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HER2-Low mBC: Optimizing Outcomes Through Patient-Centric Care

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we can optimize outcomes for patients with HER2-low metastatic breast cancer are Drs. Shipra Gandhi and Pavani Chalasani. Dr. Gandhi is an Associate Professor of Oncology at the Roswell Park Comprehensive Cancer Center in Buffalo, New York. It's great to have you with us, Dr. Gandhi.

Dr. Gandhi:
Thank you so much for having me.

Dr. Turck:
And not only is Dr. Chalasani a fellow ReachMD host, but she's also the Division Director at the GW Cancer Center in Washington, DC. Dr. Chalasani, thanks for being here today.

Dr. Chalasani:
Thanks for having me, and it's great to see you again.

Dr. Turck:
Well, to start us off, Dr. Gandhi, would you tell us how we can confirm a patient's HER2 status and when retesting might be needed?

Dr. Gandhi:
So once we have a tumor biopsy from the patient, biomarkers are tested that include estrogen receptor, progesterone receptor, and HER2. So HER2 is tested using IHC, and it is categorized into HER2 IHC, 0, 1+, 2+, and 3+. So a few years back, this was HER2 0, 1+, and 2+; 2+ which is FISH non-amplified was considered as HER2-, and HER2 IHC 3+, or IHC 2+, that is FISH amplified, was considered as HER2+. So this was treated as HER2- and HER2+. And recently, in the last few years, with the approval of trastuzumab deruxtecan, we actually have a new category of breast cancer, if I may say, called HER2-low. So HER2-low is now defined as IHC 1+, or IHC 2+, that is FISH non-amplified. So that is how we test for HER2 in the tumor biopsies. And retesting is generally needed if a patient who was diagnosed with stage I, II, III breast cancer now recurs and has metastasis, then we would biopsy that metastatic site and retest it for the HER2 IHC again. Because over a period of time, or with the receipt of treatment, the HER2 status may change, and it is important to know what the current HER2 status is in order to give the appropriate treatment.

Dr. Turck:
So then once we confirm that, Dr. Gandhi, what strategies would you recommend for approaching the systemic management of HER2-low metastatic breast cancer?

Dr. Gandhi:
Yeah, so HER2-low metastatic, if I'm seeing a patient with HER2-low metastatic breast cancer, it is important for me to first know whether this is hormone receptor-positive or hormone receptor-negative. If it's hormone receptor-positive, then in the first line, the standard management is CDK4/6 inhibitors with an aromatase inhibitor. And then in the second line, the management is guided by the mutation status of the tumor. So if it's ESR1 mutated, it's elacestrant. If it's PIK3CA mutated, then we generally go for alpelisib or capivasertib. If it's AKT mutated or there's PTEN loss, we go for capivasertib. And then, generally, I would give one more line of chemotherapy. And then after DESTINY-Breast04, I draw my management based on that. So DESTINY-Breast04 was a phase 3 randomized clinical trial that enrolled patients with HER2-low metastatic breast cancer and randomized them to trastuzumab deruxtecan versus chemotherapy or physician choice, and there was a progression-free and overall survival advantage seen with trastuzumab deruxtecan there. Majority of the patients, I would say 9/10 of the study population, were hormone receptor-positive. So based on that,

I'd give my patients trastuzumab deruxtecan after they've progressed on one line of chemotherapy, followed by sacituzumab govitecan after that.

However, if the tumor is hormone receptor-negative to begin with, the approach is slightly different there. In that case, the frontline management is guided by the PD-L1 status. So if the PD-L1 CPS score is 10 or higher, I would give that patient chemotherapy with pembrolizumab, versus if it's PD-L1 negative, which is CPS, less than 10, then I would just treat with chemotherapy.

And then the approach is slightly different from what I do for hormone receptor-positive. If the tumor is HER2-low, I would still go for sacituzumab govitecan first and trastuzumab deruxtecan after that; the reason being that for sacituzumab govitecan we have slightly more evidence from a phase 3 ASCENT trial, which was a randomized trial only enrolling patients with triple-negative breast cancer and showed progression-free and overall survival advantage with sacituzumab govitecan. So the reason I'm giving T-DXd later is because in DESTINY-Breast04, there were only 60 patients who were hormone receptor-negative. So I think we have slightly more evidence for sacituzumab govitecan for HER2-low, compared to we have for trastuzumab deruxtecan. And then after, I give chemotherapy.

Dr. Turck:
Turning to you now, Dr. Chalasani, I'll ask you the same thing. Would you provide us with your insights and thoughts on the systemic management of HER2-low metastatic breast cancer?

Dr. Chalasani:
Actually, I completely agree with Dr. Gandhi. So the main thing while we do have HER2-low as a potential new status for most of the tumors and as a new classification, it definitely implies a treatment decision change in the metastatic setting in the early stages with stage I, II, and III. It's also important for us to know, but we don't have any treatment decisions yet in those stages, but in the metastatic settings, they do. One of the things, like I said, Dr. Gandhi covered this perfectly, the only thing is what I would just add on is traditionally, when we've been documenting things, when we transcribe the pathology notes into our documents or things, and these are patients who could have had a tumor like five or six years or 10 years ago. Traditionally, we try to summarize and synthesize this and put it as HER2-, but I think in the past few years, everyone has been taking time to look and actually document if it is 0 or 1 or 2+ because right now, with the trastuzumab deruxtecan and some of the newer HER2 targeted antibody drug conjugates, the HER2 could be 1 or 2+, also. There are trials actually going on, even if it is by immunohistochemistry 0, maybe there is still some expression. So I think now it is important for us to do on the HER2 setting and going from there.

