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

How ADCs Are Transforming HER2+ Metastatic Breast Cancer: Discover the Latest Clinical Trend

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Welcome to CME on ReachMD. This activity, entitled “How ADCs Are Transforming HER2+ Metastatic Breast Cancer: Discover the Latest Clinical Trend” is provided by Prova Education.

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[CHAPTER 1]

Dr. Cortes:
In this first chapter, we will be going over the role of HER2 status in metastatic breast cancer. I am Dr. Javier Cortes.

Dr. Hurvitz:
Hi, and I’m Dr. Sara Hurvitz.

Dr. Cortes:
Hi, Sara. So, let’s get started. Sara, can you please give us some background on HER2 status?

Dr. Hurvitz:
Absolutely. In the 1980s, it was discovered that about a quarter of patients diagnosed with breast cancer have an alteration in the gene for HER2 where it is amplified, leading to overexpression of the HER2 protein. This was subsequently shown to be associated with a much worse outcome compared to HER2 non-overexpressing, or non-amplified breast cancers, which would’ve been a very sad ending to that story had a class of therapeutics not been developed to target that HER2 protein on the cell surface.

The first of these, of course, was trastuzumab, first approved in 1998 for metastatic HER2-positive breast cancer. And if you fast-forward now to 2021, there are 8 FDA-approved HER2-targeted agents available for patients with HER2-amplified or overexpressing breast cancer. And we now have data emerging suggesting that patients diagnosed with HER2-positive breast cancer, instead of having the worst prognosis, have as good a prognosis or even a better prognosis than those with HER2-negative disease because of the availability of these targeted agents.

More recently, a newer class of breast cancer has been defined known as HER2 low-expressing breast cancer. Meaning the tumor is not amplified for HER2, there is not overexpression of HER2, but there is a subtle or moderate expression of HER2 at the 1+ or 2+ level as measured by immunohistochemistry or staining. The reason this is important is not because this is a biologically distinct subtype with its own behavior, but because there are some molecules in development that may be able to use that expression of HER2 to gain access to the tumor cell and kill the tumor cells. About two-thirds of hormone receptor-positive HER2-negative breast cancer have low expression of HER2 and a smaller proportion, but still significant proportion, of triple-negative breast cancer has also got some low expression of HER2. So this is an evolving field. And in the near future, we may have therapies that work for this subtype of breast cancer.

Dr. Cortes:
It is great news. I think that the prognosis of patients with HER2-positive metastatic breast cancer has dramatically changed over the last years.

So before we wrap up, Sara, can you give us 1 or 2 key takeaway messages from this chapter?

Dr. Hurvitz:
Absolutely. So approximately 20% of patients have HER2-amplified or overexpressing metastatic breast cancer. We now have 8 therapies that target this, including 3 monoclonal antibodies: trastuzumab, pertuzumab, and margetuximab; 3 tyrosine kinase inhibitors [TKIs]: lapatinib and neratinib and tucatinib; and now 2 antibody-drug conjugates: trastuzumab emtansine and trastuzumab deruxtecan. So the outcome for patients diagnosed with this subtype of breast cancer is looking quite hopeful based on the number of therapies that we have to target it.

Dr. Cortes:
Sara, thank you very much.

In Chapter 2, we will be using a case to demonstrate optimal therapy selection for the management of HER2-positive metastatic breast cancer. Please stay tuned.

[CHAPTER 2]

Dr. Hurvitz:
Welcome. In the first chapter, we covered the role of HER2 status in metastatic breast cancer. In Chapter 2, we will be going through a case presentation to demonstrate optimal therapy selection. I'm Dr. Sara Hurvitz.

Dr. Cortes:
Hello. I am Dr. Javier Cortes.

Dr. Hurvitz:
All right, let's get started. Here's the case. A 44-year-old female who's single felt a left breast lump on her own. Her mother was diagnosed at the age of 82 with breast cancer. A mammogram and ultrasound was done in 2017, and the left breast showed an 11 x 7 mm mass with no abnormally enlarged lymph nodes. A biopsy of this mass revealed invasive ductal carcinoma, ER positive, PR positive, 90% and 80%, respectively, grade 2 with a Ki-67 of 5%. The HER2 was 2+ by immunohistochemistry but was FISH positive.

