Transcript Details
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Salivary Toxicity from PSMA-Targeted Radiopharmaceuticals in mCRPC

Announcer Intro:
Welcome to *Project Oncology* on ReachMD. Today, we'll hear from Dr. Geoffrey Johnson about his recent study that looked at salivary toxicity from PSMA-targeted radiopharmaceuticals in metastatic castrate-resistant prostate cancer, or mCRPC for short. Dr. Johnson is a Nuclear Medicine Specialist and Radiologist at the Mayo Clinic in Rochester, Minnesota. Here he is now.

Dr. Johnson:
When you look at patients who are suffering from prostate cancer who are receiving PSMA therapy, we can see on our images that the medication we're giving not only goes to their cancer, which is great because that's what we want, but it also goes to some other things in their body, including the salivary glands. And we've known for over 80 years that the same is true for some other radiopharmaceutical therapies, like iodine for thyroid cancer. And we knew in those populations that we could cause xerostomia or dry mouth, and we would try to do things to prevent or reduce the impact of that or the possibility of that problem for the patients.

For most patients who are receiving lutetium PSMA-617, which is a currently FDA-approved drug, at the dose that we give it to them at 200 millicuries per dose up to six cycles, it's really only a minor number of them that have a more mild set of symptoms. Not that it doesn't impact their life, but when you're considering the benefit of the therapy, it doesn't sway us or the patients very often to do anything different. Obviously, we'd like to prevent it, but we don't have a lot of tools that we know are going to reduce that side effect, although people are starting to study them. It really becomes important; however, when you start looking at the next generation of therapies—so the alpha-emitting therapies, in particular, actinium PSMA-617 has been known to cause fairly severe dry mouth to the point that many patients, and sometimes the majority of patients on given studies, will drop out of the study because of the severity of that side effect, and as a result we now have to strongly consider how we're going to design a better version of the drug and how we're going to try to mitigate that.

So there's a lot of discussion right now about how you design your molecule to avoid going to the salivary glands, and if it goes there, to have it wash out really quickly and not stick and stay because if you wash—if it's just going to go through the salivary glands into the saliva, it's not likely to stay there long enough to cause that kind of toxicity. So there's a number of different approaches that people are doing to try to come up with better versions, and a number of the drugs that are actually in trials have as one of their key statements as to why this is worth putting into a trial that they are less likely to cause salivary toxicity.

You wouldn't think about salivary toxicity as earth-shattering. You'd say, 'Well, maybe a patient has dry mouth so they take something external to put in their mouth to keep it moist,' but saliva is a critical part of life, and when you have a patient who has severe and chronic dry mouth, it is a big impact on their life. It's very hard to chew; the mouth doesn't heal well; it gets infected; it gets injured; it can't respond, normally to the environment. And the amount of intervention that's needed to stay on top of that to prevent those kind of consequences is pretty substantial, so it's not a thing to be ignored by any means especially, if someone's going to live for quite a long time after they get this therapy, and certainly not something I would want to think lightly about.

One of the problems is that the same PSMA receptor that's on prostate cancer is also expressed by cells in the salivary glands. It's interesting to note that even with iodine therapy, which doesn't have any receptors in the salivary gland because the body gets rid of

iodine through the salivary glands as a way of excretion in addition to going through the urine and the kidneys, you're going to see it there anyway, and it can cause a side effect. So in addition to just being excreted through the salivary glands, the small molecule PSMA therapies we currently have also stick to the salivary cells, and so there's only so much you can do to try to prevent that.

Now you can say the main thing you want to do is you want to make sure that whatever doesn't stick that's just flowing through the salivary glands get through fast because the radiation is coming off the medication over time, so how long it dwells there is going to lead to more injury than if it washes through quickly. So what we really recommend is that the patients stay very well hydrated. In fact, when we give them the therapy, we tell them to prehydrate. We give them hydration while they're getting the therapy and really work on hydration afterwards. That's the only one that, based on our knowledge of iodine therapy over many, many years, we know has a very good prevention of side effects.

We don't really know with confident data any of the things that we're advising patients on are really going to help prevent severe dry mouth, and that's really where I would come in. Once the patient has that symptom, they're being handled by a different subspecialty, and it's a lifelong problem that people in ENT and other parts of general medicine deal with not just from the therapies we give but because of other types of medications and illnesses. So what we tend to focus on is the prevention, and apart from saying, "I need a better drug,"of which I would say I'm a coinventor of a drug that's going into clinical trials right now that's an alpha emitter that is designed to have lower salivary activity, there are other ones as well out there. There are antibodies, which look like they don't get into the salivary glands.

Unfortunately, with some of these next-generation alpha-emitting therapies, even that's not sufficient. So there are people who think about other things. They might put another medication into the patient along with the PSMA therapy to try to steer where it's going. They may change the charge of the molecule. They may change the size of the molecule. A lot of those things are now going into studies, and we don't yet know whether we can tell patients they're helpful.

Announcer Close:
That was Dr. Geoffrey Johnson speaking about salivary toxicity from PSMA-targeted radiopharmaceuticals. To access this and other episodes in this series, visit *Project Oncology* on ReachMD.com, where you Be Part of the Knowledge. Thanks for listening.