

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

The Timing of Radium-223 Therapy in 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 How common is castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no visceral disease?

OS Nobody knows the exact number, but approximately 90% of the 27,500 prostate cancer deaths per year in this country are from cancer that has metastasized to bone, so that represents about 25,000 men. Approximately 20% to 25% of these men have visceral disease, so I would estimate a yearly incidence of approximately 20,000 men. The prevalence is higher—perhaps 30,000 to 40,000—because men live an average of 24 months with metastatic prostate cancer.

H&O What are the possible sequences of therapy in these patients?

OS The number of possible sequences is enormous. The 5 agents that have been approved as front-line therapies by the US Food and Drug Administration (FDA) for prolonging survival in metastatic CRPC are sipuleucel-T (Provenge, Dendreon), abiraterone acetate (Zytiga, Janssen Biotech), enzalutamide (Xtandi, Astellas/Medivation), radium-223 (Xofigo, Bayer/Algeta), and docetaxel. These 5 therapies can be used in any sequence, plus there is a sixth agent, cabazitaxel (Jevtana, Sanofi-Aventis), that can be used following docetaxel. The problem, of course, is that nobody knows what the best sequence is, and no agent has an FDA-approved indication as second-line or later therapy after either abiraterone or enzalutamide.

H&O What are the advantages of using abiraterone or enzalutamide as first-line therapy?

OS The majority of US physicians use either abiraterone or enzalutamide as frontline therapy for metastatic CRPC because these oral hormonal therapies are clearly effective and relatively nontoxic. Both drugs seem to be equally popular.

H&O What are the advantages of using docetaxel as second-line therapy?

OS We have good data now regarding the cross-resistance that develops between abiraterone and enzalutamide. Regardless of which one of those agents you receive first, the response rate to the second is very low. Abiraterone following enzalutamide may be slightly more effective than enzalutamide following abiraterone, but the response rate is low nonetheless. Docetaxel also loses some activity when used as second-line therapy, but the loss is not as great as with abiraterone and enzalutamide. The difference is that you are treating with a taxane rather than with another hormone.

H&O What are the advantages of using radium-223 earlier in therapy?

OS Although we do not have any formal trials with radium-223 as second-line therapy after abiraterone or enzalutamide, we do have experience with radium-223 as

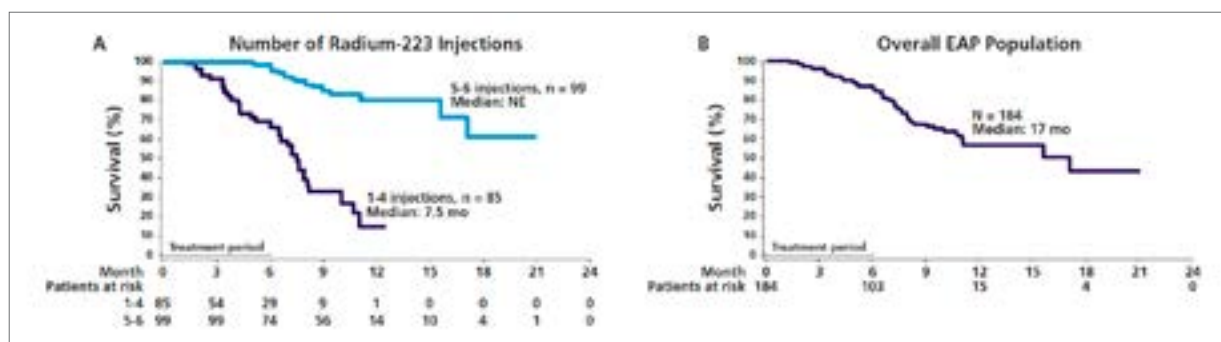


Figure. A, Overall survival by number of radium-223 injections. **B,** Overall survival in Expanded Access Program population.

