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Tailoring Treatment Plans for HER2+ Metastatic Breast Cancer

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to share strategies for tailoring treatment plans for patients with HER2-positive metastatic breast cancer are Drs. Adam Brufsky and Sara Chumsri. Not only is Dr. Brufsky a Professor of Medicine, but he's also the Associate Chief for the Division of Hematology Oncology at the University of Pittsburgh School of Medicine's Department of Medicine. Dr. Brufsky, glad to have you with us.

Dr. Brufsky:
Thank you for having me.

Dr. Turck:
And Dr. Chumsri is a Professor of Oncology at the Mayo Clinic Cancer Center in Jacksonville, Florida, where she's also the Mayo Clinic Breast Disease Group Research Co-Chair and HER2 Working Group Co-Chair. Dr. Chumsri, welcome to you.

Dr. Chumsri:
Thank you for having me, too. Thank you.

Dr. Turck:
So to get things rolling and starting with you, Dr. Brufsky, when it comes to creating personalized treatment plans for patients with HER2-positive metastatic breast cancer, what disease-specific factors, like tumor characteristics, do we have to consider?

Dr. Brufsky:
Well, obviously, I think the patient has to have HER2 3+ disease, or HER2 amplified by FISH tumor. I mean, that's the first thing. But the second thing, I think there's a lot of things to go into this, the disease-free interval, if they have relapsed disease, but to be honest with you, the vast majority of patients we see now are de novo because our early stage therapies work so well. But clearly, it's the amount of disease they have, where it is in their body. I think a big one is do they have brain metastases or not? Where it is, the degree of HER2 positivity with anything with FISH ratio over two, I'll treat and disease-free interval before their therapy. Those are probably the big ones, and whether they have brain mets is four. Those are probably the big things I think about in HER2-positive metastatic breast cancer.

Dr. Turck:
And along with those factors, Dr. Chumsri, what patient characteristics, like age or comorbidities, do we have to keep in mind?

Dr. Chumsri:
Yeah, so I totally agree with Dr. Brufsky. I think those things that he mentioned already, like, how strong the HER2 positivity brain mets because there are some medication that can penetrate blood-brain barrier that we try to use in patients with brain metastases. And those patients that have that short disease-free interval, I think those are often more difficult to treat, and you want to get more active agents early.

But besides that, I think sometimes we also consider about estrogen receptor positivity. I think there's some early data with HER2-positive breast cancer that may perhaps do well with just endocrine therapy plus anti-HER2 therapy especially if they're older, and also, of course, the age and comorbidities and other things, also taking into account if they have peripheral neuropathy from their previous neoadjuvant or adjuvant therapy, sometimes we might need to avoid more taxanes. So all of those things are all in consideration.

Dr. Turck:
Now with all this in mind, Dr. Brufsky, what are some challenges you encounter when tailoring treatment plans?

Dr. Brufsky:
Well, I think the big one is brain metastasis and prior therapy. I mean as Sara said before, I think that someone has fairly severe neuropathy from their paclitaxel, or docetaxel, a lot of people receive TCHP as their neoadjuvant therapy and then will receive maybe even T-DM1 as post-neoadjuvant therapy if they have excessive disease, and then they'll have a relapse. So they already have two drugs that were giving them a bit of neuropathy to begin with. And so that is a challenge sometimes. You have to think of regimens that maybe don't include a taxane, which is really the backbone. I think the vast majority of people will get the CLEOPATRA regimen, which is a taxane trastuzumab, and pertuzumab as first-line therapy. And so the other challenge is none of those drugs cross the blood-brain barrier. That's probably the big challenge, I think, for all of us is what do we do with somebody who presents concomitantly with disease above the neck in their brain and systemic disease below the neck. That's probably, I think, right now, at least for me and I'm sure, Sara, probably you guys too at Mayo, probably the biggest challenge that we have right now in HER2-positive disease.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Adam Brufsky and Dr. Sara Chumsri about how we can personalize the treatment of HER2+ metastatic breast cancer.

So now that we've covered the factors and challenges associated with individualizing treatment plans, let's look at some solutions. Dr. Chumsri, what are some other ways that you work with your patients to create a plan that addresses their unique needs?

Dr. Chumsri:
Yeah. So I think what Dr. Brufsky was mentioning, of course, with the brain metastasis, some of those patients, we try to use small molecules inhibitor. There's really good data with the tucatinib from the HER2CLIMB, but emerging data with the T-DXd, like from the DESTINY-Breast trials too. So I think that's opened up more treatment options for our patients.

In my practice, I think the other thing that we have is that we often talk with women is the hair loss. So I think I have a lot of women, especially in the first-line setting, when you talk about chemotherapy in combination with the trastuzumab and pertuzumab, and of course, the hair loss sometimes, it's a big shock to some of the patients.

But I think some of the additional trials coming out, things like the VELVET trial, with the vinorelbine, even capecitabine can also be considered. So some of those things also little things that play into the decision-making for these patients, too. And even if they have estrogen receptor-positive breast cancer, now perhaps, maybe we can get away from chemotherapy and perhaps consider endocrine therapy with the trastuzumab and pertuzumab. So all of those play into decision-making when we talk to patients.

