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https://reachmd.com/programs/cme/improving-the-standard-of-care-in-community-based-her2-positive-metastatic-breast-cancer/13108/

Released: 12/28/2021
Valid until: 12/28/2022
Time needed to complete: 15 minutes

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Improving the Standard of Care in Community-Based HER2-Positive Metastatic Breast Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Improving the Standard of Care in Community-Based HER2-Positive Metastatic Breast Cancer" is provided by Prova Education.

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Dr. Hurvitz:
HER2-positive breast cancer accounts for about 15%-20% of all breast cancer cases. Historically, HER2-positive breast cancer was associated with an increased risk for the development of systemic metastases as well as brain metastases and a poor overall survival. Looking ahead, there are innovative drugs that are currently in development and in clinical trials, that are showing great promise for these patients.

This is CME on ReachMD, and I'm Dr. Sara Hurvitz.

Dr. Gradishar:
And I'm Dr. Bill Gradishar.

Dr. Lin:
And I'm Dr. Nancy Lin.

Dr. Hurvitz:
Today we're going to go through 2 patient cases to illustrate therapeutic selection, management of treatment-related adverse events, and what future treatment options look like for HER2-positive metastatic breast cancer. This program follows a previous case-based simulation activity titled, "Optimizing Community-Based Decisions: HER2-Positive Metastatic Breast Cancer," where we collected the choices made by you and your peers in the second-line and third-line settings for metastatic breast cancer. In this program, we will analyze those choices and further discuss our optimal recommendations as a panel. If you haven't participated in the simulation and would like to put yourself to the test, you can find the link to the activity in the related section below. Let's get started with our first case.

Our first patient is a 48-year-old patient, who presented with ER-positive, PR-positive, and HER2-positive metastatic breast cancer with liver metastases. She received first-line treatment with 6 cycles of induction docetaxel paired with trastuzumab and pertuzumab, and she achieved a complete response by imaging in the breast and liver, as well as significant improvement in the bone metastases. She continued on maintenance therapy, with trastuzumab plus pertuzumab every 3 weeks and added in at this time an aromatase inhibitor given that the tumor was hormone receptor co-expressing. Unfortunately, the patient had disease progression 4 years later, however, with new liver and lung lesions.

Dr. Gradishar, based on this patient's characteristics, how would you approach her second-line treatment strategy?

Dr. Gradishar:
This patient clearly had disease responsive to HER2-directed therapy, had a prolonged response with her first treatment, but now has a

recurrence. I would certainly consider re-biopsying to confirm the markers, that she was indeed remaining HER2 positive as well as ER positive. But if we were having this discussion 6 months ago, we may have said something different than we say today, and that is that a while back it would have been T-DM1. But based on the recent presentation of the DESTINY-3 trial, we know that a comparison of trastuzumab deruxtecan to T-DM1 showed that trastuzumab deruxtecan was markedly better than T-DM1 in this exact setting. And specifically, what I'm referring to is the fraction of patients that responded was double in those that got trastuzumab deruxtecan, and more importantly, if you look at the time until the disease progressed, and you look at those curves, we often have used this phrase in describing the data, is that you could drive a truck through the difference between the PFS [progression-free survival] curves. So the median has not yet been reached in trastuzumab deruxtecan, and it was around 6 months or so in those patients receiving T-DM1. So a marked improvement in what our expectations are with trastuzumab deruxtecan, and there is at least a numerical advantage early on with respect to survival. So today, we would say that trastuzumab deruxtecan would be the appropriate choice in a patient like the one you described.

Dr. Hurvitz:
I agree those data were incredibly practice-changing. Dr. Lin, do you have any additional insights as to how you would treat this patient? Do you want to provide any thoughts on if there is a patient in whom you would treat with T-DM1 as opposed to T-DXd in light of these new data?

