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Empowering Choices: Navigating Early-Stage HR+, HER2- Breast Cancer with CDK4/6 Inhibition

Announcer:
Welcome to CME on ReachMD. This activity, titled “Empowering Choices: Navigating Early-Stage HR+, HER2- Breast Cancer With CDK4/6 Inhibition” is provided by MEDCON International.

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Dr. O’Shaughnessy:
Hello. I'm Dr. Joyce O'Shaughnessy from Baylor University Medical Center and Texas Oncology. Welcome to our patient-clinician connection on CDK4/6 inhibitor therapy in HR-positive, HER2-negative, early breast cancer.

Hormone receptor-positive, HER2-negative breast cancer is the most common subtype of breast cancer and accounts for over 70 to 75% of all cases globally. For early breast cancer, the goal of treatment is cure. In the HR-positive, HER2-negative setting, initial treatment consists of surgery with or without radiation therapy or chemoradiation therapy followed by adjuvant endocrine therapy for 5 to 10 years. And although endocrine therapy improves outcomes quite a lot, in certain patients with HR-positive, HER2-negative breast cancer, recurrence risk can be high and can occur in up to 40 to 60% of patients.

And in patients who do not carry a germline BRCA mutation, recent data have shown that treatment intensification with adding a CDK4/6 inhibitor to endocrine therapy can greatly improve disease-free survival outcomes in high-risk, HR-positive, HER2-negative, early breast cancer patients. This treatment is generally well tolerated with, at the end of the day, a minimal overall impact on quality of life for patients once we get the right dose for an individual patient. And so when we're planning therapy with patients, we need to remember to apply shared decision-making with patients, and we will be aligning with our patient’s goals. So in this activity, we're going to explore treatment selection for a patient with HR-positive, HER2-negative early breast cancer through clinical vignettes. So let's go ahead and get started.

Case Presentation
Carla is my 48-year-old patient who was diagnosed 4 months ago with HR-positive, HER2-negative early breast cancer after she felt a mass in her right breast.

She underwent surgery after genetic testing showed that she did not harbor a germline mutation in BRCA or other of the important alterations, and she was found to have a grade 3 breast cancer with a Ki-67 of 40%, hormone receptor-positive and HER2-negative. She is premenopausal, and her medical history includes a history of smoking, a family history of thromboembolic events, but no family history of breast cancer. She was found to have a T2 breast cancer, N2 M0 breast cancer. And she's in my office today now to discuss treatment options after she's recovered from her surgery.

Patient Vignette 1

Dr. O’Shaughnessy:
Hello, Carla. I’m so glad to see you today. How are you feeling?

Carla:
I'm doing well. Thank you.

Dr. O'Shaughnessy:
I'm glad to hear that. So let's talk about the next steps for your treatment. So your breast cancer is hormone receptor-positive, HER2-negative which is the most common subtype of breast cancer, and so what we need to be thinking about in thinking about the next steps of your therapy is that your particular breast cancer has a high rate of recurrence. And so, a very important treatment is endocrine therapy, which you would take for 5 years, but mostly it's 10 years these days for node-positive disease. And endocrine therapy is clearly very effective in improving outcomes, but unfortunately, patients who take this therapy alone still have a risk of recurrence. So for example, for patients with stage 2 disease the rate of recurrence is between 27 to 37%, and for stage 3 disease the recurrence is seen in about 46 to 57% of patients. There are other factors that increase your risk of recurrence, such as your age and the specific tumor characteristics.

So the risk of recurrence for patients who have high-risk disease is up to about 30% over the first 5 years, and so that's fairly high risk, and so there's another important treatment option, treatment intensification, which involves adding a targeted therapy called a CDK4/6 inhibitor to the standard endocrine therapy. And recent studies show that this treatment approach reduces the risk of recurrence quite substantially, and is also generally well-tolerated with side effects that are actually quite manageable. So currently there are two FDA-approved CDK4/6 inhibitors in this specific high-risk early breast cancer setting, and these are very, very important new agents that we would like you to know about, and we would like to recommend one for you. So any questions so far?

Carla:
I am a little worried about reoccurrence, and if I am at high risk, I think a more intensive treatment might be the best option. Can you tell me more about this?

Audience Education Vignette 1
Dr. O'Shaughnessy:
Assessing the risk of recurrence for individual patients with HR-positive, HER2-negative early breast cancer involves assessing various factors, such as the specific tumor characteristics, patient demographics, and genetic profiles, both germline as well as the specific tumor characteristics. Understanding the patterns and tempo of recurrence can aid treatment selection as well, and similarly, understanding the risk-benefit profiles of potential treatment options is also key.

And finally, it's important to have an open discussion with patients about their individual risk for recurrence and the pros and cons of each of the treatment options to help guide them as they decide what's the best treatment options that they feel most comfortable pursuing.

Let's return to our discussion with Carla to educate her about what her risk of disease recurrence is, and to discuss the various treatment options, especially around treatment intensification for her high-risk disease.

