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TITLE: Oral SERDs in ER+ Breast Cancer

Podcast Episode Title: Rare Cases & Treatment Challenges

Brought to you by;
Prof Shaheenah Dawood, Mediclinic City Hospital Dubai, UAE
Assoc. Clinical Professor Rena Callahan, University of Los Angeles, California (UCLA), US
Introduced by;
Tonke de Jong on behalf of COR2ED

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Tonke
Welcome and thank you for listening to this podcast from COR2ED Independent Medical Education. In this episode, the last of a three podcast series, you will hear from internationally renowned experts Dr. Shaheenah Dawood and Dr. Rena Callahan as they discuss oral SERDs, a novel therapy for ER+/HER2- advanced or metastatic breast cancer. In this final episode, the experts discuss the next two patient case studies, each presenting unique and rare situations that shed light on the challenges confronting healthcare professionals and patients alike.

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Now, with that being said, let's get started.

Dr. Shaheenah Dawood
Hello everyone. Welcome back to our podcast, and for those who are joining us for the first time, I am Dr. Shaheenah Dawood, a consultant Medical Oncologist and Professor of Oncology at Mediclinic City Hospital in Dubai, United Arab Emirates.

I am truly excited to be here for the third and final episode of our podcast series, focusing on oral SERDs in ER+ advanced or metastatic breast cancer. Throughout this series I've had the pleasure of being joined by Dr. Rena Callahan, an associate clinical professor of Haematology Oncology at the David Geffen School of Medicine, University of California, Los Angeles.

Dr. Rena Callahan
Thank you, Dr. Dawood. I'm looking forward to starting our discussion today. But before that, let's take a moment to recap our journey so far. In the first episode, we thoroughly explored the efficacy and safety profile of oral SERDs and their role in the treatment landscape. For our second episode, we delved into two patient case studies examining the complexities of treatment selection and sequencing decisions. And now here we are in this concluding podcast where we will analyse the next two patient case studies, each presenting unique and rare situations that shed light on the challenges confronting health care professionals and patients alike. I will now pass it on to Dr. Dawood to present our first case.

Dr. Shaheenah Dawood
Thank you, Dr. Callahan. Our first patient is a 36 year old premenopausal woman who was diagnosed with stage III ER+/HER2- breast cancer at the age of 28.

During the diagnostic process, a mammogram and subsequent biopsies identified a 5 cm ER+/HER2- breast lesion, along with two positive axillary lymph nodes. Considering the high risk of recurrence, the patient was prescribed adjuvant treatment consisting of abemaciclib, anastrozole, and goserelin to be administered for a period of five years. Two years after starting adjuvant endocrine therapy and abemaciclib, the patient presented with a new set of symptoms.

She reported experiencing blurred vision, persistent headaches and tenderness in the upper right abdomen. In response, a CT scan was conducted, revealing a brain lesion measuring 0.4 cm and two liver lesions measuring 1.1 cm and 1.4 cm respectively. A biopsy was performed confirming the diagnosis of metastatic ER+/HER2- breast cancer. Interestingly, when the liquid biopsy and ctDNA testing were performed, no mutations were detected.

This is a very interesting case and surely one that is not often discussed. My first question to you, Dr. Callahan, is how common are brain metastases with this biology of disease and what considerations need to be made in order to select optimal treatment in this case?

Dr. Rena Callahan
So, Dr. Dawood, this is a very interesting case, and I wouldn't say that it is the most common because this patient has ER+ disease relatively early into her adjuvant treatment and has developed brain metastases.

Brain metastases are not as common with ER+ disease that is HER2-, but we certainly see it. Usually, we will see brain metastases later on in the course of their disease, not so much when they recur on adjuvant therapy but later on, you know, third line, fourth line. But I've certainly seen this before and overall 15% of patients with ER+ disease will develop brain metastases in the metastatic setting.

So in determining treatment for this patient, we need to consider the sites of disease. So she has both disease in the CNS as well as in the liver. If she had CNS only disease, we could consider treating the CNS disease with local therapies such as surgery, radiation, stereotactic radiation and perhaps not even switching her therapy. But she has liver metastases and these liver metastases, we believe, developed while she was on treatment, presumably, she's stage III so she was staged at her initial diagnosis and did not have metastatic disease at the time of diagnosis. So this developed at some point over the last few years.

