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https://reachmd.com/programs/cme/advanced-her2-positive-gastric-cancer/12507/

Released: 05/13/2021
Valid until: 05/13/2022
Time needed to complete: 15 minutes

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# Applying Clinical Evidence in Advanced HER2-Positive Gastric Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Advanced HER2-Positive Gastric Cancer” is provided by Prova.

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Dr. Catenacci:
Advanced gastric and gastroesophageal junction adenocarcinomas remain among the most difficult cancers for clinicians to manage. The challenges include a relative lack of familiarity with practice standards regarding HER2 testing and clinical decision-making in this setting, as well as the historical lack of novel treatment options for patients who have progressed on first-line trastuzumab and chemotherapy.

This is CME on ReachMD, and I’m Dr. Daniel Catenacci. Today I’m talking with Dr. Yelena Janjigian about the role of HER2 as an oncogenic driver in gastroesophageal cancers, along with targeting HER2 with novel anti-HER2 therapies.

Dr. Janjigian, welcome to the program.

Dr. Janjigian:
It’s a pleasure to join you. Thank you for inviting me.

Dr. Catenacci:
Great. So we’re both aware of the focus on HER2 testing in patients with breast cancer and the use of anti-HER2 agents across the neoadjuvant and adjuvant setting for patients whose tumors are HER2 amplified. While HER2 is an oncogenic driver in gastroesophageal cancers, it doesn’t appear to act as a predictive biomarker in quite the same way as it does in breast cancer, especially after the development of resistance to trastuzumab. So with that, what are the current HER2 testing practices in gastroesophageal cancer, and how can they be optimized to improve agent selection and patient outcomes?

Dr. Janjigian:
That’s a great question, and we’ve known for the past 10 years, maybe more, that HER2 is an important driver in subsets of gastric cancer and esophageal adenocarcinoma. What we also know is that co-occurring alterations may drive resistance, and that’s why the degree of benefit is not as robust in some populations, as we see in breast cancer. And now we understand why. So historically, the HER2 testing in gastric cancer involved immunohistochemistry (IHC) to look for protein overexpression. And if we do IHC and find 3+ staining, in most institutions, we would stop there and treat the patients with trastuzumab. If the patients were IHC 2+ in the tumor, and FISH positive showing the chromosomal ratio of greater than 2, again, we would just stop and give patients trastuzumab. And there was such variability in response and duration of the response, that now using more sophisticated tools, such as sequencing of the tumor as well as sequencing of the plasma DNA, we understand that other alterations within RTK pathways, such as EGFR, MET, FGFR, and receptor signaling downstream, really predict outcomes and may be important to help stratify for future therapy.

So by nature of gastric epithelium, it’s different than the breast epithelium, so already the staining and overexpression of HER2 may be

more sort of patchy and not as homogenous as you would see. And over time, as you eliminate the HER2-positive clone, the overgrowth of HER2-negative clone or HER2-low expression clone becomes a therapeutic dilemma in, I would say, probably 20% of our patients, maybe 30 – depends on what tests you use.

Right now in the clinic, our patients still start with HER2 IHC for protein overexpression, and later down the line, we do get information on NGS [next-generation sequencing] and circulating tumor DNA as those tests may take a little longer to come back.

Well, a picture is always worth a thousand words, so we put together a nice animation to help you visualize some of the concepts that we just covered. Please enjoy it.

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.

Dr. Catenacci:
So moving on, then, to the next sort of setting, let's drill deeper into anti-HER2 therapy in breast and gastric cancer and the use of anti-HER2 antibody-drug conjugates [ADCs], currently either with trastuzumab emtansine or trastuzumab deruxtecan. Can you compare those and contrast those two agents with regards to their mechanisms of action, what their actual payload is, and any notion of this bystander killing?

Dr. Janjigian:
Sure. So, T-DM1 is the first ADC for HER2 that was studied in gastric cancer. And again, we've learned from the breast cancer literature and the breast cancer experience that it's a very much active drug. It has a taxane-like payload, also has a HER2 molecule that binds to the receptor and then is internalized, so in a way, all of these drugs work in a way that's a Trojan horse, right? The chemo agents are taken into the cancer cell, then dissociated, and then kill the cancer cell from within. What we found in gastric cancer in comparison in second-line setting, in the GATSBY study, when T-DM1 was compared in head-to-head to chemotherapy with paclitaxel, which is an active agent in our disease, the benefit was not superior, and so there was, you know, some benefit. It just didn't beat what the standard was at the time, which is single-agent Taxol. In head-to-head comparison, T-DM1 was not sufficient to improve outcome in HER2-positive cases in second line.

With newer or next-generation ADCs, where there is a higher cytotoxic chemotherapy payload, slightly different chemotherapies – so instead of using taxane-like drug, it's an irinotecan-like drug. So you could say it's also very active, in GI tumors in particular, and a more potent molecule where it's a higher payload and for other biologic reasons, there is, at least preclinically, even in gastric cancer, there appears to be more bystander effect. So even if you have a very focal positivity within the tumor with the HER2-positive cells, and only a few cells, the bystander effect of the neighboring cells may be more pronounced. And certainly, that data has panned out clinically in breast cancer. In gastric cancer, you know, there is some activity for IHC 2+ cases, but the majority of the activity and probably the most benefit is in IHC 3+ cases as was demonstrated in the Gastric01 study.

What's important about T-DM1 is that with the bystander effect and NCI-N87 model, which was the gastric model that this was compared in head-to-head, T-DXd or trastuzumab deruxtecan appears to have had more bystander effect, at least preclinically, and that's probably why this was a more successful strategy. This was a third-line trial that was done mostly in the Japanese and Asian cohort of patients in Asia and showed a dramatic overall response rate and survival benefit when compared to standard chemotherapy. There is a lot of caveats to this study. We will need to see confirmatory data from the Western population, which is coming and will be available, as our patients tend to have more aggressive disease overall and don't do as well in later lines of therapy. But nonetheless, it's resurrected the whole field of HER2-directed therapies beyond trastuzumab and was an important step forward for us.

