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Novel RAS-Targeted Therapy: Prevention, Monitoring, and Mitigation of Adverse Events

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Dr. O'Reilly:
This is CE on ReachMD, and my name is Dr. Eileen O'Reilly. And I'm here today with Dr. Kathryn Arbour.

So we talked about efficacy with the pan-RAS inhibitors. Let's now turn to how we manage safety and toxicity of these drugs.

So, Dr. Arbour, can you walk us through your discussion in the clinic with a patient who's receiving one of these agents and, to start, they have some rash and mucositis.

Dr. Arbour:
Yeah, so I think that when we think about these RAS(ON) inhibitors, they are distinctly different in terms of there are multiple RAS(ON) inhibitors. So to me, the toxicities aren't necessarily related to the fact that they are ON inhibitors, but maybe how many or the broad array of RAS mutations that they might target.

So, for example, in agents such as daraxonrasib that are capable of inhibiting multiple mutant forms of RAS, they are pan-RAS inhibitors or multi-RAS inhibitors, we see sometimes different toxicities than RAS inhibitors that are allele-specific, such as G12D inhibitors or G12C inhibitors.

So we'll start, I think, with daraxonrasib, which is a little bit different. It's really our first pan-RAS, multi-RAS inhibitor experience that we've had in clinic. And we've learned a lot in terms of the toxicities that might be distinct from these class of agents and how to manage them, I think, importantly. And so the common toxicities that we see when I see a patient in clinic are rash as well as GI toxicities, such as diarrhea, nausea, and vomiting. And in some instances, stomatitis.

So I tell patients to pretty much expect that they might have some degree of rash. However, prophylaxis for management of these things, we've gotten much better at that. And we've learned a lot about how to manage these toxicities. So I think the experience of the phase 1 clinical trials, now as we have them in phase 3 clinical trials, has been very informative.

With respect to the rash, sometimes drug rashes can be a little bit different. In particular, this rash is almost an acne-like-type rash that sometimes can be on the face or the chest or the scalp. We're used to these types of rashes in lung cancer for patients who are treated with EGFR inhibitors, and it's sometimes a similar rash in terms of that. And we use a lot of the same treatment strategies for it, including oral antibiotics such as doxycycline. We use topical steroids on the areas of the skin that are affected. And typically, with these treatment strategies that the rash can be affected from that aspect, as well as adjusting the dose depending on the patient's response to the agent.

Ultimately, I think close follow-up is so key for patients with these agents with their medical team to discuss and prepare patients for the

timing of when these events might occur and how to get in touch with the medical team and how to be proactive in terms of managing it, because I really do find—and Eileen, I don't know what your experience is—that early intervention and being proactive in terms of managing these particular side effects can be so helpful to patients in the long run.

Has that been your experience as well?

Dr. O'Reilly:
Yeah, absolutely. And to take this, right, a step further, we now have a hotline to our favorite dermatology colleagues, right, to have them weigh in and help us. But yes, you highlighted a few key points.

So the primary prevention is important with oral antibiotics. Topical medications on the sun-exposed area, avoiding sun if one can, can help. And just educating patients and their families about how to watch for. And as we're learning to use these drugs, we're understandably reluctant, I think, to go down on dosing given efficacy signals. And my sense from patients is they very much want to maintain dosing as long as they can. But no question, we do see sometimes some significant rashes that require dose interruption. And often, we will give it time and then potentially rechallenge at the same dose, and often then that can go okay.

Our nursing team are becoming very adept at guiding and managing patients, and I think just setting an expectation, early follow-up, and early intervention. And for the more complex rashes in particular, early dermatologic expertise and guidance is very helpful.

Dr. Arbour:
And I would add that for the other RAS(ON) inhibitors, such as elironrasib or zoldonrasib, that are G12C and G12D RAS(ON) inhibitors, respectfully, perhaps because they're not pan-RAS inhibitors and we don't quite understand exactly why, but we're seeing less rash with those, still some GI signal of toxicities, but a very different toxicity profile, which hints to your point earlier about is there going to be a role for sequencing therapies and how do we prioritize the potency of the drug and ability to target multiple RAS mutations versus tolerability for patients.

So all things and lessons learned in terms of clinic, but clearly multidisciplinary collaboration as well as really high-quality oncologic nursing care is so crucial in these aspects to really help patients through these therapies to get the most effective therapy possible.

So that's our time. Thanks for spending a few minutes with us to talk about the adverse events we see with these RAS inhibitors. Now it's up to you to put that knowledge into practice.

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