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HER2+ Metastatic Breast Cancer Therapies: Managing Adverse Events

Dr. Chalasani:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me today to discuss strategies for managing adverse events from new therapies in patients with HER2-positive metastatic breast cancer is Dr. Megan Kruse. Dr. Kruse is a Breast Medical Oncologist and Director of Breast Cancer Research at the Cleveland Clinic in Ohio.

Dr. Kruse, thanks for being here today.

Dr. Kruse:
Thank you for having me. Happy to be here.

Dr. Chalasani:
So let's dive right in, Dr. Kruse. Can you give us an overview of the current landscape in treatments we use before we go into the specifics of adverse events?

Dr. Kruse:
Absolutely. So for HER2-positive metastatic breast cancer, our treatment landscape has really exploded in the last few years and challenged some of the original paradigms we had about treatment options. Our first-line treatment is largely the same. I think the Cleopatra regimen basis of taxanes plus trastuzumab and pertuzumab, but beyond that is actually where we've seen the forward progress. And this is where we've seen a lot of development of the antibody-drug conjugates and the tyrosine kinase inhibitors, namely trastuzumab/deruxtecan and tucatinib shaping up this space.

Dr. Chalasani:
What are the most common adverse events we encounter that can occur when treating patients with HER2-positive metastatic breast cancer?

Dr. Kruse:
Yeah, I think across the treatment landscape for these metastatic patients, some of the toxicities are going to be very familiar to oncologists in general, things like fatigue is really, I think, unavoidable even with our best treatment options. It's still something that we struggle with. Certainly, with taxanes being the upfront therapy, we're still dealing with neuropathy, and many of these patients will have had prior treatment that may add to their neuropathy. So certainly something to keep in mind.

And then with HER2-targeted agents in general, I think we've had a theme over time of diarrhea being a concern and other gastrointestinal toxicities, like nausea, so that's still present. Cardiomyopathy, of course, rare but real for these patients as we make our treatment decisions and something to keep in mind if they're developing odd symptoms over the course of time. And then the one that has really impacted our treatment landscape and monitoring the most has really been the risk of interstitial lung disease, or pneumonitis, related to the antibody-drug conjugates, particularly trastuzumab/deruxtecan.

Dr. Chalasani:
So how do we monitor for these adverse events?

Dr. Kruse:
Yeah, I think that, particularly with the ILD concern, you have to have a high index of suspicion. And so from the medical oncologist perspective, a lot of that goes into the frequency of our scan monitoring and what we're actually looking for on the CAT scans of the lungs. So our practice has been to scan a little bit more frequently than we typically would for just disease monitoring, although I think

that the consensus about how frequently we do these scans is really up for debate. I've heard everything from every three weeks to every six weeks, and some providers still just doing it maybe every 12 weeks like you would with regular disease monitoring. And of particular importance there is, if you do see something that previously may not have been a big deal, like some small ground-glass changes or just some irregular opacities in the lung, they maybe don't look cancer-like, but don't look entirely normal. If a patient is on trastuzumab/deruxtecan, you have to actually take those quite seriously and intervene because that would be considered Grade 1 ILD, which is really our only opportunity to intervene, and then allow a patient to be re-trialed with therapy. Once the patients become symptomatic of course, there's the recommendation not to reinstitute the trastuzumab/deruxtecan, and that's hard because many of these patients respond very nicely.

So I think that having a high index of suspicion as the oncologist looking at these scans or cells maybe not just looking at reports is really important. And then also talking to patients about some of the more subtle symptoms that might go along with ILD in particular, like fatigue, like a dry cough even low-grade fevers I've heard reported with this. So you just have to be generally aware. And I have found that empowering patients to report those symptoms to us early on has actually been the best strategy.

Dr. Chalasani:
On the same note, how do we manage patients with these adverse events?

Dr. Kruse:
Yeah. So particularly with the interstitial lung disease, early institution of steroids is really helpful. And I think it's something that is different in our world because many times we're giving steroids when patients are symptomatic from whatever toxicity. Taking a page from the immunotherapy playbook and normally, unless we're having symptoms, we're trying to avoid giving patients steroids. But in this situation, in order to try to maintain the therapy, giving steroids early and watching for resolution of radiographic changes is actually really important. And so if you weren't getting scans more frequently before you had an abnormality that looks like ILD, you certainly have to afterward to watch for resolution and make that decision about whether treatment will be continued or not. And then I think for some of the other novel toxicities, particularly with something like diarrhea with tucatinib, we've really found that dose adjustment makes a big difference. And of course, the tucatinib is used in combination with capecitabine, and when you think about the toxicities of capecitabine, I actually find myself dose-reducing or managing symptomatically more for those toxicities than with the tucatinib. But because it's a combination regimen, you have to be aware of all of it.

And I think this is where some of the data with adjusting the capecitabine doses, some of the data we've seen with fixed dose, and maybe a seven-days-on/seven-days-off schedule with capecitabine can actually be really helpful to keep these patients on therapy for as long as they could be benefiting from it.

Dr. Chalasani:
So for those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. I'm speaking with Dr. Megan Kruse about how we address the risk and management of adverse events with the new therapies for patients with metastatic HER2-positive breast cancer.

So now that we discussed about these adverse events, Dr. Kruse, I would like to walk through some real-life patient cases. Can you share a case or two that highlights how we can take a patient-centered approach to provide them with optimal care?