Dr. Catenacci:
Absolutely. I completely agree. And it's a welcome tool in late line with response rates that high. And so it'll be interesting to see if some of the ongoing studies in the Western population, like DESTINY-Gastric02, the follow-up study which was a single-arm, phase 2 study

here, when it reads out, has similar outcomes as a second-line study and others that we're going to get to.

So for those just tuning in, you're listening to CME on ReachMD, and I'm Daniel Catenacci, a medical oncologist at the University of Chicago. And I'm here today with Dr. Yelena Janjigian from Memorial Sloan Kettering. We're discussing the role of HER2 as an oncogenic driver in gastroesophageal adenocarcinomas and the role of HER2 as a focus for interventional therapy.

So we were just discussing trastuzumab deruxtecan, and it's an antibody-drug conjugate with deruxtecan. It's a topoisomerase 1 inhibitor and is approved now in adults with advanced metastatic HER2-positive gastric or G-junction adenocarcinoma after the failure of prior trastuzumab-based regimen essentially in second line or higher. And as we just referred to previously, the actual study, DESTINY-Gastric01, which was conducted in the third-line setting or higher in Asia, ultimately recently led to approval in second line or higher.

So, Dr. Janjigian, given your comments and what we've discussed here so far about ADCs and this recent approval, can you hypothesize as to how this agent might be considered in other settings of this disease and potentially talk about DESTINY-Gastric03 and DESTINY-Gastric04?

Dr. Janjigian:
So, to me, it's important to move these agents to earlier lines of setting and starting with first line and eventually, hopefully, a neoadjuvant setting. We don't want to wait for our patients to receive these agents in later lines because in the Western patients, data suggest that in certain centers, only 40% of them even get on to receive second or third line. And also, by that point, the tumor is so complicated and noisy – HER2 is lost, EGFR is amplified, MET is amplified – it'll be very difficult to really make a big difference, and a sustainable overall response rate is rare.

So in my opinion, these drugs – and this is what we're doing with the next generation of studies is – should be moved up to first-line setting. ADCs and, of course, the caveats of interstitial lung disease and other pulmonary toxicities need to be considered, and patients will need to be monitored closely. But that's where the field is moving to, and also in combination therapies.

Dr. Catenacci:
That's great. We've talked about trastuzumab deruxtecan and how moving it as early as possible as it makes sense to make sure that patients get access to it. As you noted, many patients don't get later-line therapy for various reasons in this country, and there's evolution of the tumor towards negative at that point.

So that sort of leads us to the next segment here in terms of talking about all of the new agents that are sort of in this space, and we should talk about each one of them. So can you give us some information on each of those studies, their specifics about their approaches, and then how are we going to sequence all of these things if they all end up being successful?

Dr. Janjigian:
Absolutely, so the more the merrier, I say, and these patients live longer now. And the more options we have, the longer these patients will be well.

I think both MAHOGANY and MOUNTAINEER are very innovative studies that are important and we need to complete. I'll let you speak to that. But innovative about MAHOGANY is that it has a chemotherapy-sparing approach as well. You know, answering the question, is there a biomarker that can actually tell us in which patients we could de-escalate therapy, right, and use chemotherapy at a later line? Can we use a high PD-L1 and a high HER2 overexpression as a way to know which patients can potentially be chemotherapy free?

For MOUNTAINEER, it has also a potentially unique angle because that study is also allowing ctDNA as a selection criteria, which is very forward-thinking because, obviously, we all ask for repeat biopsies, but not all centers can do it quickly enough, and central confirmation is cumbersome and leads to delays. Having a small molecule inhibitor, tucatinib, is another interesting advantage because potentially, theoretically, it can cross blood-brain barrier, where what we noticed, the longer you live with this disease, right, we never used to see brain mets with our disease because patients passed away quicker. But now that we have people live for years, brain mets are becoming an issue that we need to address.

Dr. Catenacci:
Absolutely. I was going to say the same thing. With all of these tools, they may be most useful in certain situations and tailor to the patient in front of you. And, right, the longer a patient's on anti-HER2 therapy, we see a sort of a reservoir site, sanctuary site, to evade the therapies as in the CNS. And so we see that now with HER2-amplified tumors and others. So maybe tucatinib would be very useful there, of course. So, yeah, it's a very active first-line and second-line situation now with the number of promising agents, and we look forward to all of those studies reading out and providing these new options for our patients. And having too many options is a good thing, and I agree with you 100%.

So, well, this has certainly been a fascinating conversation, and before we wrap up, Dr. Janjigian, can you share your one take-home

message with our audience that we've been talking about here, with anti-HER2 therapies for HER2 gene amplification?

Dr. Janjigian:
Yeah, I think it's critical to do biomarker testing routinely and reflexively in all patients, and only if you're really regimented about it and you routinely test everyone will you be able to pick up some of these rare biomarkers. HER2 is one of them. Certainly, MSI or MMR deficiency needs to be tested. PD-L1 is still, I believe, useful, even if we get approvals irrespective of PDL-1 status, and EBV [Epstein-Barr virus]. The only way you will be able to guide your patients is if you know the biology of the tumor. So doing sequencing and assessing germline testing, as well, is very helpful as it will inform the liquid biopsy results and the circulating tumor DNA.

Dr. Catenacci:
Yeah, I would share those last thoughts as well. So unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Yelena Janjigian, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Janjigian:
Thank you. It's a pleasure.

Announcer:
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