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HER2-Directed TKI Combinations in mCRC: Improving Adherence Through Proactive ADR Monitoring and Management

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

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Dr. Strickler:
Hi, I'm John Strickler, Associate Professor of Medicine at Duke University Medical Center in Durham, North Carolina. I'm going to talk to you today about HER2-directed tyrosine kinase inhibitor combinations in metastatic colorectal cancer, improving adherence through proactive ABR monitoring and management.

There are a number of anti-HER2 therapies available to us in the clinic. Focusing specifically on the tyrosine kinase inhibitor class, there are two different combinations that we have available to us. One is lapatinib and trastuzumab, the others tucatinib and trastuzumab. We initially tested lapatinib a number of years ago in patients with metastatic colorectal cancer. And based on data out of the Heracles trial, we found that the most common adverse events associated with lapatinib and trastuzumab were diarrhea, rash, fatigue, paronychia, and conjunctivitis. There were no treatment-related, severe life-threatening or fatalities related to the lapatinib/trastuzumab combination fortunately, but 6 patients, or 22% of patients treated on the Heracles regimen of lapatinib/trastuzumab had grade 3 adverse events, 4 patients had fatigue, 1 patient had a skin rash, and 1 patient had increased bilirubin. Fortunately, there were no treatment-related cardiotoxicity events and no patients interrupted treatment. I will point out that the dose of lapatinib was reduced in 3 patients, or 11% of patients.

Tucatinib is a second tyrosine kinase inhibitor that's available to us in the clinic. Unlike lapatinib, tucatinib is a highly selective inhibitor of HER2. So tucatinib is potent against HER2, but has minimal inhibitory effects against HER1, otherwise known as EGFR. And because of that, it has lower rates of diarrhea and rash.

In the MOUNTAINEER study of tucatinib and trastuzumab for patients with HER2 positive metastatic colorectal cancer, fortunately, there were no treatment-related deaths, 95% of patients had an adverse event independent of causality. But grade 3 or greater adverse events were rare. There were 8 patients, or 9% of patients, had a tucatinib-related adverse event that was grade 3 or greater, and 7% of patients had a trastuzumab-related grade 3 or greater adverse event. Severe adverse events that were to tucatinib related or trastuzumab related were also quite rare. And in fact, only 5 patients, or 5.8% of patients, had an adverse event that led to study treatment discontinuation, a quarter of patients experienced an adverse event that led to tucatinib dose modification.

The most common treatment emergent adverse events for tucatinib and trastuzumab, as shown here, is diarrhea. In most cases, those adverse events are grade 1 or grade 2. Fatigue and nausea have also been shown in the MOUNTAINEER study. The most common grade 3 or greater tucatinib-related adverse events were ALT increase which occurred in 2% of patients and diarrhea which occurred in 2% of patients. Because diarrhea is the most common adverse event associated with tucatinib, it's important to review some of the features of that adverse event. In the MOUNTAINEER study, 50% of patients had grade 1 or mild diarrhea, 10% of patients had grade 2

or moderate, and as mentioned, grade 3, which is more severe was quite rare at 3% of patients, but there were no treatment discontinuations due to diarrhea, and tucatinib modifications for diarrhea were quite rare. There was 2% of patients with the dose reduction, 3.5% of patients with a dose hold.

One adverse event to be mindful of with tucatinib is hepatotoxicity. This is rare, but when it occurs, it can be severe, 3.5% of patients had a grade 3 or greater increased ALT, 2% had an increased AST that was grade 3 or greater. And 5.8% of patients had hepatotoxicity that led to either a tucatinib dose modification or discontinuation. Now cardiotoxicity is associated with trastuzumab, not so much associated with the tyrosine kinase inhibitor. And in the MOUNTAINEER study, 3.5% of patients had an asymptomatic left ventricular ejection fraction decrease that led to dose modification or discontinuation.

As with any oral medication, it's critical to have high levels of adherence. And there are a number of best practices to improve adherence to tyrosine kinase inhibitors. First is patient education. Second is involvement of the entire care team in that patient education from the patient to the doctor to the pharmacists, nurses, family, and caregivers. We also find that it's helpful to have increased clinic visits and nurse outreach during the first 1 to 2 months of treatment, particularly as the patient is becoming accustomed to this new treatment, and any adverse events that they may be experiencing. As mentioned, diarrhea is the most common adverse event associated with tyrosine kinase inhibitors, and proactive use of anti-diarrheals can improve adherence and improve the patient experience on this treatment.

Additionally, it's important to be proactive, as at times, dose modifications may be necessary for intolerable rash, fatigue, or other adverse events.

Thank you very much for joining me today.

Announcer:
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