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https://reachmd.com/programs/cme/clinical-considerations-targeted-therapies-across-multiple-tumors/11752/

Released: 08/21/2020
Valid until: 08/21/2022
Time needed to complete: 15 minutes

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Clinical Considerations for Targeted Therapies Across Multiple Tumor Types

Announcer:
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Dr. Hurvitz:
Over the past few years, HER2 has been identified as a biomarker and oncogenic driver across multiple tumor types, including breast, non-small cell lung cancer, colorectal cancer, and gastric cancers. And as research on HER2 continues to emerge, so, too, do questions related to its expression across multiple tumor types. Also, questions relating to the anti-HER2 mechanisms of action come up, as well as overcoming anti-HER2 resistance. This is CME on ReachMD, and I’m Dr. Sara Hurvitz.

Dr. Sands:
And I’m Dr. Jacob Sands. Together, we’ll focus on these three critical issues related to HER2 expression. We’ll break through the complexity of these topics and use 3D animation to help visualize the most important concepts.

So, to start us off, Dr. Hurvitz, could you discuss the data that implicates HER2 as a biomarker and oncogenic driver across multiple tumors and which patients and malignancies should be tested for HER2 expression?

Dr. Hurvitz:
Sure. In 1987, Slamon and colleagues identified that approximately a quarter of patients with breast cancer were characterized by amplification and/or overexpression of HER2. This alteration was shown to be associated with much more aggressive tumor biology and a worse prognosis, which would have been a sad ending to that story had HER2-targeted therapy not been developed. Fast forward now to 2020. We now have seven FDA-approved HER2-targeted therapies for breast cancer, and we now have data showing that patients with HER2-positive breast cancer have as good as – or better than – the prognosis associated with other types of tumors that are HER2 normal, and so, literally, HER2-targeted therapy has altered the natural course of this disease.

In addition to breast cancer, other cancers have also been evaluated and have been shown to have HER2 alterations, including amplification, overexpression, and even in some cases mutation in the HER2. These include and are not limited to gastric cancer, lung cancer, colon, bladder, and endometrial cancers, just to name a few. While many trials have been conducted on evaluating the use of HER2-targeted therapies for these different tumor histologies, trastuzumab is only FDA approved in breast and gastric cancer at this time. And so as a result, these are the two tumor types where testing for HER2 is considered standard of care.

An important note is that while 20 percent of breast cancer is HER2-overexpressing, a larger percentage of cancer has low expression of HER2. And while monoclonal antibodies such as trastuzumab are not beneficial for these tumors, newer drugs like antibody-drug conjugates that may take advantage of low levels of HER2 expression may actually be shown to be beneficial in this situation.

If we take a closer look at the various mechanisms of action of anti-HER2-targeted agents, Dr. Sands, can you describe them for us as

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well as the advantages and disadvantages of each of them with respect to efficacy and potential for treatment resistance?

Dr. Sands:
Yeah, so first just to outline, HER2 and HER3 are part of a class of receptors. These lead – really lead to signaling through the PI3-kinase/AKT pathway, and that pathway itself impacts cell growth and proliferation, impacting survival and apoptosis. So blocking that pathway can itself be therapeutic.

So there are some of these that are external to the cell. So, for example, trastuzumab and pertuzumab, these are monoclonal antibodies that bind to the extracellular domain of the HER2 protein and thereby inhibiting proliferation of the cells. Trastuzumab binds at the juxtamembrane portion of the extracellular domain. This prevents activation of that pathway and therefore preventing the proliferation or promotion of cancer cells – cancer cell growth. Pertuzumab binds to subdomain II of the extracellular portion of HER2. This inhibits HER2/HER3 dimerization thereby, again, preventing the impact to that pathway. Now, neratinib, lapatinib – these irreversibly bind to HER1, -2, -3 at the intercellular signaling domain. This inhibits phosphorylation and downstream signaling pathways. Tucatinib suppresses phosphorylation of HER2 and HER3 proteins, inhibiting downstream signaling of that pathway we discussed – the PI3-kinase/AKT pathway. Now, the ado-trastuzumab emtansine – this is an antibody-drug conjugate, so this is made up of a cytotoxic payload of DM1 bound to trastuzumab via a linker. So, through trastuzumab, it binds to HER2, and that's how it gets into the cell. And at the time of lysosomal degradation, that's when it releases DM1 into the cell, leading to cell disruption and apoptosis due to inhibition of microtubule assembly. The fam-trastuzumab deruxtecan – this is an antibody-drug conjugate composed of a humanized IgG monoclonal antibody that is identical amino acid sequence to trastuzumab. This binds to the juxtamembrane portion of the extracellular domain of HER2. This is bound to a linker. The payload in this case is topoisomerase 1 inhibitor. So, like the other drug, this gets pulled into the cell after binding to the receptor, and at lysosomal degradation, it releases the payload, which is this topoisomerase 1 inhibitor. This has a high antibody-drug conjugate ratio of 7 to 8, so it releases quite a bit of drug into the cell, and that drug itself also is highly membrane permeable. So as it kills that cell and releases into the environment, it can therefore have a bystander effect, which is to go through the membranes of nearby cells, whether or not they have the receptors or not. It can permeate those membranes and therefore impact those cells as well. So this really impacts cells regardless of their HER2 expression.

