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PI3K Pathway Inhibitors: Safety and Tolerability Profiles

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Dr. Jhaveri:
Hello, everyone. This is CE on ReachMD, and I'm Dr. Komal Jhaveri, a breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York. In this short lecture today, I'll review with you the safety profile of PI3K pathway inhibitors.

So when we think about targeting the PI3K pathway and the toxicities that we see, those toxicities we think could be predominantly related to the wild-type inhibition of this pathway. So while we are focused on certainly targeting these PI3K mutations or alterations in this pathway that we think are causing activation of this pathway, there is also some wild-type inhibition that occurs with these alpha isoform inhibitors that we currently have in clinic.

And these wild-type-related toxicities include hyperglycemia, diarrhea, rash, nausea, stomatitis. And while we're seeing all of this, I think we see that across the class, but there are some differences or some variations that we see in terms of the prevalence of these toxicities between these agents.

So when we think about alpelisib, which was our very first alpha isoform PI3K inhibitor that got approved with fulvestrant based on the phase 3 SOLAR-1 trial, we think predominantly about hyperglycemia, diarrhea, and rash. The discontinuation rate for alpelisib in that trial was high, in the order of about 35%. And then slowly, with more vigilance and our understanding of these side effects when we start to study trials such as BYLieve, those toxicities and those discontinuation rates were 25% or so.

But these hyperglycemia rates that are high, these rashes that are high, have led to us being vigilant about identifying which patients might be at higher risk. So when we're thinking about that, we're thinking about somebody who's a prediabetic, somebody who might be obese, somebody who has a high BMI. Those are patients who might be more prone to developing hyperglycemia with this drug.

And that's when we think about strategies such as early interventions with anti-diabetic medications. Or we now also have some data for prophylaxis with metformin in patients who might be high risk, where it might be useful to use them prophylactically to reduce the severity and the grade of hyperglycemia.

Similarly for rash, we now utilize primary prophylaxis with antihistamines in clinic to really reduce the rates of severity and grade of rash that we can see with this drug.

Now, with inavolisib, which is another PI3K inhibitor, we've seen that that drug is approved as a triplet with palbociclib and fulvestrant. So we do see some hyperglycemia there as well. In that study, the hyperglycemia rates and the discontinuation rates were lower. However, the hemoglobin A1c cutoff that was utilized in that trial was less than 6, which was slightly distinct than what was utilized in SOLAR-1, which was less than 7.

Having said that, the discontinuation rates with inavolisib in INAVO120 were 6.8%, and the rates for discontinuation due to hyperglycemia were also low.

Now, rash can be seen with inavolisib, but that is predominantly low grade, and we do not see grade 3 rash. It was not reported in the phase 1 trials and was not reported even in the phase 3 INAVO120 study. So not necessary to utilize the antihistamine primary prophylaxis for inavolisib in clinic.

We do see some diarrhea. For diarrhea, we usually think about offering antidiarrheals at the first time patient reports diarrhea, in addition to supportive management such as dietary modifications.

Last but not the least, stomatitis rates can be increased. So while palbociclib itself can give you some stomatitis, by combining inavolisib with palbociclib one can get a higher rate of stomatitis, and therefore utilizing primary prophylaxis with dexamethasone mouthwash, the way we have been doing that with everolimus in clinic, the way we do that with sometimes CDK4/6 inhibitors, should be utilized and considered with the inavolisib triplet regimen as well.

So to summarize the key discussion points from this episode, I think it's important for us to recognize that hyperglycemia, diarrhea, rash, stomatitis are common toxicities seen with the agents targeting this pathway. We do have strategies in place, both primary prophylaxis and secondary prophylaxis, that we need to be aware of.

We need to educate our nursing staff, our staff that are discussing with our patients, so that the patients can communicate that back to us, and we can intervene early and help them stay on drug with dose modifications as needed.

So thank you for this great bite-sized discussion. Our time is up, and thank you so much for listening in today.

Announcer:
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