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

Understanding Endocrine Resistance in HR+/HER2- mBC

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Dr. Kalinski:
Hi, this is CE from ReachMD. I'm Kevin Kalinsky. I'm the division director of medical oncology at Winship Cancer Institute.

We're going to be talking about endocrine sensitivity and endocrine resistance, which is a really critical issue for our patients who have metastatic hormone receptor-positive, HER2-negative breast cancer.

So as we know, when we're treating patients with breast cancer, the majority of our patients have early-stage disease. Globally, there's some differences in terms of the rates of de novo disease, though commonly, the vast majority of patients have early-stage disease that then becomes metastatic. Though, again, as I said, there can be differences based upon availability, including screening in things like this.

So there have been some guidelines that have been developed that help us think about endocrine-sensitive or endocrine-resistant disease. So if we have a patient who has early-stage breast cancer that then starts on their adjuvant endocrine therapy—because for our patients with hormone receptor-positive disease, the prediction is for the benefit of agents like tamoxifen or aromatase inhibitors. And if patients take their endocrine therapy and then have a recurrence within 2 years of starting their adjuvant endocrine therapy, there have been guidelines, including guidelines from our European colleagues through ESMO, that have defined this as being primary endocrine resistance. And that can be associated with more aggressive breast cancers, because that has demonstrated the biology of the cancer in that we would be concerned about them responding in the same sort of way to the endocrine therapy in the metastatic setting.

Also, if patients have metastatic disease that has then progressed within 6 months of that first line of endocrine-based treatment—let's say you start a patient on an aromatase inhibitor, a CDK4/6 inhibitor, and there are tumor progresses within 6 months of starting that metastatic regimen, that could be a sign of primary endocrine resistance.

So this can be a concerning feature. We see in the curves, even for patients when we saw the initial data with CDK4/6 inhibitor, that there's a small proportion of patients that have real endocrine resistance. You see a quick drop in that Kaplan- Meier curve. And though it's a small population of patients, it could still be a concerning feature.

So this remains a real unmet need because what we're seeing is that the endocrine therapy that we have is not keeping things under

control, and so it does ask the question of, well, what's the role for novel endocrine therapies or novel targeted therapies? And I will also say, one of the points just to highlight is that that's the definition of endocrine sensitivity and primary endocrine resistance and primary sensitivity or not.

But ultimately, this is not accounting for the fact that in our patients with early-stage breast cancer, especially those who have intermediate-risk or high-risk disease, that we're giving adjuvant CDK4/6 inhibitors. There's approval abemaciclib for patients with node-positive disease. And for patients with intermediate- or high-risk disease, there's an approval for ribociclib for 3 years.

And so in reality, if you're having a patient who recurs within 2 years of their endocrine therapy, those patients might also have some resistance to a CDK4/6 inhibitor as well. Which also asked the question, well, what's the role of CDK4/6 inhibitors in the metastatic setting if you have a patient who's recurred, for instance, on adjuvant abemaciclib?

So when we're talking through this series about endocrine sensitivity or endocrine resistance, it's important to keep those guidelines in mind because it's really demonstrating that the biology of those tumors are different than somebody who has a metastatic recurrence, once they've completed their adjuvant endocrine therapy a year ago, or 2 years ago.There's a real difference when somebody has a tumor that recurs on adjuvant endocrine therapy or after completion of that.

And then also in the metastatic setting, if you have a patient who recurred or progresses within 6 months of their metastatic regimen, it really suggests that the tumor is not so endocrine sensitive, and those may be patients that we think about giving chemotherapy or antibody-drug conjugates, where endocrine-based treatments may not give the same sort of benefit.

Thank you for your attention, and we will discuss other topics as well.

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