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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Patients with HER2-low mBC: Discussing the Unmet Needs and Potential Improvements

Dr. Chalasani:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me to talk about how we can address the unmet needs of patients with HER2-low metastatic breast cancer is Dr. Virginia Kaklamani. She's a Professor of Medicine in the Division of Hematology Oncology at the University of Texas Health Science Center San Antonio. Dr. Kaklamani, thanks for being here today.

Dr. Kaklamani:
Thank you for having me.

Dr. Chalasani:
So, Dr. Kaklamani, let's get right into the HER2-low category. How has HER2 testing changed? And how did the current paradigm of HER2-low come about?

Dr. Kaklamani:
So historically, HER2 testing was done so that we could determine what patient would benefit from trastuzumab and not another anti-HER2 therapy. And so we have immunohistochemistry, looking at the protein of HER2 with a 0, 1+, 2+, and 3+. And then in situ hybridization, that typically gives us a positive or a negative result. And we've defined HER2-positive as either 3+ by IHC or 2+ by IHC, but ISH positive.

But now we have a different category, this HER2-low category, which is HER2, either 1+ or 2+, but the ISH is negative. And the reason this category came about was the fact that there was data with new antibody-drug conjugates suggesting a benefit of anti-HER2 ADCs in this HER2-low breast cancer patient population.

Dr. Chalasani:
So in your clinical practice, how do you classify HER2-positive or HER2-negative, or do you use HER2-low?

Dr. Kaklamani:
So the way I look at it is in my early-stage patients, I still will think of them as HER2-positive or HER2-negative because this is the treatment that we have available. But in my metastatic patients, I will start putting in what the HER2 results are as 0, 1+, 2+. And of course, that makes it a little more confusing because many times, we have several biopsies to look at, and some of them are discordant. And so what I will typically do will be either put all of the results or put the highest score so that I remember that this is HER2-low.

Dr. Chalasani:
Now can you comment on how the treatment landscape has changed over time for patients with metastatic HER2-low breast cancer?

Dr. Kaklamani:
So the treatment landscape has changed because patients with HER2-low disease, whether they have HR-positive or HR-negative, once we get to start giving them a cytotoxic agent, we will start thinking about incorporating trastuzumab deruxtecan in that second- and third-line setting. And clinical trial data has shown that the T-DXd improves not only progression-free survival but also overall survival for our patients.

Dr. Chalasani:
Alright. So, Dr. Kaklamani, with these new treatments coming about, what are the known mechanisms of resistance for these treatments?

Dr. Kaklamani:
So mechanisms of resistance are really interesting and an issue when you're giving antibody-drug conjugates, and especially when you're trying to sequence them. We have now two ADCs available in metastatic breast cancer and a couple more coming out very, very soon. And each ADC has an antibody, a ligand, a linker, and a payload. So how are these mechanisms of resistance coming about? And the first one is a mechanism of resistance to the antibody. So for anti-HER2 antibodies, there could be either a decrease in HER2 expression, which we actually are seeing with T-DXd, but also specific mutations in the ligand-binding domain of HER2 that may actually not allow the antibody to bind HER2. So those are the known mechanisms of resistance. And there's a lot of work being done to try to find other mechanisms of resistance too.

And then there's resistance to the payload. Most of these ADCs that are being developed now are ADCs that have a payload against TOPO1, topoisomerase I. And there's been several mutations that have been seen in topoisomerase I that are accounting for resistance to these payloads. And the concern is that if you're using one ADC with a TOPO1 inhibitor and a second ADC with a TOPO1 inhibitor and the patient's cancer already has a mechanism of resistance, these ADCs are not really going to be active for the patients. So I think, or I'm hoping at least in the future, we can identify the mechanism of resistance in real-time, so that then that'll help us determine what the best strategy as far as sequencing these agents is going to be.

Dr. Chalasani:
Yeah. So are there some unmet needs when it comes to the management of care of patients with HER2-low in metastatic breast cancer? And how are they being addressed currently?

