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Management of HER2-Low MBC Following First-Line Disease Progression

Announcer:
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Dr. Schmid:
Hello. I'm Dr. Peter Schmid, and this is CME on ReachMD. It's my pleasure sharing with you today a case for the management of patients with HER2-low metastatic breast cancer following first-line chemotherapy. This scenario has seen a lot of changes happening in recent years where we also expect more changes to happen going forward.

I wanted to share this case with you of a patient who initially presented in 2017 with locally advanced left-sided breast cancer. She's received neoadjuvant chemotherapy, had a good clinical response, but still, as expected, residual disease with surgery, and received adjuvant letrozole. Unfortunately, this patient had relatively early metastatic disease recurrence with liver, bone, and lymph node metastasis only in September 2021, so she was on letrozole, an aromatase inhibitor therapy, for just over 3 and a half years.

The tumor was initially ER 8 and HER2 1+, but at this time of metastatic recurrence, it was re-biopsied and was still ER positive with ER 6, but HER2 was 0 on the immunohistochemistry. Patient was offered treatment with [an aromatase inhibitor] and ribociclib but unfortunately had a relatively disappointing response of around 10 months before she experienced further disease progression in liver and bones. Genetic testing at that time demonstrated ESR1 and PIK3CA wild-type, and so in terms of second-line endocrine therapy, she received dexamethasone/everolimus but progressed within 3 months further in the liver and bones.

The patient was offered first-line chemotherapy with paclitaxel. Stayed on this treatment for around 6 months and then had further disease progression in liver, bone, and peritoneum.

And the question here is, of course, what will be our next strategy? Should we re-biopsy this patient? Should we consider further chemotherapy with capecitabine? Is this a patient who'd maybe benefit from treatment with an antibody-drug conjugate such as trastuzumab deruxtecan or sacituzumab govitecan?

Now, if you look at the data and the way we treat patients in second-line ER-positive breast cancer, one of the questions is, is this a patient with HER2-low disease? And this patient clearly had low HER2 expression initially in 2017 and also in 2018. On the re-biopsy of her metastatic disease, the tumor was no longer HER2-low, but what we've learned is that low HER2 expression can vary over time. Patients can be considered for HER2-low-targeted therapy, regardless of what the last biopsy showed, as long as one biopsy in the past showed low expression of HER2, which is defined as 1+ or 2+.

If you look at the data currently available in this situation, of course there's a number of chemotherapy options that are mentioned in the guidelines and could be considered. Capecitabine, an excellent option. Vinorelbine, eribulin, just to mention some of those. But more recently, we have seen impressive results with antibody-drug conjugates of the third generation. The third-generation ADCs are interesting because they have a marked bystander effect and that really increases the activity, not just in patients with high-target

expression but, more importantly, with patients with low-target expression. And that's why this new concept has been developed of a therapeutic subtype called HER2-low disease. This is therapeutic, not biologic. So patients with HER2 IHC 0 or HER2 IHC 1+ or 2+ have a very, very similar biology. The tumors, essentially, behave the same way, but patients with lower HER2 expression may be considered for treatment with an antibody-drug conjugate called trastuzumab deruxtecan. And this was based on the result of the DESTINY-Breast04 trial, which was a randomized trial in patients with HER2-low disease. HER2-low is defined, as you are aware of, with IHC 1+ or 2+, or in other words with low to moderate staining in more than 10% of patients, that's IHC 2+, or faint or incomplete staining in more than 10% of the cancer cell, which is IHC 1+.

And in this trial, patients with HER2-low disease and either ER-positive or triple-negative breast cancer who had received at least one prior line of therapy for metastatic breast cancer were randomized either to the HER2 ADC trastuzumab deruxtecan or standard of care chemotherapy. About 58% of patients received this treatment as a second-line therapy. About 42% of patients as a third-line treatment. And most of the patients were ER positive. Only about 60 patients were triple negative.

If you look at the results, the primary endpoint, significant and meaningful improvement in progression-free survival. Hazard ratio of 0.37, more than doubling of progression-free survival of around 4.2 to about 9.6. And again, at the moment we see with many of those ADCs is that the response rates are impressively high at around 52.6%, and that's led to, again, to an improvement in quality of life but also an improvement in overall survival with a hazard ratio of 0.69 and about a 6-month survival benefit.

We have similar data with a second antibody-drug conjugate called sacituzumab govitecan, which uses a similar payload, a similar chemotherapy glue to the antibody, also a topoisomerase-1 inhibitor. But the antibody target is TROP2 rather than HER2. Sacituzumab govitecan demonstrated equally a significant improvement in progression-free survival and overall survival in patients with second-, third-, or fourth-line treatment compared to standard of care chemotherapy. And this was seen in patients with all subtypes of ER-positive disease, such as hormone refractory, so including HER2-low but also HER2-zero patients.

So if you look at the current guidelines, it's very clear that patients who have received one line of prior chemotherapy, who have HER2-low disease – and HER2-low disease is defined as any positive HER2-low test in the past – should be possibly considered for treatment with trastuzumab deruxtecan based on the higher efficacy compared to standard chemotherapy. Alternative treatment options are sacituzumab govitecan or other chemotherapy options.

Thank you very much for watching these case discussions. I hope this will help guide treatment selections in your practice.

Announcer:
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