Dr. Kruse:
Sure. So when thinking about this, one patient immediately comes to mind who's a younger patient of mine in her early 50s, and she was getting ready to start trastuzumab/deruxtecan. She had had progression on her first-line therapy after maintenance, trastuzumab and pertuzumab, for actually a couple of years, and so the prospect of going back on a more chemotherapy-type medication was daunting. And she recalled that from her adjuvant therapy years ago, when she was receiving an anthracycline, that actually, she had pretty significant nausea. And that was actually the thing that she took away that was most distressing from her prior treatment. So as we talked about trastuzumab/deruxtecan and some of its potential gastrointestinal toxicities, she was really worried.

And I think that this has been an important topic for providers over time to be aware of as trastuzumab/deruxtecan initially came out as more of a moderate emetogenic potential drug, and then was upgraded over time with real-world experience. And so it was recommended that the intensity of our antiemetic prophylaxis was increased.

So when I was talking to this particular patient, I had a feeling that this was going to be one of her bigger toxicities. And so to try to proactively manage that, I talked to her about starting on olanzapine at bedtime to help manage nausea. And this is a strategy that I use a lot because I think we know that olanzapine is great for sleep, for appetite, for anxiety management, and particularly, for more consistent nausea management. But it comes with its own challenges because, of course, if patients read about this or they go to the pharmacy, they'll find that olanzapine originally was an antipsychotic. And so if I don't proactively tell them why we're using this

medication, they often wonder what I think about their nausea and where I think it's coming from. And of course, we don't think that our patients are making up their nausea, this is a real toxicity, and olanzapine can be very, very helpful. But I think patients are more inclined to take it when you explain the rationale behind it and what we're actually expecting.

So sure enough, this patient, she was happy to start on this strategy, was glad to hear that we had something that might prevent nausea, but when she took it, she didn't acknowledge it, but she had significant daytime sleepiness, and that was actually impacting her quality of life. Otherwise, she tolerated the drug great. So we backed off on the dose of the olanzapine a little bit to a dose of 2.5 milligrams at bedtime, and this is actually supported by a fairly recent publication out of India in *The Lancet Oncology* looking at standard olanzapine versus lower dose olanzapine. Actually, found that efficacy for managing the nausea was pretty similar between the doses but less side effects at the lower doses you might expect.

Dr. Chalasani:
And what strategies do you recommend for educating patients and their care team about rare side effects that might occur and how they can be monitored and addressed?

Dr. Kruse:
Yes, absolutely. I think that oncology is such a team sport. There are so many people involved in the care of a patient and our hospital systems are really complex. And I think as these drugs have come out, obviously we as oncologists have had to learn a lot about them, and it's tough to expect that same level of understanding from all of the other care team members that a patient may encounter.

And I particularly think about their primary care doctors in this aspect, and also doctors that they may encounter in emergency rooms or urgent care settings because you can imagine a situation in which a patient that's on something like trastuzumab/deruxtecan comes into one of our facilities and has a cough or subtle shortness-of-breath and the providers that are taking care of them would need to know that this is related, potentially, to the medication.

So I've actually found that for some of these patients, giving them something they can carry in their wallet, like a pocket card saying what medication they're on. And of course, I think that's maybe most important for a drug like trastuzumab/ deruxtecan, but it can extend to many of the other drugs that we use in this setting that might have unique toxicity as they present in different ways, especially if a patient is not aware that that may be a toxicity that their other medical providers have to be thinking about. So I think some of that empowerment in having an automatic way for patients to alert new providers caring for them of what the toxicities may be.

Dr. Chalasani:
Before we end our discussion today, Dr. Kruse, would you like to share any final insights on managing adverse events in these patients?

Dr. Kruse:
I think that when we're managing adverse events, it's important to keep in mind that patients are on these therapies for a long time now. And so potentially the toxicities that we previously may not have given a lot of attention to because we knew that a patient may be on a therapy for three to six months, now become very, very relevant when hopefully they're on these drugs for years. And I think that quality of life can't be overstated in a condition where, yes, we do have long-term disease control, however, we're still going for palliation and not just lengthening of life, but quality of life. So I think about that when I'm talking to patients about the toxicities and what may actually be acceptable to them, and this is where the mismatch between patient experience versus our clinical trial grading of toxicity might not entirely overlap. And the other thing that factors into my equation when I'm having these conversations is the fact that the approval of doses for these drugs really isn't perfect, and I think that the maximum tolerated dose, which is really how we arrive at what we prescribe, may not be the maximum efficacious dose. And we know that from many studies where, when patients have dose reduction, they don't seem to suffer any clinical efficacy loss. And I find that that's something that maybe we're shy to do, and patients are certainly shy to consider dose reduction because they're worried about if we're going to have optimal cancer control.

And so I think us as providers being aware of symptom management studies, dose-reduction studies, and getting these studies out, and the data in some of the real-world experience is very crucial because these are the things that actually make the biggest difference in our patient's quality of life and safety on these medications.

Dr. Chalasani:
Those are great points to end on. I want to thank my guest, Dr. Megan Kruse, for joining me today to share her thoughts on recognizing and managing adverse events from therapies in patients with HER2-positive metastatic breast cancer.

Dr. Kruse, it was great having you on the program.

Dr. Kruse:

Thanks so much for having me. I really enjoyed our conversation.

Dr. Chalasani:
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