Dr. Kaklamani:
So one of the unmet needs is looking at toxicity and adverse events from T-DXd. We know that patients that are on T-DXd have a 10 to 15 percent risk of interstitial lung disease. So what do we do with these patients? What are the risk factors for ILD? How do we screen patients to try to find it at a state, at a grade 1, so that then we can re-challenge them? And if they have grade 2, is there a chance to re-challenge them with a lower dose of T-DXd? So that's one thing that would be nice to have some more data on.

We have some activity of T-DXd in CNS metastases, but it would be nice to have more data, more patients, and see how active this agent is. And can we combine it with other modalities? We know, for example, that if we give radiation around the time of T-DXd, we're increasing significantly the rate of radiation necrosis. And so those are things that we're learning more about but definitely affecting our patients. And I think one of the other things that hopefully we'll have an answer very soon is this other category, called HER2-ultralow, where there's some suggestion that T-DXd may be effective even patients that have IHC 0.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Virginia Kaklamani about unmet needs in HER2-low metastatic breast cancer.

So, Dr. Kaklamani, now that you've given us insights into some of the new treatment, can you give us your strategy when discussing the best treatment option for patients when you see them in clinic?

Dr. Kaklamani:
Absolutely. So when I see a patient that has HR-positive, HER2-negative, but HER2-low breast cancer, I will first of all try to determine whether their cancer is still endocrine sensitive or not. If it is endocrine-sensitive, then I'll proceed with my endocrine therapy. That depends also on what other mutations the tumor may have. Once I've determined that that cancer is now endocrine-resistant, I'll move on to cytotoxic therapy. And based on clinical trial data that we have so far, I'll give them a first line of chemotherapy. But then in that second-line setting, I'll start considering T-DXd. And I'm likely giving T-DXd for that patient.

Now if the patient has HR-negative breast cancer, but again HER2-low, my first-line therapy is going to likely be either immunotherapy or chemotherapy, depending on whether the tumor is PD-L1 positive or not. But then again, in that second-line setting, the consideration is to start adding antibody-drug conjugates. And T-DXd is a great option for these patients.

Dr. Chalasani:
And as a quick follow-up, how do you think the quality of life is impacted with these new treatments?

Dr. Kaklamani:
So these treatments are showing to improve, not just progression-free survival but overall survival. But as you are very nicely mentioning, in metastatic breast cancer, we have two goals. One is to improve survival, but number two is to improve quality of life and at least maintain it for as long as we can. And so the data suggests that by giving T-DXd, we can have some toxicity, such as nausea, vomiting, ILD, but ultimately, compared at least to chemotherapy, the maintenance of quality of life is better with T-DXd than it is with

chemotherapy.

Dr. Chalasani:
Okay before we end today, Dr. Kaklamani, let's look ahead for just a moment. What research is being done to help address this new category of HER2-low? Do you think there'll be any changes in early-stage breast cancer?

Dr. Kaklamani:
So I think this is a very exciting time to be in medical oncology, just because of all the new drugs that we have available. I think we first need to be able to define HER2-low better, and maybe we don't even need to define HER2-low because we can see that T-DXd is active regardless of HER2 expression, at least with immunohistochemistry. But there has to be some HER2 there for us to be able to get a benefit from T-DXd.

We're also potentially seeing that there might be a little bit of a difference based on the percentage of positivity of HER2. And so that hopefully, with better assays that are able to capture HER2 better than IHC, will be able to define. And then moving on to the adjuvant setting, these are patients in the metastatic disease that we know mostly have incurable disease. But how do we prevent cancer from metastasizing in the first place? And all of these drugs in the metastatic setting that are showing efficacy, we want to move them into the adjuvant setting to improve survival and to decrease recurrence for our patients.

Dr. Chalasani:
Those are hopeful insights to think on as we close our discussion today. And I would like to thank my guest, Dr. Virginia Kaklamani, for joining me to discuss the challenges and potential improvements to HER2-low metastatic breast cancer care. Dr. Kaklamani, it was great having you on the program.

Dr. Kaklamani:
Thank you for having me. I appreciate it.

Dr. Chalasani:
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