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

Announcer:
Welcome to CME on ReachMD. This activity entitled: Clinical Case Challenge - Navigating the HER2 Treatment Paradigm for Breast Cancer is jointly provided by Novus Medical Education and Medical Education Resources. And this activity is supported by independent educational grants from Daiichi Sankyo and AstraZeneca. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Modi:
Hi, welcome everyone to the HER2-positive breast cancer case challenge. I'm Shanu Modi. I'm a breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York City. And I think it's a great way to learn about new data and incorporate findings into one's practice by working through a case study. So let's review a HER2-positive metastatic breast cancer case together to review some of the latest information on new HER2-targeted therapies, in particular antibody drug conjugates, and how to sequence our treatments in this setting.

So, the patient I'm going to present to you is a 73-year-old woman who was diagnosed with a right-sided primary breast cancer in January of 2018. At that time, she underwent a right-sided mastectomy and sentinel lymph node biopsy, which revealed a 4-centimeter grade 3 tumor that was node negative and was estrogen receptor 20% positive, progesterone receptor negative, and HER2 positive by FISH analysis. So she was treated with six cycles of adjuvant therapy with a combination of docetaxel, carboplatin, and trastuzumab, which we often shortened to be TCH chemotherapy. And this was then followed by a completion of trastuzumab for one year. She was started on Tamoxifen in August of 2018. And was doing well until February of 2021, when she presented with a chief complaint of cough and vague abdominal symptoms.

And here are some images of a CAT scan of her abdomen. And I think you can see very clearly that there are multiple lesions in her liver. The liver looks enlarged, and unfortunately, these lesions which are quite, I think, coalesced and large in size, are present in both lobes of the liver. And so, naturally, her liver was biopsied.

And my question to you all is which of the following biomarkers should be tested in this case? Should it be A) EGFR; B) HER2; C) PDL-1; or D) TROP-2? So the correct answer is B, HER2, and let's discuss why.

So we know breast cancer is really divided into three clinical subtypes. And these are defined by the expression of the estrogen receptor, progesterone receptor, and HER2 receptor. These are the main known drivers of breast cancer, and they give us some idea of prognosis. But most importantly, they are also predictive markers of response to therapy. So it's really critically important to test for all three of these in any breast cancer tumor biopsy, as this could open up potential targeted treatment options for our patients.

We've seen improvements in survival for our patients with advanced staged disease so that today, patients with HER2-positive metastatic breast cancer have a median overall survival of almost 5 years, which is double what we were able to achieve in an era before HER2-targeted therapy. So it's really important to know the HER2 status of the patient's tumor.

So moving on then back to the case, the patient did undergo a liver biopsy and this revealed adenocarcinoma, which was consistent with the breast primary. So this is metastatic breast cancer, unfortunately. The estrogen receptor was still positive but only 10%. The

progesterone receptor is still negative. And the HER2 is still positive 3+ by IHC.

So the question is for first line therapy, what are you going to offer this patient? A) Initiate chemotherapy with TCHP; B) Initiate chemotherapy with THP; C) Initiate chemotherapy with ado-trastuzumab emtansine; or D) Wait for genomic profiling via next generation sequencing.

And I think the correct answer in this setting is B, initiate therapy with THP. So let's see why that is.

So I think the modern landmark first line trial in HER2-positive metastatic breast cancer is the CLEOPATRA study. And to remind you all, this was a randomized phase 3 trial of over 800 patients who had untreated HER2-positive metastatic breast cancer. So a first line trial. And these were patients whose tumors were centrally confirmed to be HER2 positive and patients were randomized 1 to 1, either to standard of care therapy which is combination of taxane plus single-agent trastuzumab, or the experimental arm was a taxane plus trastuzumab plus pertuzumab. So adding a second HER2-targeted agent, and this was the beginning of duel HER2 blockade therapy. And as you know, we saw statistically significant and very clinically meaningful improvement in progression-free survival and overall survival with the dual HER2 blockade arm. And that really set a new standard of care for the treatment of HER2-positive metastatic breast cancer.

So, back to our case, patient MN was started on the CLEOPATRA regimen of THP. After four cycles of treatment, the scans showed a great response. She received one more cycle and then her taxane was discontinued as she was starting to develop fatigue and neuropathy. So she was maintained on the HP antibody therapy with anastrozole until November of 2021, when she again had presentation or presented with progression of metastatic disease in the liver.

And shown here again is a picture of the CT scan, where you can see in the liver, once again lesions, you know, spread diffusely throughout the organ.

So the question now is what is your second line treatment going to be? Is it A) To continue HP and change the anastrozole to fulvestrant, an alternate endocrine therapy; B) To change the treatment completely ado-trastuzumab emtansine; C) To change the therapy to fam-trastuzumab deruxtecan, which we also call T-DXd; or D) To change the therapy to capecitabine plus tucatinib plus trastuzumab.

And I believe the correct answer for this question is C, to change the therapy to fam-trastuzumab deruxtecan, and let's see why.

So our treatment algorithm for HER2-positive metastatic breast cancer has been pretty static for almost a decade. So again, first line THP. And in the second line, our preferred regimen or option had been T-DM1, the HER2 antibody drug conjugate for a number of years. And then in the last few years, we saw an explosion really of options for the third line setting. Multiple new exciting therapies. And one in particular is the new HER2 antibody drug conjugate trastuzumab deruxtecan. And let’s look at the data for this ADC.

