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

Evolving Strategies in the Management of HER2-Positive Early-Stage Breast Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Evolving Strategies in the Management of HER2-Positive Early-Stage Breast Cancer" is provided by Prova Education.

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Dr. Geyer:
Thank you for listening to our program. Over the past 15 years, incorporation of HER2-targeted therapies into our treatment algorithms has greatly improved outcomes for women with HER2-positive early-stage breast cancer. But the need for further improvements and refinements in treatments for these patients remains.

This is CME on ReachMD, and I'm Dr. Charles Geyer from the Houston Methodist Cancer Center. I'll be talking today with Dr. Hope Rugo from the UCSF Helen Diller Family Comprehensive Cancer Center about the evolving landscape in the management of HER2-positive early-stage breast cancer. Welcome, Dr. Rugo.

Dr. Rugo:
Thank you, Dr. Geyer.

Dr. Geyer:
So let's begin. Dr. Rugo, we've seen many changes in the management of HER2-positive early breast cancer over the past few years. But before discussing these changes, could you provide our listeners a quick review on the prognostic and therapeutic implications associated with the diagnosis of HER2-positive breast cancer?

Dr. Rugo:
Certainly. It's actually a fascinating story, as you know, and the subject of a Lifetime movie. But overall, HER2 is overexpressed or the gene is amplified in about 15% of breast cancers. And this has been found – from the 80s now – to be a strong driver of tumor development and proliferation, as well as the ability to invade and metastasize. And from these early data, we found that HER2-positive tumors were very aggressive and had a poor prognosis, but also were uniquely sensitive to chemotherapy. And this, of course, led to the development of targeted antibodies and now a whole host of therapies that have completely changed the outcome of HER2-positive breast cancer to be actually, I would say, arguably the best prognosis subtype of breast cancer that we diagnose today. HER2 is a very important target.

And the definition of HER2 positivity has been an ongoing, controversial area that has been addressed by the ASCO/CAP guidelines, most recently updated to clarify some of the confusions before. I think the current guidelines are pretty good and help us a lot in terms of determining HER2 positivity. But there are still controversies. The HER2-targeted antibody trastuzumab, which was the subject of that Lifetime movie, has been transformative in the treatment of metastatic breast cancer and early-stage HER2-positive breast cancer. And in my own clinical experience, I knew we would change the world for HER2-positive breast cancer when I treated the first patient with metastatic disease who was cured of her cancer and is alive now today, more than 20 years later. Remarkable results from that first generation of adjuvant trials were reported in the early part of the last decade and have completely changed our treatment paradigm

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for early-stage, HER2-positive breast cancer and outcome.

Dr. Geyer:
It is interesting how the global guidelines have really reached a clear consensus that patients presenting with clinical stage T1c, N0 disease should undergo surgery and then receive APT if node negative and if node positive, then get more of a standard chemotherapy regimen based on the AFFINITY study. The interesting thing was that in the KATHERINE trial, we did include patients who had residual disease who had presented with T1c stage. And we found that in the patients who had received trastuzumab, their IDFS [invasive disease-free survival] rate was only 81%. And in the patients who had T-DM1, we had no recurrences. So the data certainly suggests that non-pCR [pathological complete response] patients presenting with those 1- to 2-centimeter, node-negative tumors can benefit from T-DM1 if identified. And the current guidelines effectively eliminate the possibility of identifying this important subset of patients.

So let's discuss the issues regarding adjuvant therapy in the patients who are treated with initial neoadjuvant therapy. Dr. Rugo, what management decisions and remaining challenges need to be addressed in regards to adjuvant therapy following neoadjuvant treatment both for patients with pCR and those with residual disease at surgery?

Dr. Rugo:
Well, this is, of course, a big question for us, and it does lead back a little bit to what you were talking about earlier, that these patients who have a little bit of disease after surgery, do they still need T-DM1 or not? And also, what the impact is on T1c disease. And I do want to mention that the majority of patients that were enrolled in KATHERINE had hormone receptor-positive disease. These patients have lower pCR rates. They do have ongoing risk of recurrence despite endocrine therapy. So it is an important group to consider in the neoadjuvant setting.

In patients who have a pCR, we treat with HER2-targeted therapy to complete one year of therapy. And this is a standard approach. Now, one of the questions comes up with if you gave trastuzumab and pertuzumab, do you need to give both? And that is currently the standard of care. We don't know the answer. I don't know that we'll ever know the answer to that. For patients who have a pCR, there is still some tiny risk of distant recurrence and there's a tiny risk of brain metastases. And we're really trying to understand the genomics and the clinical situation that increases that risk. It could be that patients who have stage IIIc disease have a slightly higher risk, and potentially those patients could be studied in the future in terms of adding agents that cross the blood-brain barrier.

For patients with residual invasive disease, again, the predominant group have hormone receptor-positive disease, the current standard of care is to change the HER2-targeted agent to trastuzumab emtansine and to continue for 14 cycles, as was done in the KATHERINE trial. I think the unmet needs in these patients, again, is a sort of stable risk of CNS metastases in the, maybe, 5%-6% range. You can correct me if that's not quite right, but understanding the benefit of adding tucatinib in those patients is being studied in an Alliance and Cooperative Group trial. And I think that's really important.