Dr. Lin:
Sure. I think the data are really impressive, as you've heard. And the delta, as far as PFS and as well as objective response rate is so striking that most patients, I'm going to be offering T-DXd. But there are patients who are more frail, who perhaps would be concerned about the toxicity profile of T-DXd, which is honestly a little bit harder than T-DM1, in whom I would offer T-DM1 as an alternative.

Dr. Hurvitz:
Now I think we'll move on to our second patient. Our second patient is a 55-year-old woman, who presented with HER2-positive metastatic breast cancer, and she has experienced a relatively indolent disease course. She received standard first-line therapy with docetaxel, trastuzumab, and pertuzumab and did quite well for several years, and then in second line received T-DM1, which was the standard of care at that time. Now her disease is progressing in her lungs, and she has recently developed a worsening in her migraine headaches. Imaging is done, given the increased frequency of the headaches, and she is found to have multiple brain metastases.

So I want to ask you, Dr. Lin, how you would approach this patient, who now not only has progression of disease systemically or extracranially, but also has now brain metastases. What third-line regimen would you recommend here?

Dr. Lin:
Sure. So what was chosen in this simulation was that about 50% of providers did not choose tucatinib plus trastuzumab and capecitabine. About a third of providers chose T-DXd in this third-line setting for a patient with brain metastases. I would argue that in this situation, the combination of tucatinib, capecitabine, and trastuzumab really has the strongest supportive data, and that's based on the randomized HER2CLIMB trial, and that trial randomized patients to either trastuzumab capecitabine or trastuzumab capecitabine and tucatinib. In particular, almost half the patients in this study, almost 300 patients, had brain metastases on study entry, so that's a very substantial subset of the overall population. And in that population of patients, there was significantly higher intracranial response rate, longer progression-free survival, longer time to CNS progression, and better overall survival associated with tucatinib. So I think that's very high-level evidence for the use of tucatinib in patients with brain metastases.

Dr. Hurvitz:
Level one evidence thus supporting the use of tucatinib, capecitabine, and trastuzumab in this setting, given those randomized data showing not only a progression-free survival benefit, but overall survival benefit as well. I found the data to be very compelling, and indeed, the FDA has approved this regimen in not only the third-line setting, where this study took place, but also in the second-line setting, especially for patients with brain metastases.

Keeping that in mind, Bill, I'd like to pivot back to you and just ask you if there are any patients like this, who have progression systemically as well as in the brain, in whom you would use T-DXd instead of the tucatinib-based approach.

Dr. Gradishar:
The most compelling evidence that supports an active agent in the CNS, as outlined by Nancy, is tucatinib in the HER2CLIMB regimen. But, that said, and then she emphasized the nuances that we have with these kind of patients, there may be somebody who has very limited CNS disease, you know, the little ditzel in the brain or something that's not too symptomatic, but the bulk of her problem really lies below the neck. And in that particular patient, you may choose, if you had a choice between a tucatinib-based regimen and trastuzumab deruxtecan, to take the latter, that is, trastuzumab deruxtecan, because the CNS is not the pressing issue. Whereas in other situations, tucatinib would clearly be the better choice in the HER2CLIMB regimen.

Dr. Hurvitz:
Thank you so much for those insights.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Sara Hurvitz, and here with me today are Dr. Bill Gradishar and Dr. Nancy Lin. We're just about to delve deeper into the treatment and management of patients with HER2 positive metastatic breast cancer.

And now that we have discussed these 2 clinical scenarios regarding the management of patients with HER2-positive metastatic breast cancer, let's turn our attention to the management of adverse events. While adverse events cannot be entirely avoided, there are ways to prevent, mitigate, and manage them, especially up front, with our patients being treated for HER2-positive metastatic breast cancer.

Dr. Gradishar, what are some of the main treatment-related adverse events that you see with these newer therapies, such as tucatinib and T-DXd, and how would you manage them or aim to mitigate or prevent them in the clinic?