One of the just key thing is on the DESTINY-Breast04 and some of the other studies they have used the HER2 status from whatever pathology they had at that point, again leveraging the potency of the drug and using whatever drug and antibody drug conjugate we can get into the cell, and the permeability to the neighboring to the collateral cells, which may not have that kind of HER2 expression also, again, just leveraging on that potency of the drug delivery and the mechanism. They've used it just based on whatever pathology they had because frequently this is something we encounter in practice, like one of the tumors, one side is 1 or 2+, the other one is 0, can we still use it? And I think based on the current published data, they have used it.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Shipra Gandhi and Pavani Chalasani about managing patients with HER2-low metastatic breast cancer.

So with those approaches to systemic management in mind, let's look at patient-centered care. Dr. Chalasani, how do you work with patients to tailor their treatment plans?

Dr. Chalasani:
So like Dr. Gandhi was mentioning earlier, when a patient comes in the most important thing that we try to look for is, what is the status, what is the disease burden? And that is one of the main things. And again looking at, in addition to the HER2-low status, what is the hormone receptor, which is mainly driving it? And then their prior history, prior toxicities, those things are important. One of the things again, for consideration in terms of treatments are where do they live? What is the travel time? And what is the frequency? Which these are all taken into account for us to figure out what is the best systemic strategy.

Now taking all those individualized patient factors, which actually do drive in terms of the decision-making, in terms of which is optimal as they progress through treatments or lines, trastuzumab deruxtecan or sacituzumab govitecan, for a different line, all the regimens are taken into consideration, and then we go by that. But I do think significant patient factors, like in terms of their toxicities, what their current symptoms are, what is the disease burden we are up against, and again, their preferences are taken into account when we are trying to come up with the regimen.

Dr. Turck:

And as a follow up to that, Dr. Gandhi, how can we help our patients better understand the complexities of HER2-low metastatic breast cancer?

Dr. Gandhi:
Yeah, so I think when I see a patient because it's HER2-low, and we have recent approval for trastuzumab deruxtecan, first of all, we have to make our patients understand that if they are diagnosed with stage I, II, III breast cancer, even though if they are HER2-low, we still do not have any data suggesting that we could use trastuzumab deruxtecan in the early stage setting. So the approval for trastuzumab deruxtecan right now is only for the metastatic setting. And if I have a patient with me, and I'm trying to see what is the next line of treatment for the patient, I would want to see the report of a HER2-low in the metastatic site. And if I do not have that, then I explain to my patients that the way the clinical trial was designed, you could, as Dr. Chalasani already explained that HER2-low could have been tested in any sample, so that could even have been in the primary tumor. So I would tell my patients that I even look at their primary tumor to see if there is a HER2-low that I can find somewhere in the biopsy report.

And if none of the biopsies that I have on hand are HER2-low, then I might even discuss with my patients about the need for rebiopsy to see if I can find even one single tumor sample that's HER2-low because that would make them eligible to get trastuzumab deruxtecan.

So I think this is an important conversation to have with the patient that if there is no biopsy at hand that's HER2-low, we probably need to retest another metastatic site to see if we can find even one HER2-low sample.

Dr. Turck:
Now before we close, Dr. Chalasani, would you tell us why individualized care and education are so important and how they can impact patient outcomes?

Dr. Chalasani:
There are nuances in terms of, like Dr. Gandhi was mentioning, when we are talking to patients. HER2-low is a new category. It is not HER2- like we were always thinking. But in the early stage, HER2-low is still HER2- in terms of all treatment decisions. But even in the metastatic setting, the HER2-low on the tumor sample makes treatment options available for the patients. But I think we also have to educate that it is not HER2+ or amplified tumor because frequently because of the overlap in the trastuzumab deruxtecan, and with hopefully, a few more being coming available for patients. It's critical for us to educate and tell them that it is HER2-low, not HER2+, so that there's nuances there.

Now the other thing is also just navigating that, again, in the early stage. I think we frequently come across patients saying, 'Oh, I'm in HER2-low, can I get the T-DXd?' And it's like, 'No, it is still HER2-.' I think the first few years, especially in the past two years, there were a lot of times we had to discuss, and I had patients who come in and say, 'Oh, I guess I'm HER2+ now because I'm getting T-DXd.' And we were like, 'No, it is actually in the HER2-low category.' So actually having to try to come up with a way on going through the testing, and what that has changed and how treatments are, I think that has been more critical. Because previously we would say this is the result, but it's negative, so we're not going to use any treatment, which was pretty straightforward in terms of letting them know, but now it's a little bit more nuanced in terms of that. And trying to just tell what options are available, especially with the newer ones coming up.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guests, Drs. Shipra Gandhi and Pavani Chalasani, for joining me to discuss strategies for optimizing outcomes for patients with HER2-low metastatic breast cancer. Dr. Gandhi, Dr. Chalasani, it was great having you both on the program.

Dr. Chalasani:
Thank you for having us.

Dr. Gandhi:
Thank you for having me.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.