So we need to switch therapy. Then we need to consider what she has already been on. She recurred while she was on adjuvant endocrine therapy and right at that two year time point. So we're wondering if she has endocrine sensitive disease. Two years of endocrine therapy in the adjuvant setting is kind of our line of demarcation for whether we consider a disease endocrine sensitive. And she basically recurred while on abemaciclib. So that calls into question her resistance to CDK inhibitor.

So for her I would consider those factors and not re-treat her with a CDK inhibitor if she recurred while she was on a CDK inhibitor, especially if it was abemaciclib, and would also consider her mutational status. So she's had the liquid biopsy and we haven't found any mutation. We have not found any *ESR1* mutation, have not found a *PIK3CA* mutation or another and that's not so unusual. The development of an *ESR1* mutation is acquired over time, and she's still in the adjuvant setting. So that's pretty uncommon.

So for her, I'd consider other therapies that may treat disease both in the body and the brain and try to stick with the targeted therapy. Perhaps you could give her everolimus with endocrine therapy or an oral chemotherapy such as capecitabine. TDxd could also be considered if she's HER2 low. But typically that's a little later on in her disease.

So now I'm wondering, Dr. Dawood, do you think that liquid biopsy was appropriate in this case, given the lack of biomarker identification? Would you recommend repeating this analysis or exploring other diagnostic methods?

Dr. Shaheenah Dawood
Thank you for the question. Dr. Callahan. This brings up several interesting points. So first, when performing a liquid biopsy, it is important to note that you are not always going to get the biomarkers that you are looking for.

So the results may be true and there in fact may not be an *ESR1* mutation here. Post progression on an aromatase inhibitor, the probability of acquiring an *ESR1* mutation is approximately 40% and not 100%. Similarly, not everyone is going to have a *PIK3CA* mutation.

Second, when performing a liquid biopsy, it is also important to note that tumour burden does impact the results of this diagnostic modality. The higher the tumour burden, the more likely you are going to capture enough ctDNA to profile and determine biomarkers of interest.

In this particular case, the tumour burden is low and as such, I am not 100% sure if we truly do not have any biomarkers of interest here. A biopsy was done on the liver lesion and I would send that sample for analysis to make sure we are not missing any biomarkers that would help guide therapy.

The cases of a patient who relapsed shortly post completion of adjuvant abemaciclib while still on adjuvant endocrine therapy. She has essentially, I think, endocrine resistant disease, despite the findings at two years. I think that that's a controversy that we're always going to debate about. Is this really endocrine sensitive or endocrine resistant? But determining biomarkers of interest here, such as *ESR1* mutation, *PIK3CA* mutation, those other agnostic markers that patients may have, like HER2 mutation, MSI, TMB, I think these are going to be very important to determine in this particular patient since she has relapsed so quickly after her two years of abemaciclib while still on endocrine therapy.

Dr. Rena Callahan
Thank you for your answer, Dr. Dawood, and I definitely share your thoughts there. So what if resection of the brain metastases was done? Would you send that for profiling? And I'm curious to know if an *ESR1* mutation was present, you found it somehow, would it affect your management?

Dr. Shaheenah Dawood
Very interesting question and a very interesting scenario overall. Strictly speaking, if I had sent the liver lesion for profiling, I would not necessarily send the brain lesion for profiling unless it was within the context of a clinical trial or for academic reasons, where I would like to determine differential signatures between the two metastatic sites. I do not think that the information would add to the clinical data I would need to treat this patient.

However, if there was not enough tissue from the initial liver biopsy that was done to send for profiling, I would send the resected brain lesion for profiling. Now in the presence of an *ESR1* mutation with low burden of disease. She's not in visceral crisis and she has been on adjuvant CDK4/6 inhibitor for two years. I would certainly consider using an oral SERD like elacestrant in this particular case.

So now I'm wondering, Dr. Callahan, how would you have approached this patient if she had recurrence of disease at the same sites with the same tumour burden, but it now occurs three years post completion of five years of endocrine therapy and two years of abemaciclib? And I think this scenario is really important because this will come up in the future as we start to increasingly incorporate the use of adjuvant CDK4/6 inhibitors. So really a futuristic question that us community oncologists are going to face.

