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Differentiating Safety Profiles of CDK4/6 Inhibitor Combination Regimens

Announcer:
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Dr. Rugo:
This is CME on ReachMD, and I'm Dr. Hope Rugo. In this brief lecture, I'm going to compare side effect profiles of CDK4/6 inhibitors that are used to treat patients with early-stage, hormone receptor-positive, HER2-negative breast cancer. And specifically, I'm going to discuss abemaciclib and ribociclib in combination with endocrine therapy.

As you know, abemaciclib is approved in combination with endocrine therapy as treatment for high-risk, early-stage, hormone receptor-positive breast cancer. And ribociclib has reported important data with improvements in invasive disease-free survival and distant disease-free survival in patients with high-risk, early-stage, hormone receptor-positive breast cancer also in combination with endocrine therapy.

So how do we evaluate the side effect profiles of these 2 combination regimens? First, there are important differences in terms of the treatments that were given to patients in these 2 trials, the monarchE and NATALEE trials. First, treatment with abemaciclib was given for 2 years, ribociclib was given for 3 years, and at a dose reduction compared to the dose approved for metastatic disease, 400 versus 600 mg. Second, in the monarchE trial, the physicians could use an aromatase inhibitor or tamoxifen as the partner endocrine agent. In the NATALEE trial, because of drug-drug interactions with tamoxifen and ribociclib that could risk prolonged QT interval, patients were restricted to receive nonsteroidal aromatase inhibitors, so anastrozole or letrozole.

The toxicity really mirrors what we've seen in the metastatic setting. Abemaciclib is associated primarily with diarrhea, although the rate of grade 3 diarrhea is low. This was the most common reason for discontinuation of therapy. In contrast, ribociclib is associated primarily with neutropenia, although the grade 3 neutropenia risk was substantially lower with 400 mg compared to the 600 mg used in the metastatic disease setting.

Interestingly, both trials reported that the discontinuation rate was highest in the first few months after starting treatment. Presumably, this is, of course, in part due to poor tolerance with additional side effects after patients have already gone through surgery and, for many of these patients, chemotherapy and radiation therapy for their early-stage disease.

So what are the other side effects that we think about for both drugs? Fatigue may be an issue, as well as some hair loss with grade 1 alopecia. The fatigue can be managed by dose reduction and dose holds, as well as looking at other causes for this fatigue, such as polypharmacy and depression. The alopecia can be managed with low-dose minoxidil, which works very well for patients who have significant hair loss that impacts their quality of life from these agents.

Other side effects that are more unique to the specific agents, ribociclib has neutropenia, but it also can cause elevated liver enzymes. This was a significant reason for discontinuation of drug in the NATALEE trial. In general, QT interval hasn't really been a problem for

most patients treated with ribociclib.

And then lastly, abemaciclib and ribociclib may be associated with increases in unusual events such as venous thromboembolic disease and interstitial pneumonitis. The rates are extremely low, but venous thromboembolic event rates are a little higher with abemaciclib than with the other CDK4/6 inhibitors and are higher with tamoxifen, although the rates are still well below 5%. So we don't generally combine abemaciclib with tamoxifen if we can avoid it, and I generally use something like an aspirin for some degree of anticoagulation, if that combination is required. And I also advise patients about the risk.

One of the big areas of management, of course, diarrhea and neutropenia, are important. For diarrhea dose reduction and anti-diarrheal agents play a big role, as well as diet control. And we do use preventive loperamide extensively in patients, and this dramatically reduces the diarrhea and the impact on quality of life and improves adherence. For neutropenia, dose delays work very well. Just delaying a few days allows count recovery. Checking the white blood cell count later in the day improves the neutrophil count, interestingly. And then dose reductions, as needed, are also effective.

I hope that you found this brief overview of the most common toxicities associated with abemaciclib and ribociclib in combination with endocrine therapy, along with some clinical pearls about management, helpful for your everyday practice.

Announcer:
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