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Safety and Tolerability of ROS1 Tyrosine Kinase Inhibitors

Announcer:
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Dr. Drilon:
Hi, I'm Dr. Alexander Drilon from Memorial Sloan Kettering Cancer Center, and we are going to talk about the safety and tolerability of ROS1 tyrosine kinase inhibitors.

To begin, when we look at this diagram showing you all of the ROS1 TKIs, well most of them, that have known activity against ROS1 and/or another kinase. And what's interesting is that thus far ROS1, when it's inhibited, has not been shown to cause meaningful side effects in the clinic. However, in contrast, the other kinases that these pills inhibit like TRK, for example, and MET, are associated with unique side effects that you see in this Venn diagram. And we'll go through each of these in the next few slides.

So, we'll begin with the multi-kinase inhibitors that inhibit not only ROS1 but also TRK. And for the approved drugs, those are entrectinib and repotrectinib. So, what happens when you inhibit TRK? Well, the TRK family of proteins is very intimately involved in the development and maintenance of the nervous system, so you can see neurologic side effects. And those are summarized here from a paper that we published. And we observed that patients can gain weight on these inhibitors because of the inhibition of TRKB. They can have dizziness, ataxia, or orthostasis. If you go to the far right, you'll see that paresthesias can also develop. But interestingly, when you discontinue these drugs, because they can reset the threshold for feeling pain, there are some patients who can develop full-body withdrawal pain that can very quickly resolve once the TKI is resumed. So, it's important to keep an eye out for that if someone has a procedure and they need to stop their targeted therapy, for example.

Now, we're focusing on repotrectinib, which is the most recently approved ROS1 TKI that also inhibits TRK. And you see the side effects that we had mentioned in the prior slide make their way into the adverse event table, where dizziness is the most common side effect. Paresthesias are also there. And something we didn't mention is that patients can have taste changes with the drug. So, these are things to watch out for. Fortunately, the dose discontinuation rate of repotrectinib was low at 7% and the dose reduction rate was a little over 1 out of 3 patients.

How do we manage these side effects? That same paper as this table, showing you several things that you can do on the pharmacological front to help. For weight gain, which sort of creeps up on patients over time, there are agents that are known weight loss medications that can be used. The injectables, unfortunately, are much more effective than oral pills like metformin for dizziness. If it's vertiginous or ataxia, you might try something like meclizine. If there is an element of autonomic insufficiency and orthostasis, you can try drugs like midodrine. And for withdrawal pain, it's unfortunately pain medication just to get them through it until you can restart the TKI.

Now for lorlatinib, this has other side effects that are much more common like dyslipidemia that you see in 8 out of 10 patients. And I won't go through the details here, but there are tables like this which allow you to see the relative rise in cholesterol or triglycerides, and

accordingly, either introduce a lipid-lowering therapy and/or modify the dose, meaning lower the dose of lorlatinib. But certainly, you should check cholesterol before someone starts lorlatinib and while they're on therapy.

And finally, much less common than the hyperlipidemia that we saw in the last slide is cognitive dysfunction or mood changes. And these come in various forms, as you see in the table; something to definitely look out for. And the best approach to this really if it's a moderate to severe adverse event is to stop the therapy. And if you consider it safe, resume patients on a lower dose. So, if it's severe and despite dose reductions you're still getting the same changes in cognition, personality, and mood, then of course, come off the drug and considered doing another therapy,

Putting all of that together in this table, there are unique side effects that these TKIs might have, although other things like fatigue, etc., may be shared. We did not go into crizotinib which as you know could cause some edema; ceritinib, gastrointestinal toxicities. But the punchline is just to make sure you know what to look out for with a particular drug that you're using.

And in summary, these drugs, as you've seen, can have very distinct side effect profiles, but supportive care and/or dose modification can help your patients that experience these adverse effects.

Thank you for your attention.

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