EAP, Expanded Access Program; mo, months; NE, not estimable owing to a short follow-up and large percentage of patients in the overall population (70%) still alive at the time of analysis.

first- and second-line therapy from the Expanded Access Programs. A variety of access programs were set up in the United States and internationally when FDA approval was considered imminent, and a review of the US data on 184 patients—which I presented as a poster at the most recent American Society of Clinical Oncology (ASCO) annual meeting—showed that using radium-223 as first-line rather than second-line therapy increases the likelihood of completing 6 cycles of treatment.

H&O Could you discuss this study in more detail?

OS This study was of special interest for several reasons. First, it gave us a chance for the first time to look at the use of radium-223 outside of a clinical trial setting. The setting was somewhat restricted because individuals had to qualify for the early-access protocol, but it was not a formal clinical trial. We found that radium-223 was well-tolerated in this setting, with fewer than 20% of patients stopping treatment because of adverse events. Second, the trial gave us the opportunity to look at administering radium-223 following abiraterone, enzalutamide, or both, and we found that this was a safe approach.

Finally, our analysis showed that patients who received both abiraterone and enzalutamide before radium-223 treatment were less likely to receive all 6 cycles of radium-223 than those who had not received both of these hormonal therapies (29% vs 57%; $P=.003$). We do not yet know the implications of this finding. As is the case with many therapies, however, waiting to use radium-223 until multiple other agents have stopped working means that it is less likely to be effective. In observational studies derived from the Expanded Access Program, patients who received 5 or 6 radium-223 injections lived longer than those who received 1 to 4 injections (see the figure). Thus, this study showed a trend toward better overall survival among patients who received 5 or 6 radium-223 injections.

If you are treating patients with radium-223, ideally you would choose those patients for treatment who are able to receive 6 cycles, which is the FDA-approved number of cycles to administer.

We do have good data from the ALSYMPCA (Alpha-radin in Symptomatic Prostate Cancer) trial showing that radium-223 can prolong survival after docetaxel. Results were published first in the *New England Journal of Medicine*, and further analyzed for an article in *Lancet Oncology* that found a hazard ratio for improved median survival of 0.70 with previous docetaxel use and 0.69 with no previous docetaxel use.

What we learned from the Expanded Access Program is that radium-223 can be safely administered with the newer hormonal agents such as abiraterone and enzalutamide, which is what we expected to see. We also saw encouraging survival data for those who received radium-223 concomitantly with abiraterone, but more data are needed, and we did not have enough data on enzalutamide to gain any insights. We would expect abiraterone and enzalutamide to be similar in this regard. Now we need to run prospective clinical trials to determine whether using radium-223 earlier, in combination with the newer hormones, is actually better.

H&O What other studies are relevant to this discussion?

OS An international Expanded Access Program also produced very interesting results, based on 696 patients from 14 countries. These results also were presented as a poster at the ASCO annual meeting. As with the US study, the international study showed a trend toward improved survival with radium-223 and concurrent abiraterone vs radium-223 alone.

The international study also made the novel observation that patients who received radium-223 plus denosumab (Xgeva, Amgen) seemed to live longer than those who received radium-223 alone, and there were no

additional safety concerns. Again, this was not a randomized trial, but there is a potential rationale to support the use of this combination given the ability of denosumab to promote mineralization of the inorganic bone matrix. The inorganic bone matrix, especially hydroxyapatite, is the area where radium-223 is deposited in osteoblastic lesions. The combinations of denosumab/radium-223 and abiraterone/radium-223 should be examined in clinical trials.

H&O What do we know about combination therapy for metastatic CRPC?

OS No combination therapies have been approved by the FDA; everything is approved as a monotherapy. But clinical trials exploring combination therapy in metastatic CRPC are very important, and we are now approaching an era of combination therapy in clinical trials.

An ongoing international trial currently is looking at abiraterone with or without radium-223 (NCT02043678)

and a proposed trial will look at enzalutamide with or without radium. These are important trials that can help us determine whether specific combinations of therapy are better at prolonging survival than sequential therapy.

Suggested Readings

Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*. 2014;15(12):1397-1406.

Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

Saad F, Carles J, Gillessen S, et al. Radium-223 in an international early access program (EAP): effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients [ASCO abstract 5034]. *J Clin Oncol*. 2015;33(15)(suppl).

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