Dr. Rena Callahan
Yes this is really an interesting question and we don't have a lot of data in this setting because adjuvant CDK inhibitors were pretty recently approved, in the past few years. And so this gets back to considering the length of time since she had received both the endocrine therapy, the aromatase inhibitor, as well as the CDK inhibitor abemaciclib. So this is three years after she could still have endocrine sensitive disease, she could still be sensitive to CDK inhibitors. So I would consider re-treating her with aromatase inhibitor and first line CDK inhibitor as we would do when patients have recurred after this length of time who had never received adjuvant CDK inhibitor.

It'll be interesting to see how much time she actually is able to be on that therapy and progression free. But you can use the same agents because three years has elapsed. And then we have the tissue biopsy in this setting. We should get a liquid biopsy, send that for molecular profiling, look for the mutations that we have already discussed and then consider those when we are choosing mostly her second line therapy and then go over patient specific factors as well. What is she looking for? What kinds of toxicities does she find acceptable at this point? And in this way, we can come up with a treatment plan that makes sense to both us biologically and her, because she has to live with these toxicities and tolerability issues.

So thanks for this discussion. Let's move on to our next patient. Our next case is a 34 year old premenopausal woman who was initially diagnosed with stage II ER+/HER2- negative breast cancer at the age of 31. Following her diagnosis, she underwent adjuvant treatment with tamoxifen for a period of five years. However, 28 months into the planned treatment of five years, a slight elevation in alkaline phosphatase prompted further investigation. A PET-CT scan revealed the presence of sclerotic bone lesions in the femur. Subsequent biopsy confirmed the diagnosis of ER+/HER2- metastatic breast cancer.

To address the metastatic disease the patient's treatment plan was modified and she was prescribed first line therapy consisting of palbociclib, exemestane, and goserelin. Unfortunately, after only five months of treatment, she displayed signs of treatment resistance and a follow up PET-CT scan indicated development of diffuse osseous metastatic disease.

As we go through these cases, it really does show how each patient is unique, requiring tailored treatment strategies and sequencing decisions. On that note, Dr. Dawood, allow me to ask you the first question. Do you think there is a role for liquid biopsy in the setting of bone only disease?

Dr. Shaheenah Dawood
Thank you for the question, Dr. Callahan. You very importantly pointed out that each patient's case is unique and a personalised treatment strategy has to be developed for each and every one of them.

In this particular case, there is diffuse osseous metastatic disease and as such, the tumour burden is high. And I would be very comfortable requesting a liquid biopsy here. I have several patients where I have been able to determine biomarkers of interest with bone only

disease. However, like I said, burden of disease does matter as it increases the probability of capturing ctDNA for profiling.

Now, if the patient had an *ESR1* mutation, how would you proceed Dr. Callahan? Would you perhaps consider elacestrant in this case?

Dr. Rena Callahan
Dr. Dawood I would definitely consider elacestrant in this case, because she has an *ESR1* mutation. She has diffuse osseous metastatic disease, but she is not in visceral crisis. So it would be appropriate to treat with elacestrant.

Some things, however, that we have to consider in terms of our expectations of duration of therapy on elacestrant would be the fact that she developed disease progression after only five months of the CDK inhibitor, palbociclib. And the analysis has been done with elacestrant in the EMERALD trial that duration on CDK inhibitor therapy predicts for a greater benefit on progression free survival on elacestrant. Patients that were on CDK inhibitor for a year had between eight and nine months of progression free survival on elacestrant. This patient was closer to six months. So while it is certainly an appropriate treatment option, she may not have that length of progression free survival.

Dr. Shaheenah Dawood
I completely agree with you. I think that when we're treating our patients, we really need to set those expectations both for ourselves and for the patient. And you're completely right. Five months on palbociclib, she progressed quite rapidly and had diffuse osseous metastatic disease. And this is why it's important to profile our patients so that we can get the most appropriate therapy to our patients.

So thank you for that insight. But let me ask you another interesting question that may come up. So we profile all our patients in terms of doing either liquid biopsies or tissue profiling. What if when you're doing these next generation sequencing diagnostic studies, you pick up more than one biomarker of interest? So, for example, in this particular patient, what if she had a *PIK3CA* mutation and an *ESR1* mutation and she is post progression on a CDK4/6 inhibitor? What would be your ideal treatment strategy in terms of sequencing? And if you decided to give elacestrant in that post progression on the CDK4/6 inhibitor, would you be comfortable giving targeted therapy, like alpelisib, post progression on an assessment?