And also, of course, we need to manage the toxicity in these patients because some patients do have nausea, liver enzyme elevations, and thrombocytopenia. So there's a lot going on. And I think the newer agents may give us further advantages.

Dr. Geyer:
Yeah, thank you for that. It was very interesting comments. I did want to just bring up one quick item, though, related to the KATHERINE data. We often get questions about should we retest residual disease for HER2 status to make sure the patient should still receive T-DM1? And in KATHERINE, we actually had over 800 paired specimens where we had the diagnostic core as well as a residual disease. And we found that 70 of those patients who were clearly HER2-positive on their core, on central testing, were negative on their residual disease. So it does happen in somewhere around 8% of patients. The interesting thing was that among the 42 patients who went on to receive trastuzumab, we had 26% recur, certainly indicating they had risk for recurrence. In the 28 T-DM1 patients, we have yet to have a recurrence. So these results can only be considered exploratory because of the small numbers. But it's unlikely the question will ever be successfully addressed prospectively. And I think the data really provides no support for withholding T-DM1 based on negative retesting results.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Charles Geyer, and here with me today is Dr. Hope Rugo. We've been discussing the evolving strategies in the management of HER2-positive early-stage breast cancer.

Dr. Rugo, one important aspect in the management of our patients with breast cancer is reduction of their burden of therapy. To this end, could you describe how the emergent subcutaneous HER2-targeted monoclonal antibodies might fit into a meaningful therapeutic strategy in HER2-positive early breast cancer? That is, what are the advantages and disadvantages of these therapies?

Dr. Rugo:
Well, this is also a really timely and important topic, particularly given where we are in our pandemic and people's burden of coming into the center and screening, etc. Subcutaneous trastuzumab and pertuzumab have been shown to be identical in terms of efficacy, and I

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think convincingly so. Trastuzumab given by itself, as well as trastuzumab/pertuzumab given in a combined subcutaneous injection.

The major side effects from giving these agents are just local. And I found, particularly with the combination of trastuzumab and pertuzumab, that patients will get local erythema with the first dose. And interestingly, we don't see it with repeated doses so much. And again, this is my anecdotal observations. But it's been interesting to talk about this with patients.

So patients who come from fairly far away, coming in and getting an injection and leaving on Saturday is a huge benefit to these patients. They can actually have their port removed much earlier. You know, we generally always kept the port in for a year. And patients really see that port as a sign of cancer, a sign of their abnormality. It hits things. You know, a patient was just recently telling me that her kid was always hitting it and it hurt. And they can get infected, of course, and clotted. So having the port removed early has been just a gift to my patients now with early-stage disease who are continuing on with either trastuzumab after the shorter course regimen for node-negative disease, so called the APT or TH regimen [paclitaxel plus trastuzumab] or patients who are continuing with trastuzumab and pertuzumab using the combination. They really like coming in. Now, one of the things that's come up with some of my patients is that they love the nurses and it's like a social group, right? Well, they still have that social interaction by coming in and getting their subcutaneous injection. And maybe someday this will be a drug which can be administered at home. But it really does reduce the burden of therapy and [in] surprising ways for our patients. And it's a big advantage. I think the disadvantages are relatively modest because this local injection reaction appears to be fairly well tolerated and short lived.

Dr. Geyer:
I agree. Our patients have been particularly fond of having the port removed and continuing the therapy subcutaneously to finish out the year of treatment. We also have found that it does shorten chair time and makes more efficient use of the office and the treatment environment. So it's been, I think, a real advance for our patients.

Well, Dr. Rugo, thank you for sharing your insights on the evolving landscape and management of HER2-positive early breast cancer. But before we wrap up, can you share with our audience kind of one take-home message?

Dr. Rugo:
It's always hard to give one message, but I think the key is that we're individualizing therapy for HER2-positive breast cancer in a real way. People can get therapy that's appropriate for their cancer, the biology of their cancer. And we now have options to reduce the burden of treatment over the year of therapy.

Dr. Geyer:
Yeah, I think our progress over the past 15 years in these patients has been remarkable, and it's been primarily because of the monoclonal antibody-based therapy with trastuzumab and pertuzumab. But now with T-DM1, we have greatly improved our outcomes for patients who don't have the pCR, who haven't responded. I think we're really getting closer to our goal of cure for the large majority of our patients who present with these formerly very aggressive high-risk cancers. And the second-generation ADCs [antibody-drug conjugates], tucatinib, I think, offer exciting potential for even further improvements.

Dr. Rugo:
I agree. And I think the one message, really, in addition to what we've talked about, is how important it is to think about treating before surgery for the majority of patients with HER2-positive early-stage breast cancer. This is really going to allow us to personalize therapy, both to reduce the intensity and toxicity of treatment and to increase it with some of these newer options when it's needed to improve outcome.

Dr. Geyer:
Thank you, Hope.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Rugo, for joining me and for sharing your perspectives on this important topic. It was great speaking with you today.

Dr. Rugo:
And it was great speaking with you as well. Goodbye, and thank you for listening.

Announcer:
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