Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/treating-mcrpc-with-lutetium-177-and-radium-223-expert-insights/17803/

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

Treating mCRPC with Lutetium-177 and Radium-223: Expert Insights

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, we'll discuss PSMA-targeting and radium-223 for the treatment of advanced prostate cancer with Dr. Alan Bryce. Dr. Bryce is the Chief Clinical Officer at City of Hope Arizona, a Professor of Medical Oncology and Therapeutics Research, and a Professor of Molecular Medicine at the Translational Genomics Research Institute in Arizona. He also presented a session on this exact topic at the 2024 ASCO Genitourinary Cancers Symposium. Let's hear from him now.

Dr. Bryce:
I had the pleasure of participating in the clinical case discussion forum where we were discussing the various treatment options available for patients with mCRPC who'd already received an androgen receptor pathway inhibitor. And my specific task was to talk about the choice between radium-223 and lutetium-PSMA. So I should say they already had an androgen receptor pathway, and they'd already had docetaxel, right? So this could be first- or second-line or even third-line in the mCRPC setting. But in the era of treatment intensification and triplet therapy in the first-line setting for hormone-sensitive disease, it's conceivable that a patient will be eligible for lutetium or radium as their first mCRPC therapy.

So when we talk about radium and lutetium, there's two key differences between the drugs. Remember: they're both radioisotope-based therapies, but one, radium, is just a naked isotope injected into the body and kind of passively targeting the bone compartment, whereas the other, lutetium-177, is actually a targeted radioligand therapy in which the isotope, the lutetium, is connected via chelator to a targeting molecule. And so the difference here is that whereas lutetium-PSMA targets prostate cancer cells by targeting the PSMA protein that's expressed on the surface of prostate cancer cells, radium acts by the fact that it is selectively uptaken into the bone compartment. So, remember, radium is on the same part of the periodic table as calcium, so when it's ingested into the body, it will get selectively absorbed into cortical bone and concentrated there. And so the radiation is concentrated at the bone, and it then should be effective in targeting cancers that are present within the bone. Right? But it's not effective at treating anything outside the bone compartment.

When thinking about the clinical scenarios, like I say, the targeting is one aspect of the differences between the drugs. The other aspect of the differences is the difference between alpha and beta emitter therapy. So when we talk about radioisotope therapy, alpha and beta emitters are the two large categories right now, and the difference is about the actual radioactive molecule that's causing the cell damage. So an alpha particle is large. It's the equivalent of two protons and two neutrons with a relative particle mass more than 7,000 times greater than a beta particle, which is one electron. And in this context, radium-223 is the alpha emitter, and lutetium-177 is a beta.

Now the other two other key differences with these molecules: 1) Alpha particles don't travel very far. They only travel about the equivalence of 10 cell breaths before they lose their energy and lose their ability to cause DNA damage and cell death; 2) They have a very high energy. And so we focus on something called the linear energy transfer, which is how much energy does this alpha particle deliver to a cell when it hits the DNA, and it delivers something between 60 to 230, say, kiloelectron volts per micrometer. And what that means in layman's terms is that it requires as few as one alpha particle hitting a cancer cell in order to cause cell death. Maybe 1 to 10 alpha particles is all that's needed, so a very limited range. It doesn't go very far, but when it hits cancer cell, it kills it. Okay? And this is relevant to radium because it concentrates in the bones, and it's really good at osteoblastic metastases like prostate cancer where the cancer cells spread out through the cortical bone, but they don't form a mass. But if you get a lytic bone lesion, which is a mass, then really, alpha radiation is only going to hit the very outer rim of that lytic bone lesion. It's not going to hit the center, right?

On the other hand, with beta particles, they're much smaller. They have a much larger range, up to 50-fold greater range. So instead of

10 cell breaths, you could talk about 500 cell breaths. But they have very low linear energy transfer, .015 to .4 kiloelectron volts per micrometer, so now you're talking about maybe 1,000-fold less energy transfer than alpha particles. And what that means is instead of 1 to 10 alpha particles causing cell death, it takes 100 to 1,000 beta particles to cause cell death. So with beta radiation, you need a lot more individual drug molecules in a given area in order to cause cell death, but because the distance these particles travel with energy is so much greater, you really get much greater crossfire. So more molecules over an area. And so you can think that through, and what you start to realize is beta radiation is probably better for large heterogeneous tumors where you won't get uniform distribution of drug. Alpha particles are better when you know you can target the cancer cell and hit it. Beta particles probably aren't logical for micrometastatic disease. You just can't get enough concentrated drug delivery at a given site to cause cytotoxicity.

So when we talk about adverse events for the radioisotope therapies, again, they're going to be a function of the type of radiation and the targeting properties. So when we talk about radium, because it targets the bone compartment, the major side effects are really around myelosuppression, anemia in particular. Some drug will be excreted in the GI tract, so there can be some nausea; there can be some loose stools. There can certainly be some fatigue.

When we talk about lutetium PSMA, again, there is myelosuppression due to the radiation, but there's also the fact that PSMA is also overexpressed on lacrimal glands and salivary glands, right? So amongst healthy noncancerous tissue, the highest expression of PSMA is going to be on those glands, and so a major side effect of lutetium is dry eyes and dry mouth.

There is no specific reason why a patient can't end up getting both lutetium and radium at some point in their treatment course, but the cumulative myelosuppression would be an issue, so it's something to be thoughtful about.

I also encourage physicians to continue regular imaging of patients while on these drugs, either of them. I would continue to image patients every three months. So if you see progressive disease on either drug, then like any other drug, discontinue the drug that's not working and move on to something different. And that's not necessarily how the studies have been understood in general, but I would absolutely encourage people to be very mindful of monitoring for progression or response and monitoring for bone marrow health. I think if you do those two things, these are very useful tools in our toolbox for fighting metastatic prostate cancer.

Announcer:
That was Dr. Alan Bryce talking about how PSMA-targeting and radium-223 can be used to treat advanced prostate cancer. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!