Dr. Hurvitz, could you focus on the mechanisms of anti-HER2 treatment resistance and possible approaches to overcoming that resistance?

Dr. Hurvitz:
Absolutely. There have been a number of mechanisms of resistance to HER2-targeted therapy that have been described. One way is by incomplete blockade of the HER family receptors, leading to continued activation of the pathway by dimerization of alternative partners, for example, HER1 with HER2, HER2 with HER3, et cetera. Another way is by overexpression of alternate partners, for example, HER3, or increased expression of the ligand for HER3, neuregulin. And another way is by constitutive activation of pathways signaling downstream of HER2.

Dr. Sands:
So there are a variety of mechanisms of resistance for patients with HER2-amplified breast cancer. What about the large subgroup of patients identified as having consistently low HER2 expression on their tumors? What do the data tell us about this group of patients?

Dr. Hurvitz:
Yes, well, HER2 expression or overexpression/amplification is identified anywhere in 15 to 25 percent of breast cancers. A much larger proportion of patients have consistently low levels of HER2 expression throughout, which is quantified as 1+ or 2+ by immunohistochemistry. Although at one point scientists thought that HER2 low-expressing breast cancers might be amenable to therapy, such as trastuzumab, very large trials, including the NSABP clinical trial B-47, have shown that there really is no benefit in targeting these HER2 low-expressing tumors with a monoclonal antibody strategy. On the other hand, newer studies are indicating that we may be able to use the low level of HER2 expression in HER2 non-amplified cancers in order to target chemotherapy to the tumor cell by way of an antibody-drug conjugate such as trastuzumab deruxtecan.

I think the excitement surrounding ADCs as well as excitement surrounding the HER2-selective tyrosine kinase inhibitor tucatinib, which is able to penetrate the blood-brain barrier, is really growing and is underscored by the FDA approval of two agents just in the last several months.

So with that being said, Dr. Sands, we're now gaining a deeper understanding of the impact of HER3 expression on resistance to anti-HER2 therapy. Can you please address for us HER3 overexpression and where in the situation anti-HER2 antibody-drug conjugates or anti-HER3 antibody-drug conjugates might fit in to overcoming anti-HER2 resistance?

Dr. Sands:

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Yeah, HER3 cannot be autophosphorylated, so this is a little different than HER2, but HER3 dimerizes with other receptors, especially HER2. This leads to a conformational change in HER2, impacting downstream signaling of the PI3-kinase/AKT pathway. So, by blocking HER2, we block that pathway. But in doing so, this can lead to overexpression of HER3 and then HER3 can dimerize with HER2. And that also, then, leads to activation of that pathway and therefore becomes a mechanism of resistance for HER2-directed therapy. HER3 overexpression is correlated with a poor prognosis. HER3-containing heterodimers are therefore tumor promoting, activating that pathway, and HER3 overexpression can also follow EGFR-directed treatment in lung cancer. This leads to resistance of the EGFR-targeted therapy as well. HER3 dimerization with HER2 signals that pathway that HER2-directed therapy blocks, the PI3-kinase/AKT pathway.

So we previously discussed another mechanism for treating cancer cells with HER2 expression that's not pathway dependent, and that's the antibody-drug conjugates that we discussed. HER2 expression can be targeted for the delivery of the cytotoxic therapy via these antibody-drug conjugates, so they bind to HER2 and get into the cell in that way. And the bystander effect that we discussed is also something that can end up impacting nearby cells whether or not they have the HER2 or HER3 overexpression. So increased HER3 expression can also serve as a target for these antibody-drug conjugates as well, and the U3-1402 – this is a compound that has attracted attention in lung cancer specifically for patients that have progressed on initial EGFR-directed therapy. There's a phase 1 study that's reported a manageable safety profile and some ongoing responses, so this is an area of interest in lung cancer.

But I think the best way to really understand this is to see it visually, which is why we have a short animation to help put all this together.

