Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/side-effects-of-ret-directed-targeted-therapy/14842/

Released: 12/07/2022
Valid until: 12/07/2023
Time needed to complete: 1h 03m

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

Side-Effects of *RET*-Directed Targeted Therapy

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

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Drilon:
Hello, I'm Alexander Drilon. I'm a medical oncologist from Memorial Sloan Kettering Cancer Center. This presentation is on the side effects of RET-directed targeted therapies. It's important to first walk again through the history of the development of targeted therapy for RET-dependent cancers, recognizing that the older agents that were used to treat RET-dependent lung or thyroid cancers, for example, were largely multikinase inhibitors, and you see that in the graph here. The names of these drugs are listed at the top. These include cabozantinib, lenvatinib, regorafenib, sorafenib, sunitinib, and vandetanib, among others. And below, you'll see that while these drugs inhibit RET and RET mutations, in addition to wild type RET, which is what our target is for RET fusions, the drugs inhibit a number of other unintended targets, like VEGFR1, VEGFR2, VEGFR3, EGFR, KIT, FGFR1, and other targets like MET. And this has consequences in terms of side effects that we see in the clinic.

In the table on the right, you'll note the phase two trials of cabozantinib, vandetanib, and lenvatinib in RET-fusion-positive lung cancers. And here you'll see in the orange columns that the dose reduction rates were fairly substantial, ranging anywhere from 23 to 73% for cabozantinib, for example, with a drug discontinuation rate that ranged from eight to 20%. And this was mediated by a number of side effects like hypertension, rash, and diarrhea from hitting those non-RET targets by these multikinase inhibitors. And so, you can imagine that many patients will have their dose modified while they're on therapy. And the point we're making with the table on the left is that these drugs, even at full doses, only have modest inhibition of RET if you look at plasma exposures when you do pharmacokinetics. For lenvatinib and cabozantinib, for example, we only expect about a 50% inhibition of the RET target. And if you're lowering somebody's dose, then you can imagine that we're seeing even less with dose reductions, and this is probably why the older drug had the low response rates and progression-free survival that we saw with these trials.

In 2017, we saw the entry of selective RET inhibitors into the clinic. And these were rationally designed to hit the target RET while avoiding many of the other kinases you saw in the prior slides. These, again, are pralsetinib BLU-667 and selpercatinib LOXO-292. And this has an impact not only on the activity of these drugs but also on how patients tolerate these agents. In simple terms, these drugs are much cleaner than the prior agents, and the thought was that the side effect profile would also improve.

And we certainly saw a difference. These selective RET inhibitors were much better tolerated compared to the older drugs. So, selpercatinib and pralsetinib, you'll see here, have a low rate of treatment-related AE discontinuation, 2 to 4%, and also lower rates of dose modification compared to drugs like cabozantinib. And we've certainly treated many patients who have been on for several years who have tolerated chronic dosing of the drug because the pills have much fewer side effects compared to older agents. A few things to call out, of course, are dry mouth, that we see more commonly with selpercatinib. Some peripheral edema. Sometimes you can see that around the eyes. And with pralsetinib, because it inhibits the JAK family of kinases, you see myelosuppression like anemia, decrease in white blood cells or neutrophils. But there are shared toxicities like an increase in liver function tests and hypertension, of which we're

seeing much lower grade hypertension compared to the older drugs that inhibit VEGFR2 more meaningfully.

Are there other side effects to watch out for? Certainly, and one of them is an allergy. And this can happen with selective RET inhibition. In this paper, we have the hypersensitivity that can occur with selpracatinib, specifically. This was observed in patients who did not have prior immune therapy but seemed more pronounced numerically in patients who had prior exposure to immunomodulatory therapy like pembrolizumab, for example. You'll see in the similar plot on the right that many of these events occurred fairly early, within the first six weeks, for example. And that's typical of an allergy to a drug. But thankfully, the majority of these were easily managed with the administration of steroids and a dose reduction, and patients were able to stay on drug thereafter.

One other interesting side effect to watch out for with any RET inhibitor, including the selective and multikinase inhibitors, is this phenomenon of the development of chylous effusions. And maybe to focus your attention, look first at the pictures on the lower left where you see that certainly there are cases where you remove a pleural effusion, or you remove ascites, and you see, frankly, chylous fluid that looks white and creamy. But otherwise, there are cases, like in panel D, where you might see a more typical coloring of the fluid that's removed, in which case, if you're suspicious, you must send off a triglyceride level to confirm that a chylous effusion is indeed present. A lot of other strategies to manage this are outlined here. Dose modification has been considered. Of course, draining the fluid or placing a catheter. But overall, to date, it's important to recognize this rare side effect because it may be mistaken as progressive disease. And the clue is that often a lot of the patient's masses might have shrunk substantially over time, but you are seeing slowly the buildup of fluid either in the pleural cavity or in the abdomen. And in that case, you should have a high suspicion for that being a side effect rather than progression in a pleural effusion or ascites. So with that, we end this section. Thank you for your attention.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.