Dr. Rena Callahan
Great question. You know, these mutations, I'll just focus on *PIK3CA* and *ESR1*, because that is relevant, very relevant in our treatment decision making, especially in the second/ third line setting. So that co-mutation, it's not uncommon and occurs in 10 to 15% of these tumours. And elacestrant has shown activity in these double mutants. So then I would consider what are the toxicities of therapy, what is the tolerability. And certainly elacestrant is a very tolerable therapy when you're comparing it with *PIK3CA* targeted agents such as alpelisib, it is much, much more tolerable and doesn't require that same level of monitoring.

So I would choose elacestrant here as my first choice over *PIK3CA* targeted agent in this second line setting. And then after disease progression while on elacestrant, an oral SERD, then I would consider using alpelisib. Part of it, it depends again what is the patient looking for in terms of tolerability? What is her disease doing? Is she in visceral crisis at that point? All of those same disease specific and patient specific factors come into play again.

Dr. Shaheenah Dawood
Thank you, Dr. Callahan. Again, very interesting insights that maybe I can make it even more interesting. We know that capivasertib is going to be on the horizon very soon. So how would you put that into the whole sequencing strategy? Patient has an *ESR1* mutation and a *PIK3CA* mutation.

Dr. Rena Callahan
Right, that's is, the questions are getting harder and harder and it's, you know, it's an embarrassment of riches, right? Where we're very fortunate to be able to have so many therapies and so many on the horizon for our patients. You know capivasertib, the data that we've seen so far I think is impressive, but it does have toxicities, ocular toxicities, other things that we have to monitor. And so still in this setting, elacestrant is very tolerable, and it's also very effective in the post CDK inhibitor setting. In the EMERALD trial 100% of patients had prior CDK inhibitor therapy, about 70% had visceral metastases, and elacestrant performed very, very well. It was very tolerable. So I think I would still give elacestrant in the second line, saving capi for later line therapy.

Dr. Shaheenah Dawood
Thank you, Dr. Callahan.

Dr. Rena Callahan
So thank you, Dr. Dawood, for sharing your knowledge and expertise throughout this episode. It's been an absolute pleasure discussing these cases with you. As we wrap up this podcast, we not only conclude today's episode, but also reach the end of our entire series.

Dr. Shaheenah Dawood
Thank you so much, Dr. Callahan, for sharing your valuable insights on this topic. Your input has truly made this conversation engaging and without a doubt will provide our listeners with invaluable insights.

Today we really delved into the complexities of treatment selection and sequencing in each of the unique and rare situations in the two patient cases presented. For today's clinical takeaways, we suggest that when deciding whether to adjust the current treatment dosage or switch therapies, it is essential to consider various factors, including disease progression, tumour burden, treatment related toxicities, patient preferences, and of course, quality of life.

Additionally, it is recommended to maximise endocrine therapy options with and without targeted therapy in ER+/HER2- advanced or metastatic breast cancer. It should also be noted that current phase three data do not confirm the benefits of CDK4/6 inhibitors beyond

progression of disease after prior CDK treatment, and that further investigation is necessary to determine the optimal approach.

And finally, duration of progression free survival on CDK4/6 inhibitor therapy can help guide sequencing decisions. For oral SERDs, specifically elacestrant, patients who received prior CDK4/6 inhibitor treatment for longer duration derived the greatest benefit.

We hope our audience finds this information helpful in their clinical practice and thank you all for joining us throughout this series. I have loved every single minute of it.

Dr. Rena Callahan
Absolutely. Thank you, everyone.

Tonke
We hope you found this podcast informative and enjoyable. If you like this episode, you should look on the COR2ED medical education channel for more. In particular, you can find the first podcast of the series where Dr. Callahan and Dr. Dawood discussed oral SERDs efficacy, safety and place in the treatment landscape. Also, check out the second episode where the experts discuss two other patient case studies with ER+/HER2- advanced or metastatic breast cancer and delved into the intricacies of treatment selection and sequencing to maximise outcome.

Don't forget to rate this episode on the COR2ED website and share our podcasts on social media, or maybe with your colleagues. Thanks for listening and see you next time.

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