So this is now the second approved HER2 antibody drug conjugate and if we compare it to T-DM1, you know, while it has the same HER2 monoclonal antibody backbone, it has very different linker and payload technology. And that's really the key to its difference. It uses a novel topoisomerase-1 inhibitor payload, and there's twice as many chemo molecules linked to each antibody so it delivers a lot more chemo to the cancer cells.

And most importantly, T-DXd has a cleavable linker. And what that means is when the linker cleaves off the chemo, the chemo retains membrane permeability, and it can now not only kill the HER2-positive cell, but enter and kill neighboring cells. And this is what we call the bystander effect, and it allows T-DXd to have activity across a broad range of HER2 expressing cancers. And so overall T-DXd has some really improved and advantageous pharmaceutical properties that differentiated actually from all other HER2-targeted therapies available today.

And I think the really important trial for us, and that's relevant for this case, is the DESTINY-Breast03 study, which was a randomized phase 3 trial comparing T-DXd to T-DM1, the original second line preferred standard of care therapy. So this was a head-to-head comparison. This is for patients with HER2-positive metastatic breast cancer who had prior taxane and trastuzumab therapy, 60% also had prior pertuzumab. So the majority of the patients on this study were a conventional second line population by today's standards. And over 500 patients were randomized. And this was the first study to compare these two antibody drug conjugates head-to-head.

And the primary endpoint was progression-free survival. And these are the dramatic progression-free survival curves from that trial. And I think you can see very quickly, very easily, just how much more effective T-DXd is versus T-DM1. The median, I mean, the hazard ratio for PFS was 0.28. And the P value is 10 to the minus 22. So these results are not by chance. They are very robust findings. And the median P and the PFS improved from T-DM1 at 7 months up to 25 months with T-DXd. That's a tripling of the duration of control of the cancers with T-DXd therapy. So these are really I just think exceptional data in favor of T-DXd.

I will also point out here on this slide, you'll see the overall response rate with T-DXd is 80%. That's more than double what we saw with T-DM1. And in fact, it's very similar to what we saw with CLEOPATRA. And now CLEOPATRA was a first line trial and this is, you know, we're seeing those similar results in a later line setting with T-DXd, so it's very impressive activity for this novel antibody drug conjugate. And I think based on these data, it's now our preferred second line therapy post progression on the CLEOPATRA regimen.

So coming back to the case. So patient MN is initiated on trastuzumab deruxtecan in November of 2021. Her scans in February of 2022 show an improvement in the hepatic lesions and stability in her lung lesions. In April of 2022, she presents to the doctor for her next treatment with T-DXd, but is complaining of a dry cough, some shortness of breath, and is just failing to thrive, not doing great. So her doctor orders a chest x-ray followed by a CAT scan of the chest and abdomen and pelvis.

And here are the images here for you. And you can see I think very quickly that there are some ground-glass sort of inflammatory findings now present in her lungs.

So, she is given a diagnosis of interstitial lung disease which is a known toxicity of T-DXd. What now is your management strategy? Is it A) To initiate prednisone at 0.5 milligrams per kilogram BID for at least 14 days, followed by a slow taper; B) To permanently discontinue trastuzumab deruxtecan; C) Once symptoms resolve, to resume trastuzumab deruxtecan at a reduced dose; or D) Which is a combination of A and B, which is start steroids and permanently discontinue; or E) Which is combination of A and C, which is to initiate steroids and then once recovered, to resume therapy.

And I think the clear answer here is D, to initiate prednisone at 0.5 milligrams per kilogram BID for at least 14 days and then do a slow taper and to also permanently discontinue trastuzumab deruxtecan, and let's discuss why.

So lung toxicity is a really special and important toxicity of T-DXd, and it ranges from asymptomatic findings up to some cases of fatal interstitial lung disease. And you know, we've seen this toxicity in all of the T-DXd trials. In one of the earlier studies the DESTINY-Breast01, they saw about 15% of patients had some evidence of lung toxicity. Thankfully, most is grade 1 and 2. and reversible. But there again were a few fatal cases of grade 5 ILD events. The median onset of the lung toxicity is 4 to 5 months. But there - it appears to taper off after about a year into therapy. So really important to have a high index of suspicion early on when these patients are on treatment. But something that has to be monitored throughout their course on therapy.

There have been analyses looking to identify risk factors that might put patients at higher risk. And there's pooled analyses that suggest perhaps higher doses, frankly, that we don't use in breast cancer. Patients who have baseline lower oxygenation to start with, and patients with lung comorbidities, and certainly patients with a history of pneumonitis should not be offered to T-DXd therapy. So these are risk factors to be aware of when weighing the risks and benefits of this therapy for your individual patient.

There are also widely available guidelines on how to manage and approach patients with ILD. I think the key is to have awareness and to act promptly. And so the first and foremost thing is when you suspect ILD is to hold drug, to interrupt therapy And then launch an investigation into possible etiologies. And if this is really lung toxicity, then to begin steroid therapy quickly.

And so I think to summarize, in this case, I think we learned a few important things. Biomarkers, especially ER, PR, and HER2 should be tested on all new breast cancer cases, including metastatic recurrences in order to optimize treatment selection for our patients.

Trastuzumab deruxtecan can be considered a new standard of care in the second line setting for HER2-positive metastatic breast cancer based on the DESTINY-Breast03 trial.

And finally, identification and prompt management of serious adverse events like interstitial lung disease is really critical to be able to administer these new anti-HER2 therapies safely.

Thank you for joining me on this case. I hope it was instructive for you and your clinical practice.

Announcer:
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