

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Daniel J. George, MD

Prostate Cancer in Focus

Radium-223: the Newest Option in Metastatic Castration-Resistant Prostate Cancer



Oliver Sartor, MD
LaBorde Professor for Cancer Research
Medical Director, Tulane Cancer Center
Departments of Medicine and Urology
Tulane Medical School
New Orleans, Louisiana

H&O Could you provide some background on radium-223?

OS Radium-223 (Xofigo, Bayer and Algeta) is a bone-seeking radiopharmaceutical that patients receive via injection. It is approved by the US Food and Drug Administration (FDA) to relieve pain and prolong survival in patients with metastatic castration-resistant prostate cancer (mCRPC) who have symptomatic evidence of bone metastasis. Because radium-223 selectively targets bone, it is not indicated for men who have visceral disease—which is the case for as many as one-quarter of men with mCRPC.

Radium-223 is the third radiopharmaceutical to be approved by the FDA for use in mCRPC. The first was strontium-89, which was approved in 1993, and the second was samarium-153 (Quadramet, Jazz Pharmaceuticals), which was approved in 1997. Both strontium-89 and samarium-153 are beta emitters.

H&O What makes radium-223 different from other agents for metastatic mCRPC?

One of the things that makes radium-223 unique is the emission of an alpha particle; it is the first alpha emitter in all of medicine. Alpha emitters contain 2 protons and 2 neutrons, and are approximately 7000 times more massive

than electrons. Despite their high energy, alpha particles traverse only a short distance. Typically, they travel less than 100 microns in tissue, so they deposit a large amount of energy over a short space. This has the advantage of limiting the damage to normal tissues adjacent to the cancerous region.

Another unique quality of radium-223 is that it prolongs survival. It is the first systemic radioactive agent to do so; strontium-89 and samarium-153 palliate pain but have no effect on survival. Thus, radium-223 joins agents such as docetaxel, cabazitaxel (Jevtana, Sanofi-Aventis), sipuleucel-T (Provenge, Dendreon), abiraterone acetate (Zytiga, Janssen Biotech), and enzalutamide (Xtandi, Astellas and Medivation) as agents that prolong survival in mCRPC.

Finally, radium-223 is the only agent that has been demonstrated in a single trial to have activity in both patients who have previously received docetaxel and those who have not previously received docetaxel. In contrast, trials of other agents for mCRPC failed to stratify for this important variable. Abiraterone is approved for use both before and after docetaxel, and separate trials were conducted for each disease state. A trial called PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) was recently halted after it found that enzalutamide prolonged survival when used before docetaxel.

H&O What have been the most important studies related to the treatment of mCRPC?

OS The FDA approval of docetaxel in 2004 was critical because docetaxel was the first agent shown to prolong survival in patients with mCRPC. One pivotal trial was the TAX 327 trial by Tannock and colleagues, which was published in the *New England Journal of Medicine* in 2004. The TAX 327 trial demonstrated that you could prolong survival in patients with mCRPC, which was an important first step.

The research really started to heat up in 2010, with the introduction of sipuleucel-T immunotherapy. Also that year, cabazitaxel was approved for use after docetaxel, based on the results of TROPIC (Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen) that were published by de Bono and coauthors in the *Lancet* in 2010. Cabazitaxel was the first drug to demonstrate improved survival in patients who had progressed after docetaxel.

The next agent that was shown to prolong survival was abiraterone, in the COU-AA-301 (Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) trial that was published by de Bono and colleagues in the *New England Journal of Medicine* in 2011. This was a landmark trial because it elucidated that what we had previously referred to as hormone refractory disease was not really refractory to hormones. Abiraterone prolonged survival by blocking the synthesis of androgens.

Abiraterone was first approved in 2011 for use after docetaxel, and was subsequently approved in 2012 for use before docetaxel. This second indication was based on the results of the COU-AA-302 trial (Abiraterone in Metastatic Prostate Cancer Without Previous Chemotherapy), which were published by Ryan and coinvestigators in the *New England Journal of Medicine* in 2013.

Enzalutamide was approved in 2012 for patients following docetaxel on the basis of a phase 3 trial by Scher and colleagues that was published in the *New England Journal of Medicine* in 2012. Enzalutamide is expected to receive FDA approval in 2014 for use before docetaxel in mCRPC.

H&O Could you talk about the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial that you took part in, and what it revealed about the use of radium-223?

OS In ALSYMPCA, which was published in the *New England Journal of Medicine* in July of this year, we randomly assigned 921 patients to receive either radium-223 or placebo in combination with best standard of care, meaning any type of hormonal therapy.

All of the patients had symptomatic bone pain, which could simply mean that they were at least taking a mild analgesic such as acetaminophen for the pain—the participants did not need to be on opioid pain relievers in order to qualify for the trial.

ALSYMPCA was set up as a single trial to look at patients who had either received docetaxel or not; it did not matter for enrollment whether patients received radium before or after docetaxel. Survival, which was the primary endpoint, was prolonged in both cases: radium-223 increased median overall survival from 11.3 to 14.9 months (hazard ratio, 0.70).

Secondary endpoints included symptomatic skeletal events, such as radiation to bone, surgery to bone, pathologic fracture, and spinal cord compression. ALSYMPCA found a substantial reduction in the risk of symptomatic skeletal events with radium-223. There was also some evidence that pain improved, although this was not designed as a pain trial.

As I mentioned earlier, the patients in ALSYMPCA were using any type of hormonal therapy recommended by their physician. Although this was a placebo-controlled trial, the patients were taking more than just a placebo. This stands in contrast to the AFFIRM trial with enzalutamide, in which patients in the placebo arm received only a placebo. At the time that we performed and designed ALSYMPCA, abiraterone and the newly approved hormone enzalutamide were not available. The hormones that were being used were ketoconazole (which was a precursor to abiraterone) and nilutamide, flutamide, or bicalutamide (which were precursors to enzalutamide).

The toxicity with radium-223 in our study was minimal. Six percent of the participants had grade 3 or 4 thrombocytopenia, and 3% of the participants had grade 3 or 4 neutropenia. The worst side effect that may have been related to the use of radium-223 was a single case of thrombocytopenia. One-quarter of the patients taking radium-223 had diarrhea, which was generally grade 1 or 2, and 18% of patients experienced vomiting (in the placebo group, 18% of patients had diarrhea and 14% experienced vomiting). The bottom line is that this is a very well-tolerated therapy.

H&O What is your current approach to treating patients with mCRPC?

OS I view it in terms of first-line vs second-line agents. The 2 agents that are approved only in the post-docetaxel space are cabazitaxel and enzalutamide. Everything else is potentially a frontline agent: docetaxel, sipuleucel-T, abiraterone, and radium-223. As I mentioned before, radium-223 can be used as either first-line or second-line therapy.

Depending on the circumstances, any of these frontline agents may be used. If your patient has bone-

predominant disease, radium-223 can be an appropriate choice. If your patient has a relatively low burden of disease, sipuleucel-T can be a very good choice.

If you want to use hormonal therapies, abiraterone is an excellent choice and docetaxel is still a very reasonable option. Although we use docetaxel less often as a frontline agent than we did 3 years ago, we still use it frequently.

I would love to have comparative effectiveness data that would tell us which drug is best for which patient, but we do not have that information and can not sit around and wait for it. We just have to make the best choices we can with the available information.

Suggested Readings

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