Liver, lungs and bones were without metastases. She underwent a lumpectomy and sentinel lymph node biopsy shortly thereafter, revealing a 9 mm stage 1 breast cancer. She received paclitaxel/trastuzumab for 12 weeks followed by the trastuzumab to complete a year. Tamoxifen was initiated after the chemotherapy, and she did receive radiation therapy. Six months later, while on the trastuzumab maintenance and the tamoxifen, she was noted to have grade 1 AST and ALT increase, as well as an increase in her GGT and her tumor marker was noted to be elevated. A scan was done revealing liver metastases that were small. She was offered trastuzumab emtansine.

Dr. Cortes, can you discuss some of the recommendations for this patient?

Dr. Cortes:
Well, I think this is, Sara, a quite a rare clinical case because a priori this patient had quite a good prognostic breast cancer; it was very tiny HER2-positive breast cancer based on the FISH, on the ISH assessment. So I think she was very nicely treated with a combination of paclitaxel/trastuzumab. We know that for tiny tumors it might have very good activity with a very small number of patients with a metastasis afterwards, about 1% or so. So I think she was nicely treated. But unfortunately, 5 to 6 months later, as you described, this patient had a liver metastasis.

And I think that T-DM1, which is a treatment of her is, in my opinion, the most reasonable approach to treat this patient. Unfortunately, this is absolutely unexpected, and I think that, again, unfortunately, we do not have any data to support the use of pertuzumab here because for treated patients, pertuzumab has not offered any benefit at least in terms of progression-free survival. So I think that T-DM1 is the preferred option here.

Dr. Hurvitz:
I couldn't agree with you more.

Well, she did go on and receive T-DM1 and did quite well with it for about a year or so when her liver enzymes again began to increase, both AST and ALT, as well as GGT. She began to develop a little bit of liver dysfunction with her INR going up, however, no bilirubin abnormality. Her tumor marker began to rise. A bone scan was negative. And then she underwent a liver biopsy at that point revealing

the ER was 10%, the PR was 5%. It was a grade 2 breast cancer metastasis, and again, the HER2 was 2+ by IHC, but ISH or FISH positive with a Ki 67 of 15%.

Now assuming, Dr. Cortes, that all the potential drugs are available to you at this point, what would you offer to this patient whose disease is progressing on T-DM1?

Dr. Cortes:
I think that we have great opportunities with tucatinib, trastuzumab, and capecitabine based on the HER2CLIMB data showing superiority compared with a trastuzumab and cape. We also can continue with any chemotherapeutic agent, eribulin or whatever, plus anti-HER2 therapies, capecitabine or trastuzumab. We can discuss the role of neratinib plus cape. Or we can discuss the role of trastuzumab deruxtecan, which is an antibody-drug conjugate which has some very beautiful activity in a large phase 2 study. Last but not least, I would like also to highlight the potential role of margetuximab, which compared with trastuzumab and a chemotherapy, might enhance or increase the progression-free survival.

So I think that we have different opportunities here. In my opinion, the best two options could be tucatinib-based therapy or trastuzumab deruxtecan. I think that we should not forget that the randomized trial HER2CLIMB makes that tucatinib-based therapy a very interesting approach. But in my opinion, always my opinion, the 61% of overall response rate and the very prolonged progression-free survival with trastuzumab deruxtecan in patients, even heavily pretreated, makes this compound as my best option. So I would go in favor of trastuzumab deruxtecan first, and I would say maybe tucatinib-based therapy as the second option.

Dr. Hurvitz:
Yeah, I think your points are really well taken. Just very briefly, would your answer be different if she had a brain metastasis?

Dr. Cortes:
That's a terrific comment. So certainly, certainly. I'm convinced, and we are running different trials in PFS with brain metastases with trastuzumab deruxtecan, and I would really like to use it, but it is true, that in the HER2CLIMB patients with brain metastases, even patients with the novel or progressive brain metastases were allowed to be included, and this group of patients, also tucatinib did much better. So I think that with the data we have today, tucatinib could be a very good option for patients with progressive brain metastases. But if stable brain metastases, I would also go for trastuzumab deruxtecan. But again, I think both of them are very, very good approaches.

Dr. Hurvitz:
So let's turn back to our patient. She did receive trastuzumab deruxtecan, and she had normalization of her liver markers, improvement of her tumor markers down to normal, PET/CT and liver MRI confirmed a complete response, which I've seen with this drug, as well, very phenomenal.

Dr. Cortes:
So imagine that the patient would have had low HER2 expression, okay? It's negative. Can you tell me something about the future outlook for considerations around low HER2 expression?