Announcer:
The HER family of receptors plays a central role in the pathogenesis of several human cancers. Amplification or overexpression of the HER2 occurs across many tumors, including breast, gastric, colorectal and non-small cell lung cancers. Amplification refers to the presence of multiple copies of the HER2 gene, whereas overexpression indicates a high concentration of HER2 receptors on the cell surface. Amplification has been associated with shorter disease-free and overall survival, while overexpression may lead to more aggressive growth and proliferation. Immunohistochemistry, or IHC, is used to determine the number of HER2 receptors on a cell. Fluorescence in-situ hybridization, called FISH or ISH, determines the number of HER2 genes in a cell. Historically, ICH scores of zero and one plus have been considered negative and low HER2 expression, respectively and are not offered anti-HER2 therapy. An ICH score of two plus is equivocal, requiring an ISH score of greater than 2 to be eligible for anti-HER2 therapy. A patient with a three plus score is eligible for anti-HER2 therapy. A paradigm shift is occurring for patients with low HER2 expressing tumors as emerging data clearly indicates that ICH scores of one plus or two plus, but lacking HER2 amplification may be suitable candidates for an anti-HER2 therapy, most likely an antibody-drug conjugate.

Many potential resistance mechanisms to anti-HER2 therapy have been described that ultimately lead to reactivation of the HER2 pathway or its downstream signaling. One that has long been overlooked is the hetero-dimerization of HER2 and HER3 once HER3 bind its ligand neuregulin. Through its activating interface, HER3 engages and allosterically activates HER2. Phosphorylation of its C-terminal tail leads to recruitment of adapter proteins leading to activation of Ras and PI3K. Recruitment and activation of PI3K leads to phosphorylation of membrane phosphoinositides producing PIP3, which in turn docks the PH domain-containing proteins PDK1 and Akt. Membrane-bound Akt is phosphorylated and activated by PDK1 and TOR-complex 2 (TORC2). Activated Akt proceeds to phosphorylate a plethora of cellular substrates involved in diverse biological processes. These include: Epithelial-mesenchymal transition *or EMT* and metastasis, Removal of cell cycle inhibition, Inhibition of the cell death pathway, support tumor progression and angiogenesis, Support of tumor cell growth and survival, and Support of tumor cell growth associated with HER2 activation of the Ras/Raf/MEL/MAPK pathway. Through these and other pathways, the HER2/HER3 heterodimer is the predominant driver of PI3K signaling in cancer.

Dr. Sands:
So, Dr. Hurvitz, now that we have a better understanding of low expression of HER2 and co-expression of HER2 and HER3, what are the emerging approaches to targeting HER3 in the treatment of various malignancies? And why is it important in optimizing treatment outcomes for many of our patients?

Dr. Hurvitz:
Yeah, a number of agents are in development to target HER3, including HER3 peptide vaccines, pan-HER small-molecule inhibitors, HER3 monoclonal antibodies or bispecific antibodies, and other antibody-drug conjugates as well. As a whole, HER3-targeted monoclonal antibodies have not yielded super exciting results. There was a study of MM-121 combined with cetuximab with or without irinotecan that did show some responses achieved, although the tolerability of the triplet regimen was not excellent. There are other anti-HER2/3 monoclonal antibodies that have also been looked at, including U3-1287 or patritumab. This drug made it all the way to phase 3 before being terminated. However, it has been utilized in the molecule you were talking about, U3-1402, to create this antibody-drug conjugate. So U3-1402 is comprised of the patritumab antibody that targets HER3 linked to a cytotoxic payload, which is

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a topoisomerase 1 inhibitor. It's the same payload that we see with trastuzumab deruxtecan. This ADC was studied in a phase 1 trial of heavily pretreated metastatic breast cancer of all subtypes – hormone receptor positive, triple negative, HER2-positive – and yielded an objective response rate of over 40 percent in heavily pretreated setting. So this is very promising and is also showing some promising data, as you mentioned, in lung cancer as well.

Dr. Sands:
Yeah, and speaking of the antibody-drug conjugates, just to throw another one out there, DS-1062 is a TROP2 antibody-drug conjugate that's being studied in non-small cell lung cancer. This has deruxtecan as the payload, topoisomerase 1, and the receptor it binds to is TROP2. Although we really have seen responses irrespective of the TROP2 expression, response rates in early studies have been reported around 27 percent, generally well tolerated, so this is another one that in the lung cancer community we're really keeping an eye on.

Dr. Hurvitz:
Yeah, I would agree completely. We recently had the FDA approval of sacituzumab govitecan for triple negative breast cancer, also an ADC-targeting TROP2, so very exciting time.

So that does bring me to the end of our discussion here. I would like to thank Dr. Jacob Sands for joining me and for sharing his insights on the increasing importance of HER2. Thank you.

Dr. Sands:
This was a lot of fun. Thank you, Dr. Hurvitz.

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