Patient Vignette 2
Dr. O'Shaughnessy:
Absolutely. So, as I mentioned, the targeted therapy used in the treatment intensification regimens is a CDK4/6 inhibitor. Now this is a class of drugs that targets these proteins that drive cell division. They're called the cyclin-dependent kinases 4 and 6, CDK 4 and 6, and they're used to treat hormone receptor-positive breast cancer. They are the critical protein enzymes that are important for cell division. And recent studies have shown that the addition of one of these CDK4/6 inhibitors to endocrine therapy substantially reduces the risk of recurrence and the risk of developing metastatic disease by up to 34% at 5 years when compared to just taking the endocrine therapy alone.

And the CDK4/6 inhibitor that I would recommend for you is abemaciclib, and the other one is ribociclib, but I would recommend the abemaciclib to you because of the higher risk of the breast cancer. Your cancer had 4 lymph nodes positive and the abemaciclib has the most robust data. The longest and the largest dataset that we have shows benefit from abemaciclib in women who have 4 or more lymph nodes positive. And so, abemaciclib is given orally. It's twice a day for 2 years' time. Now, I'd be seeing you regularly for checkups and making sure, in the beginning, that you weren't having any side effects that we needed to basically modify the dose, for example, or treat the side effects. It actually gets much, much better over time, but in the beginning of the therapy, we'd be seeing each other every 2 weeks for 2 months, and then we'd be able to stretch it out to every 1 to 2 months, because it becomes much more tolerable, the side effects.

Audience Education Vignette 2
Dr. O'Shaughnessy:

Currently, we have two FDA approved CDK4/6 inhibitors for HR-positive, HER2-negative, early breast cancer patients, and we especially prioritize the CDK4/6 inhibitors for patients who do not carry a germline BRCA mutation. We have abemaciclib, which is taken for 2 years for high-risk women. And most recently, the FDA approved ribociclib, another CDK4/6 inhibitor that is taken for 3 years, again, for intermediate to high-risk patients.

I'll now briefly review the efficacy findings from the pivotal phase 3 monarchE trial. So the high-level overview of the efficacy data, now with 5 years of median follow-up where we have robust data to look at 5-year invasive disease-free survival, shows that in the intent to treat population, there's a 6.4% absolute improvement in IDFS. And if we look at the cohort 1 population where patients had 4 or more lymph nodes positive, or 1 to 3 nodes positive, either with grade 3 disease and/or T3-T4 disease, it's a 6.9% absolute improvement in 5-year invasive disease-free survival.

Let's briefly look at the efficacy results from the phase 3 NATALEE trial, which is investigating ribociclib for 3 years in HR-positive, HER2-negative, early breast cancer patients that are at intermediate to high risk of recurrence. And the overview of the efficacy results from NATALEE really came out at ESMO 2024. And there we saw that the 4-year invasive disease-free survival was improved by 4.9% with the addition of the ribociclib to standard nonsteroidal aromatase inhibitor therapy. And so it is notable that in the NATALEE trial, the dose of ribociclib is 400 mg daily, 21 days on and 7 days off, which is lower than the dose that was studied for metastatic disease.

Patient Vignette 3
Carla:
Thank you for explaining that. What are the side effects of these medications?

Dr. O'Shaughnessy
So given your personal history of having smoked in the past, as well as the fact that you've got a family history of some thrombosis, you're at actually increased risk for having a thrombosis yourself. But that doesn't mean I can't give you safely the abemaciclib; I would like to avoid tamoxifen for you, but I can prescribe an aromatase inhibitor, that's a different sort of anti-estrogen medicine, instead of the tamoxifen, which is highly, highly effective. And then we would just monitor you closely, especially during the first 6 months of treatment, and we'd want to hear from you right away if you developed any swelling or pain in your leg, you'd want to call us right away. Again, it's quite uncommon, but if you did develop a thrombosis, we'd temporarily stop the abemaciclib and resume the therapy once we had you on anticoagulation, so we could still continue it actually.

Carla:
Thank you for explaining this. I'm a little less nervous knowing that VTEs don't happen all the time, and there's a way to manage them if they do. But what are the common side effects that I might have from the therapy? And how am I going to be feeling? Am I going to be feeling sick all the time from all these medications?

Dr. O'Shaughnessy:
Most of the side effects seen with the abemaciclib are really mild and really quite manageable. And patients who take this treatment over the 2 years really do end up maintaining a good quality of life with, over time, minimal negative impact on their quality of life. However, rarely, severe side effects can happen, and we can manage some of them proactively, and then we may need to interrupt the dosing, delay it until the toxicity gets much better. And usually in that case, we'd end up having a dose reduction. If there was significant toxicity that led to treatment interruption, we would reduce the dose.