Dr. Hurvitz:
Absolutely. This patient could have – and I've seen the case where we retest at the time of liver biopsy and the IHC is 2+ but the FISH is negative. And in this situation, we have some very interesting clinical trials ongoing of HER2-targeted antibody-drug conjugates. As we know, T-DM1 does not work in HER2 low-expressing breast cancers that are not amplified. However, trastuzumab deruxtecan is showing very interesting phase 1b data for the HER2 low-expressing breast cancers with objective response rates on the order of about 40% or more. This is very exciting given the fact that HER2 low-expressing breast cancer is actually fairly common, especially in hormone receptor-positive disease. So this is an area that's rich and ripe with research, and I'm looking forward to seeing data come out. Maybe we'll have another therapy available for patients defined by low expression of HER2.

Dr. Hurvitz:
So this has been great. Before we wrap up, Dr. Cortes, can you provide us with one key takeaway, just one, from this chapter?

Dr. Cortes:
Terrific drugs which are already there, which are upcoming in many, many countries. Trastuzumab deruxtecan, one of them. Tucatinib-based therapy, another one. This is a great, great, great time for patients that unfortunately will not be cured, but many of them will live for a very prolonged period of time.

Dr. Hurvitz:
Thank you so much, Dr. Cortes.

So in Chapter 3, we'll be discussing how to manage adverse events. Stay tuned.

[CHAPTER 3]

Dr. Cortes:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Javier Cortes and here with me today is Dr. Sara Hurvitz. We are discussing how antibody-drug conjugates, ADCs, are transforming HER2-positive metastatic breast cancer.

Welcome. In Chapter 2, we walked through a clinical case presentation. And now in Chapter 3, we will be discussing a very important issue: how to manage adverse events in our patients with HER2-positive metastatic breast cancer. I am Dr. Javier Cortes.

Dr. Hurvitz:
And I'm Dr. Sara Hurvitz.

Dr. Cortes:
So, Sara, we always have to be mindful of adverse events associated with some of the current treatment options. Can you please share with us some of your strategies to manage all these events?

Dr. Hurvitz:
Absolutely. So we have mentioned in our prior chapters some of the exciting new therapies, trastuzumab deruxtecan and tucatinib combined with capecitabine and trastuzumab, and we know that each of the drugs that we have available for HER2-positive breast cancer carries with them their own unique side effect profiles.

When it comes to trastuzumab deruxtecan, I think it's important for patients to be aware of the nausea and diarrhea, as well as significant hair thinning or alopecia associated with this agent. And that clinicians carefully tailor medication use to help patients mitigate these side effects in terms of having antiemetics on hand; I'm personally using antiemetics up front for patients. And having them be aware of the fact that hair loss is very common with this. One of the key potentially life-threatening side effects associated with trastuzumab deruxtecan is interstitial lung disease [ILD] or pneumonitis. And so I would be very careful to not put a patient on this who has a history of pneumonitis or significant pulmonary fibrosis or ILD at baseline. And I'd watch patients very, very closely, advising patients to notify me if they develop any shortness of breath, dyspnea, fever, etc. Moreover, when looking at a patient's scan, which is typically done to assess whether their tumor is responding to treatment, when looking at the CT scan, if you begin to see ground-glass opacities or infiltrates, it's important to stop the medication and reassess and consider use of steroids. So even with asymptomatic grade 1 pneumonitis, it's important to stop therapy and monitor very closely and stop permanently if you reach grade 2.

With tucatinib-based therapy, as with other TKIs, the main side effect we need to be aware of is diarrhea. So having patients have anti-diarrheal medications on hand at home and have a very good communication pathway set up with their clinician to manage it if they are developing dehydration is very key. Also, it's important to follow liver enzymes, which can sometimes be altered. And with all of these drugs, it's important to follow cardiac imaging and monitoring periodically given that targeting HER2 can be associated with cardiomyopathy.

Dr. Cortes:
So, Sara, terrific, terrific discussion. Before we wrap up, can you please provide us with one key takeaway from this chapter?

Dr. Hurvitz:
Be very mindful of the adverse event profile associated with the drug that you're starting and utilize that to properly select patients for a given therapy. It's not all about efficacy. It's about the therapeutic index.

Dr. Cortes:
But unfortunately, we have to stop here. That's all the time we have, today. So I would like to thank you very much.

Dr. Hurvitz:
Thank you, Dr. Cortes. The pleasure was all mine.

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