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HER2 Testing Strategies Across Tumor Types Amidst Guidelines Gaps

Announcer:
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Dr. Pant:
This is CME on ReachMD, and I'm Dr. Shubham Pant. Today I'll provide a brief overview of HER2 testing strategies in solid tumors.

Now the HER2 pathway, as we know, is involved in cells' proliferation, survival, and metastases. HER2 is part of the HER family. There are transmembrane tyrosine kinase receptors that also include HER1, HER3, and HER4. And HER receptors have no known ligand and instead regulate downstream signaling pathways through heterodimerization with their family members or, when HER2 expression is high, homodimerization with themselves. And downstream transcription factors regulate cell proliferation, survival, differentiation, invasion, and metastases.

Now it's really important. They're activating HER2 mutations and amplifications so you can have HER2 overexpression. And that's very important because there are drugs approved for both these indications. So we really need to test to find these activating mutations or overamplifications.

Now there are 3 primary testing modalities for HER2. And HER2 testing has been traditionally performed by immunohistochemistry and in situ hybridization, but in the last few years, NGS-based techniques are increasingly being used. So immunohistochemistry is essentially when mono- or polyclonal antibodies bind to the HER2 protein and it detects HER2 protein expression on the cancer tissue. HER2 testing results using IHC are categorized as positive, which is HER2 3+; equivocal, HER2 2+; or negative, which is HER2 0 and 1+. You can also do in situ hybridization, in which HER2 DNA probes are labeled, usually with fluorescent dye, and it detects whether HER2 gene amplification is present, and it can quantify the level of amplification. And this is normally used for HER2 2+ IHC, which is equivocal. But in the last decade, next-generation sequencing has taken center stage and the measure of HER2 copy number differences between normal tissue and it allows for other concurrent genomic alterations also.

Now the NGS is testing for HER2 amplification, when you have a tumor tissue, you can either do HER2 IHC testing, like we said, it could be IHC 0, 1+, 2+, or 3+. If you have IHC 2+, then you reflexively would do FISH. You should also do NGS HER2 testing, in which you either see a copy number increase or no copy number increase, for amplification, and you can also look at those HER2 activating mutations; you can identify them.

Now remember, HER2 scoring algorithms can be different, especially in breast and gastric cancer. In breast cancer, let's say for positivity, you've got to have complete circumferential intense membrane staining in greater than 10% of cells, and that's per the ASCO-CAP Guidelines, and that is interpreted as HER2 IHC 3+; whereas, in gastric or esophageal, you can have complete or basolateral intense membrane staining greater than equal to 5 cohesive cells, and that can be HER2 3+ positive. So there are some differences.

Now remember, also, the HER2 alterations, and when you have overexpression, there can be concordance and discordance rates. That

means sometimes with patients, we do not have enough tumor tissue, so we send it for next-generation sequencing. We do not have enough tumor tissue, and in those patients, we can do ctDNA, or circulating tumor DNA, also known as liquid biopsy. And there are certain tests and trials which have shown that concordance or the discordance rate. For example, an exploratory analysis from a basket trial which looked at trastuzumab and tucatinib, they looked at the ctDNA and the tumor tissue and the concordance and the discordance. And what they found was there was 82% concordance between immunohistochemistry and blood-based NGS. So you can have a high concordance rate in both.

To summarize, remember, if you do not test, you will not find, so you have to do both HER2 amplification and HER2 gene mutation, activating gene mutations, because there is an approval in non-small cell lung cancer with activating HER2 mutations. So definitely test this in your patients.

Well, my time is up. I hope you found this update useful. Thank you so much for listening.

Announcer:
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