain lesions.

She's now 3 years into treatment and still on trastuzumab maintenance. She has only local disease progression and an endoscopy shows a persistent primary. We then treated her with capecitabine and radiation with good palliative response and then we resumed trastuzumab maintenance.

Now, 4 years into treatment, she has further local progression of disease on trastuzumab maintenance. So, after disease progression on first line FOLFOX pembrolizumab and trastuzumab, what is an appropriate second line option for this patient? So, randomized trials actually address all of these answers. There was a negative, uh, second line trial, uh, for combining lapatinib with paclitaxel versus paclitaxel alone. So, uh, lapatinib would not be used in second line. There also is a randomized phase 2 trial from Japan looking at continuing trastuzumab into second line treatment after progression on first line trastuzumab was also a negative trial. So, trastuzumab plus paclitaxel was no better than paclitaxel alone, so we would not continue trastuzumab into second line treatment. And the other negative, the other, uh, false choice would be trastuzumab emtansine. That also failed in a phase 3 trial, second line trastuzumab emtansine was no better than paclitaxel alone. So, there actually are two correct answers here. We could treat the patient with paclitaxel ramucirumab or we now have regulatory approval for trastuzumab deruxitac- deruxtecan in second or later line treatment of HER2 positive disease.

So, what are the data for trasti- trastuzumab deruxtecan? This is trastuzumab conjugated to a topoisomerase 1 inhibitor that achieved a 43% response rate in a phase 1/2 trial and this led to a positive randomized phase 2 trial, DESTINY-Gastric01 which led to approval for second and later line, uh, trastuzumab deruxtecan in HER2 positive patients. What are the data for this drug? The primary endpoint of the randomized phase 2 trial which compared trastuzumab deruxtecan verus physician choice chemotherapy showed a substantial increase in response rate, 14% for chemotherapy, compared to 40% for trastuzumab deruxtecan and you can see on the graphic here that there were significant improvements in progression-free and overall survival. So, this, uh, was an Asian trail that led to approval of this drug in Japan and also the U.S. regulatory authorities approved this drug in the United States, uh, for second or later line, uh, treatment of HER2 positive patients. There was a recommendation in the second line that we, uh, should consider validating persistence of HER2 overexpression, 'cause remember we have the other option second line of paclitaxel, uh, plus ramucirumab.

So, we now have data from a western trial of trastuzumab deruxtecan to validate responses was gastric, uh, DESTINY-Gastric02, uh, this treated, uh, nearly 80 patients in the phase 2 setting with, uh, uh, trastuzumab deruxtecan. Patient h- all had to have validated persistence of HER2 positivity and the response rate was very similar to the Japanese, uh, randomized phase 2 with a response rate of 40% and, uh, little bit short of progression-free survival of about 6 months. So, uh, uh, we do have a validation that this, uh, drug is, uh, similar activity in a western population.

So, our patient now started trastuzumab deruxtecan and scans showed a response at 2 months. However, 4 months into treatment, she developed a dry cough and dyspnea and intermittent fevers and a CT scan of the chest showed presence of pneumonitis, a unique toxicity to this drug. So, given the diagnosis of pneumonitis, what should we do? Should we initiate prednisone 1 mg/kg per day for at least 14 days with a taper? Should we also permanently discontinue trastuzumab deruxtecan? Should we reinitiate trastuzumab deruxtecan once pneumonitis resolves? It turns out the correct answer is to initiate steroids and permanently stop trastuzumab deruxtecan. The only situation in which we reintodu- in- reintroduce the drug is for grade 1 pneumonitis, but for more significant grade 3 or 4, uh, we would treat the pneumonitis with steroids with a taper and not reintroduce the drug.

So, we can see in the course of this patients history over more than 4 years that, uh, it is critical to t- uh, test HER2 overexpression in all patients with newly diagnosed

gastroesophageal adenocarcinoma and in addition, we should do testing for mismatch repair protein deficiency, which may identify the rare MSI high patient and also we should do PD-L1 testing, probably less of an issue for HER2 because pembrolizumab is approved irrespective of PD-L1 status. And the standard of care now in first line is chemotherapy trastuzumab and pembrolizumab. In second or later line settings, trastuzumab deruxtecan is the first HER2 targeted therapy to improve overall survival compared to standard of care and we must monitor carefully and perform prompt intervention for adverse effects associated with these drugs, in particular pneumonitis, uh, to optimize patients clinical outcomes.

Thanks very much.

Announcer:
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