So, for example, diarrhea starts to occur within a week or 2 to 3 after you've started the therapy. It's the most common side effect that we have. And we do recommend taking an anti-diarrheal medicine such as loperamide to reduce the diarrhea and stop it if you do start to have the diarrhea. And it turns out that a low-fiber, low-fat diet can lessen the chances of having severe diarrhea. But if you do develop diarrhea that's very bothersome, and that usually means more than 4 loose stools a day and particularly with taking the loperamide, we would interrupt the abemaciclib, let it get much better, and then we would talk about a dose reduction. And of course, if you have diarrhea or any other side effect, it's really important that you call my office so we can help you manage it. Because our ultimate goal here is for you to stay on therapy. We may have to modify your dose, but that's perfectly fine; we do not lose the efficacy of the abemaciclib if we reduce the dose, and so we really want to work closely with you over the first couple of months so we make sure we get the dose that's right for you.

We do have data from the clinical trial of the abemaciclib for early breast cancer that shows us that it's really important that patients stay on therapy for the full 2 years because they have better outcomes with regard to reducing the risk of breast cancer recurrence. So that's why we really strive to make sure that the side effects are very, very tolerable, very minimal, and that we have the right dose for you.

Audience Education Vignette 3
Dr. O'Shaughnessy:

Most of the adverse events seen with adjuvant abemaciclib and ribociclib are low grade and manageable.

With regard to abemaciclib, the main toxicity is diarrhea, and it is something that occurs within the first 2 or 3 weeks. We really do need to manage the diarrhea, see patients frequently over the first couple of months, and some patients do require a dose reduction for the diarrhea. The abemaciclib can also cause some low-grade nausea, occasionally some vomiting. It's really quite mild with regard to myelosuppression, but we can see some neutropenia. It has a low risk of a venous thromboembolic event, but that's a low risk.

With regard to ribociclib, the main toxicity is neutropenia, so that's something we're going to be monitoring every couple of weeks for the first 2 months or so. There are patients who will require a dose reduction for neutropenia, although febrile neutropenia is very, very unlikely. And then the other toxicity is liver function abnormality. We do need to monitor the liver function tests for the first couple of months, and some patients will require a dose reduction as well for recurrent grade 2 or grade 3 liver dysfunction, but it's only about 8.9% of patients who have grade 3 or 4 liver function abnormality. We do also need to monitor the EKG, the QTC for patients at baseline and after about 2 weeks on therapy. We've just got to make sure the patients don't have prolongation of their QTC, either before they start or after 2 weeks on therapy.

Patient Vignette 4
Dr. O'Shaughnessy:
So what do you think so far? Are you comfortable with the information that we've discussed so far?

Carla:
It's a lot of information but I appreciate you explaining what to expect from treatment.

Dr. O'Shaughnessy:
You're very welcome. And so if it's okay, if you feel comfortable moving ahead, let's plan starting the treatment within the next couple of weeks. We do want to do some baseline laboratory tests before starting therapy, your blood counts, your liver function tests, and then we'll go ahead and get started on therapy. And then we'll see you regularly, usually every 2 weeks for the first 2 months, and we can spread it out. And then we want you to call the office if you have any concerns or questions or, like I said, the diarrhea is more than 4 times a day in spite of the loperamide, definitely want you to call the office, because we will probably hold the medication until the toxicity resolves, and we may want to reduce the dose. And so, because the key is for you to be able to stay on the medication to be able to really get the benefit.

Carla:
Thank you so much, Dr. O'Shaughnessy. I am comfortable with the potential side effects and having to be on the treatment for 2 years. I just want to do whatever it takes to reduce the risk of recurrence, and I really feel like this is the best option for me:

Dr. O'Shaughnessy:
Glad to hear it. I really do think it is the best strategy. It's very effective, and our team is going to work really, really closely with you and any of your family members too on this next phase of treatment, but I'm very confident we'll be able to find a dose that works for you, and you'll be able to get the efficacy from this treatment.

Carla:
Thank you so much.

Dr. O'Shaughnessy:
You're welcome. Sure.

Audience Education Vignette 4
Dr. O'Shaughnessy:
Taking the time to thoroughly discuss treatment options and what to expect from therapy with our patients is really, of course, a crucial part of that shared decision-making process. It's also important to involve the patient's family member or caregivers, so that they're also aware of what to expect from therapy, especially the potential side effects. And then finally, it's really helpful to emphasize to the patient that we need to work together to help them adhere to the therapy so that they can derive the most benefit from the treatment.

The case presented in these vignettes can be adapted to address the many scenarios we face daily in our practices when discussing adjuvant treatment options for high-risk, HR-positive, HER2-negative early breast cancer patients. So when we're prescribing treatment intensification for these patients, the goal is to, of course, maximize efficacy, and so it's very important that we apply shared decision-making strategies with consideration of the patient preferences, the potential advantages of treatment, the side effects, and the importance of treatment adherence to getting the ultimate efficacy that the patient really desires.

So thank you for joining me for these patient-clinician connection vignettes on shared decision-making in the management of patients

with HR-positive, HER2-negative, early breast cancer. Goodbye now.

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