Dr. Gradishar:
Starting out with trastuzumab deruxtecan, the side effect that got everybody's attention immediately was ILD [interstitial lung disease] and pneumonitis. And in fact, in the initial trial in breast cancer, there were a few patients that actually died from ILD. In the DESTINY-3 trial comparing trastuzumab deruxtecan to T-DM1, we didn't see that level or grade of toxicity. It was mostly low-grade toxicity and relatively infrequent. I think there are a couple things that we have to be aware of. One is we have to have a heightened sensitivity to any respiratory symptoms the patient may have. At the same time, we have to recognize that if we're scanning, looking for things like that, recognizing that patients have had radiation in the past, so you might see lung changes that aren't related to a drug toxicity but may be related to prior therapy. So for most patients, they aren't going to experience ILD, but we have to make patients aware of this as a potential side effect and encourage them to tell us if they're having any respiratory symptoms.

If there is any increased grade that we equate with that symptom, then we may have to hold or stop the drug. But certainly, for low-grade ILD or pneumonitis, introduction of steroids early often is sufficient to mitigate the side effects and allow continuing the therapy. If you look at the package insert, there is relatively vague but at the same time common sense guidelines for how to manage this. And I think as we get more experience, we may have more granular recommendations.

With respect to tucatinib, probably the biggest concern most people have is with the GI symptoms, including diarrhea. And not unlike other agents that can cause GI symptoms, we simply have to make patients aware of the potential for this side effect, and if they experience it, using agents such as loperamide or other similar agents to mitigate that side effect, allowing patients to continue on. And since it's given with a triplet of drugs, meaning trastuzumab, capecitabine, and tucatinib, it may allow us to adjust one of the other drugs, specifically capecitabine, which could offset the side effect that they're complaining about, that is, say, diarrhea. So we may not have to adjust the dose of tucatinib.

Dr. Hurvitz:
Thank you so much for that great overview. I think it is notable that in our simulation, about 50% of the providers did not select to hold therapy for grade 1 pneumonitis, and now as we know, and on studies evaluating T-DXd, for grade 1 asymptomatic ILD, where we only see it on imaging, it's important to hold therapy and monitor closely. So thank you so much for going in depth on the management of these AEs.

Dr. Lin, do you have anything you want to add in terms of the management of toxicity with these newer agents that we haven't touched upon?

Dr. Lin:
I think that it can be tempting with T-DXd, given the very high response rates, to really be fairly loose about the timing of the restaging imaging. But I'm fairly strict about it with T-DXd, not because I'm worried that the disease has progressed, but because I want to get a look at the lungs on a regular basis, really looking for that asymptomatic grade 1 ILD, to be able to intervene early on it rather than waiting for patients to become symptomatic. Then the other point is just that T-DXd is associated with more nausea than T-DM1, and so patients do need to have premedications appropriately to prevent nausea.

Dr. Hurvitz:
This has really been a very fascinating conversation with both of you, but before we wrap up, Bill and Nancy, do you have any take-home messages that you'd like to share with our audience? First with Bill?

Dr. Gradishar:
Well, I think the most exciting thing is that we have a continued introduction of new drugs we can offer patients, and with each step we take, I think we are moving the curve to the right, where patients are living longer, and although it's not the subject tonight, there are

even other drugs coming along. So I think the prospect for patients living a longer life is good, and at the same time, we're learning how to manage the side effects so the patients can have good quality life.

Dr. Lin:
Yeah, I would echo those comments and say that the survival numbers that we quote patients, as far as 5-year survival estimates in HER2-positive metastatic breast cancer, are mostly based in the pre-tucatinib, pre-T-DXd era, and I think it'll be really interesting to see how those numbers might change and improve as we have better therapies for the metastatic space.

Dr. Hurvitz:
Unfortunately, that's all the time we have today. I want to thank our audience for listening in, and thank you, Bill and Nancy, for joining me and sharing all your valuable insights and expertise. It was great speaking with you today.

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