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Case: A Patient With High-Risk HR+/HER2- EBC Potentially Eligible for CDK4/6 and/or PARP Inhibitor

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Harbeck:
Hello. This is CME on ReachMD, and I'm Dr. Nadia Harbeck. With me today is Dr. Hope Rugo. We'll begin our case discussion with the case vignette.

Hope, would you like to present your case?

Dr. Rugo:
Yes. Thanks, Nadia. This is a really interesting case of a 42-year-old woman who has completed childbearing and presented with a stage II, node-positive, grade 2, invasive ductal cancer, ER 90%, PR 80%, HER2 1+ without gene amplification, and a Ki-67 of 30%. She came to us in consultation, and as part of our evaluation for our neoadjuvant I-SPY2 program, we did a 70-gene test, so-called MammaPrint. And this came back as high risk with a score of -0.402 which is consistent with high 1, so it's the lower side of high risk. But she has a pathologic mutation in BRCA2 on germline testing with a family history, interestingly, that was primarily 2 generations before, with a grandparent and really poorly characterized. So I think it really shows the importance of testing in patients where family history may be limited, and there could be just a single family member that brings this up with premenopausal breast cancer.

So she elected to pursue neoadjuvant chemotherapy. And at the time, received weekly paclitaxel for 12 weeks, followed by dose-dense doxorubicin and cyclophosphamide for four cycles, and she had an excellent clinical response. And as often happens in these hormone receptor-positive tumors, you can't even feel the tumor very well, and it looked, by our measurements on study, that her functional tumor volume had significantly decreased, but we could see the nodes were smaller, but they still looked somewhat abnormal. And then she underwent bilateral mastectomy by her choice, with implant reconstruction, and had node sampling with the sentinel node and a few additional nodes, which is our standard practice in patients with positive nodes at the time of surgery. And she had an excellent response in breast, so only 2 mm of low-cellularity residual disease in her breast. But unfortunately, 2 out of 5 positive nodes that were involved with carcinoma, and the largest focus was 5 mm. So true macro metastasis with extra nodal extension, although very minimal, 1 mm.

So she plans a later ovarian surgery to remove her ovaries, but will do that after she recovers from her treatment and her reconstruction. So she starts on goserelin monthly injections with daily letrozole. And she saw radiation oncology, and they thought, because of her age and the node involvement, that she should receive post-mastectomy radiation.

So then I always talk to the patients about the fact that we're going to need more treatment after they finish radiation therapy. And so she comes back, and really the discussion has to do with what additional therapy we're going to add on. And based on the OlympiA trial, and I think the importance of targeting really what we believe to be the biologic driver of malignant conversion, we would recommend

olaparib for 1 year. But in this patient, we would also consider, after the year of olaparib, giving 2 years of abemaciclib. So it is a long duration of therapy, but that's generally what we'd recommend in a patient in this situation, because of her risk of recurrence, both early and late.

How would you manage a patient like this, Nadia? And how would you decide on the sequencing of treatment?

Dr. Harbeck:
We would have probably done the same. In the luminal cases with an uncertain chemotherapy indication, we tend to go for primary surgery and then look at the nodal number and then decide on chemotherapy. And also that we do this endocrine induction therapy quite frequently. But she had node-positive disease, had a high Ki-67 of 30%, I think, and a high-risk MammaPrint, so I think that was pretty clear-cut indication here for chemotherapy, so you might as well do it in the neoadjuvant setting.

And then, obviously, endocrine therapy should be with the GnRH plus an AI. And then afterwards, she has an indication for olaparib with the non-pCR. In some countries, you have to measure the CPS + EG score. I certainly think if there's a high risk of recurrence, I would give olaparib for 1 year. And for Germany, we are in a fortunate situation that we could also add the abemaciclib. And in the monarchE study, in node-positive disease, we needed just to verify one lymph node, and then we could put the patient into the trial, and we didn't have to count the number of lymph nodes in the case of neoadjuvant chemo. I think that's very important. And she has a high Ki-67, so she would have been eligible for the monarchE study.

So I think it's a good treatment plan. I realize in some countries, people don't have the choice of sequencing both the PARP inhibitor and abemaciclib.

How would you go about this, Hope? What's your recommendation for those colleagues?

Dr. Rugo:
Yeah, I think it is difficult, because sometimes you can only choose one and you have to consider the cost for the patient in many countries. In the US, generally, we've been able to get this funded without too much difficulty in the high-risk population.

But I think that if I could only give one drug to a patient like this, in addition to their endocrine therapy, I would probably give the olaparib with the idea of treating the biologic, again, driver of malignancy. And also, the patient hasn't received a platinum, and so we know that disease is not going to be up-front resistant to DNA-damaging agent. And that's important, because there is some interaction between resistance to platinum and resistance to PARP inhibitors, or less responsiveness. So in this situation, I would use olaparib for 1 year if I didn't have access to a CDK4/6 inhibitor as subsequent therapy.

And I think when we're talking to patients about this, it really is very much a shared decision process and an up-front management of side effects with early dose reductions in patients. Because when we're not on trials, we can dose reduce and go back up again, we can manage patients' quality of life as we're going through this treatment with our multidisciplinary team, and that makes the biggest role, I think, in achieving an effective treatment plan.

Dr. Harbeck:
Yeah, I absolutely agree. And I think for colleagues who have to choose one over the other, I think it may also be important that the data we thought was true from the metastatic setting, that patients with a BRCA mutation don't respond so well to CDK4/6 inhibitors, may have been biased also because this is retrospective data by the collectives that were treated and the therapy response. But if you look at the monarchE data we just saw at ESMO breast, that actually abemaciclib works independent of the BRCA mutation status. And I think that's very reassuring, that we can give abemaciclib to these patients and they will derive benefit. But I would agree. If I had to choose one over the other, I would choose olaparib based on the non-cross-resistant drug, a completely new mechanism, and as you said, it's the driver of the disease overall in this particular patient.

So I thought it was a very informative case, but we have to point out that these coincidences of BRCA mutation and indication for adjuvant CDK4/6 inhibitor are very few patients, and it's around 5%, I think, in our collective, so keep that in mind.

And I would like to thank you, Hope, again for this interesting discussion, and thank our audience for tuning in.

Dr. Rugo:
Thank you.

Announcer:
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