Dr. Turck:
And Dr. Brufsky, would you tell us about the role of the multidisciplinary team when caring for patients with HER2-positive metastatic breast cancer?

Dr. Brufsky:
Yeah. I think there's a lot more consultation actually, in this sort of patient because a lot of them have very, very intense responses. I mean complete responses. And so we talk to surgeons sometimes, if they've had a complete response for every year or two, you say, do we do any local therapy on their breast? Even though, really, there's no data to support it right now, I think that the data is very mixed. But if you've had a complete response, except everywhere about like a lump in your breast, I think a lot of us would consider removing that. And we also talked to radiation therapists in a multidisciplinary way. If someone presents, for example, a good one is someone who's been on, say, a great example, Dr. Chumsri said, if someone comes with a couple bonus that are HER2-positive, we decide not to give them cytotoxic chemotherapy, put them on maybe HP, trastuzumab, pertuzumab, and maybe an anti-estrogen, like anastrozole, and they've done well for a few years, and all of a sudden they have a single bone met. That's it, somewhere else. We call that now oligo progression. And so do we radiate it? Or do we just change therapy completely? And I think that's a real question that requires multidisciplinary consultation. Surgery is the same thing. You have that same patient. Now she has a breast mass that's enlarged, but the rest of her tumors are fine, and she's doing really well. And most people on HP and an anti-estrogen do incredibly well, and she has an enlarging breast mass. Do we do surgery on her? Or change her therapy completely?

Those are the multidisciplinary consultations we have in metastatic disease in the HER2-positive range. I'm curious to see what Dr. Chumsri says at Mayo, but that's kind of how we do it at Pitt.

Dr. Chumsri:
Yeah, same here. I think you brought up a good point. We often, especially with anti-HER2 therapy being so good now that we often see these like tiny, little oligo progression. And I think based on that phase 2, that CURB trial, that did not show much of the benefit of doing SBRT and continuing on treatment, at least in the subset of breast cancer patient. We have some discussion during our tumor board. But on the other hand, that particular trial did not have a whole lot of HER2-positive breast cancer on it, though, so it's probably had to

extrapolate the data on HER2-positive breast cancer patients that's doing so well. So in those cases, we still consider doing some of those targeted treatment, what Dr. Brufsky mentioned.

Dr. Brufsky:
Because we have a ton of great, new targeted treatments. Absolutely tremendous targeted treatments.

Dr. Turck:
And I'd like to ask each of you about novel therapies and recent therapeutic advances in this area. Dr. Brufsky, let's start with you.

Dr. Brufsky:
Well, I think the one big thing that we really didn't talk about is trastuzumab deruxtecan. And I think that it's an antibody-drug conjugate that really has revolutionized our field completely, even in the HER2-positive space. I think as second-line therapy, after progression on, say THP, you have a progression-free survival of over 28 months and an overall survival benefit. And it really allows us to do all the things we talked about before, really tailor the early-line therapy, maybe to a milder therapy because we always know we have T-DXd to fall back on with a substantial survival benefit.

The only real side effect of T-DXd, it has nausea and does have a little bit of thrombocytopenia, but about 10 percent of the patients get interstitial lung disease and have to come off the drug. But other than that, I think that it really has revolutionized the way we treat HER2-positive metastatic breast cancer

Dr. Turck:
And, Dr. Chumsri, what are your thoughts about recent advances that have captivated your attention?

Dr. Chumsri:
Yeah. So there are several new cool drugs that are coming out, and I'm so excited in the later lines therapy, things like cancer vaccine, even CAR T therapy, and other small molecules inhibitor that are very targeted and selective. But besides that, like in earlier stage disease, I think we are excited to see the data with some of the oral SERDs in combination with the anti-HER2 therapy, as well as some of the CDK4/6 inhibitor, like in the PATINA trial and other trial they're looking at, perhaps maybe we can do better and give patient longer progression-free survival without not much toxicity.

Dr. Turck:
Now before we close, Dr. Chumsri, from a global standpoint, how can all the different treatment and care considerations we've talked about today really impact our patients' outcomes and qualities of life?

Dr. Chumsri:
Yeah. So I think what we were just talking about, now that anti-HER2 therapy, we have a lot of treatments available for patients, a lot of many effective treatment that will work so well for patients, I think, quality of life now becomes important, so we can tailor and get the treatment that's easier on some patients. I think it's very reassuring to see some of the longer follow-up data from the CLEOPATRA trial, like with the eight-year follow-up, and there were actually like 16 percent of patients that actually still don't have disease progression with the first-line therapy, which is phenomenal. And I think we are so excited for some of the trials, things like STOPHER2, looking at maybe perhaps you are carrying some of these small subset of exceptional patient that had response, but we do need those brave ladies to participate in the trial to see perhaps we can maybe even stop this therapy. But the outcomes are fantastic, excellent, and I'm really curious to see what's more to come.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guests, Drs. Adam Brufsky and Sara Chumsri, for joining me to discuss personalized approaches to HER2-positive metastatic breast cancer care. Dr. Brufsky, Dr. Chumsri, it was great having you both on the program.

Dr. Brufsky:
Thank you very much.

Dr. Chumsri:
Yeah, thank you for having me. Thank you.

Dr. Turck:
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