Radium-223 Dichloride for Metastatic Castration-resistant Prostate Cancer: The Urologist’s Perspective

Neal D. Shore

Radium-223 dichloride (radium-223) is an important therapeutic option for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no visceral disease. The unique mechanism of action of this first-in-class alpha-emitting radiopharmaceutical underlies its favorable safety profile and low incidence of myelosuppression. In the pivotal phase 3 ALpharadin in SYMptomatic Prostate CAncer Patients study, radium-223 reduced the risk of death by 30% and prolonged time to first symptomatic skeletal event by 5.8 months. This article summarizes current guidelines and clinical studies that led to the approval of radium-223 as an overall survival therapy, and discusses the urologist’s perspective on using radium-223 in clinical practice.

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Prostate cancer is the fourth leading cause of US cancer deaths and the most common cancer managed by urologists, with >233,000 new cases estimated for 2014.1 On diagnosis, approximately 12% of patients will have locally advanced disease, and 4% of newly diagnosed patients will present with metastatic disease.1 Although newly diagnosed localized disease may be cured with intervention therapy, approximately 30% of patients develop recurrent disease and may progress to castration-resistant prostate cancer (CRPC).1,2 As the clinicians chiefly responsible for diagnosing, treating, and monitoring prostate cancer patients, urologists are uniquely positioned to provide a detailed discussion of therapeutic options and promote shared decision making with patients regarding approved CRPC treatment options.

Although CRPC treatment options with unique mechanisms of action (MOAs) have burgeoned since 2010, the disease eventually evolves via selective pressures, with clonal expansion of cells harboring resistance mutations. Unfortunately, this contributes to the annual prostate cancer—specific death rate of 30,000 for US men,1 of which approximately 90% will have evidence of bone metastasis.1 Bone metastases are a clinically significant cause of morbidity and mortality, often resulting in debilitating bone pain, pathologic fracture, and spinal cord compression; they may also require either radiation or surgical intervention.4,5 Bone-metastatic CRPC (mCRPC)—associated events can cause functional disability, reduced quality of life (QOL), further complications that may impact survival, and ultimately health care cost escalations.4,6 Urologists dedicated to evaluating and managing therapeutic options for patients with progressive CRPC must be knowledgeable of approved therapies that can delay disease progression and prolong survival, and they must proactively manage the relatively ubiquitous metastatic skeletal disease and the associated potential complications.

Radium-223 dichloride (radium-223) is a first-in-class alpha-emitting radiopharmaceutical approved for treating CRPC patients with symptomatic bone metastases with no known visceral metastatic disease.1 Clinicians caring for patients with progressive CRPC should understand the radium-223 MOA, its role in the treatment plan for appropriate CRPC patients, and its administration, efficacy, and safety profile. This review summarizes the phase 3 registration clinical trial results, approved radium-223 indications and administration, ongoing and planned radium-223 studies, and, importantly, a urologic perspective on implementing radium-223 in clinical practice. Current CRPC treatment guidelines and phase 1-3 clinical studies of radium-223 for CRPC and symptomatic bone metastases were reviewed and their implications for using radium-223 from the urologist's perspective considered.

OVERVIEW OF RADIIUM-223

Mechanism of Action

Radium-223, an alpha-emitting radiopharmaceutical, mimics calcium in forming complexes with the bone mineral hydroxypatite, which specifically targets bone metastases.5,9 Radium-223 preferentially targets new bone

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Address correspondence to: Neal D. Shore, M.D., F.A.C.S., Department of Urology, Carolina Urologic Research Center, Myrtle Beach, SC

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growth surrounding bone metastases while emitting alpha particles within the tumor microenvironment. Whereas beta particles generate primarily single-stranded deoxyribonucleic acid breaks that may be overcome by cellular repair mechanisms, alpha particles have high linear energy transfer with enhanced ability to induce lethal double-stranded deoxyribonucleic acid breaks, thus eliciting greater cytotoxic effects on bone-metastatic tumor sites.9,10 The relatively large particle size and high linear energy transfer of alpha particles translates into a short effective range of <100 μm (2-10 cell diameters) compared with other radioisotopes11; therefore, radium-223 is bone targeted with a relatively low impact on myeloproliferative tissue, thereby minimizing myelosuppression-associated adverse events (AEs) compared with earlier generation bone-targeted radio-pharmaceuticals that use beta and gamma isotopes (Fig. 1).8,10

**Early Radium-223 Clinical Studies**

In both first-in-human phase 1 trials in breast and prostate cancer with documented skeletal metastases, single-dose radium-223 was well tolerated at all therapeutically relevant doses (46-250 kBq/kg intravenously [IV]), with no dose-limiting hematologic toxicity and only mild and transient myelosuppression (neutropenia, leukopenia, and thrombocytopenia).12,13 In a follow-up, phase 1, dose-escalation study in advanced prostate cancer with skeletal metastases, radium-223 was well tolerated at a total dose of 250 kBq/kg.12,13

In subsequent phase 2 studies in CRPC patients with symptomatic bone metastases, radium-223 was well tolerated with a positive effect on pain assessments (Brief Pain Inventory functional index; Table 1).14-16 Radium-223 was associated with reduced serum markers of bone turnover, including bone alkaline phosphatase, procollagen I N propeptide, C-terminal cross-linking telopeptide of type I collagen, and type I collagen cross-linked C-telopeptide, suggesting a role for bone markers in better understanding the radium-223 efficacy signals.

**Phase 3 ALSYMPCA Trial**

The phase 3 Alpharadin in SYMptomatic Prostate CAncer Patients (ALSYMPCA) trial was a randomized, double-blind, placebo-controlled, multicenter, multinational trial of patients with histologically confirmed, progressive CRPC with ≥2 bone metastases detected on skeletal scintigraphy, no known visceral metastases, and asymptomatic disease.17 In ALSYMPCA, symptomatic disease was defined as regular use of opioid or nonopioid analgesic medication or treatment with external beam radiation therapy (EBRT) within the previous 12 weeks for cancer-related bone pain. The primary end point was overall survival (OS); key secondary end points included time to first symptomatic skeletal event (SSE), changes in prostate-specific antigen (PSA) and alkaline phosphatase levels, safety, and QOL assessments. SSEs comprised the need to administer EBRT for bone pain, new symptomatic pathologic bone fracture (vertebral or nonvertebral), spinal cord compression, and tumor-related orthopedic surgical intervention. Morphometric assessment for asymptomatic fractures was not performed on a routine basis.

Patients were randomized 2:1 to receive 6 injections of radium-223 (50 kBq/kg IV) or a saline placebo infusion; a cycle comprised 1 injection every 4 weeks, and a completed course consisted of 6 cycles. During the trial evaluation, patients received the best standard of care (BSOC) at the investigator’s discretion; this may have included ketoconazole, glucocorticoids, antiandrogens, estrogens, or focal palliative EBRT. A total of 921 patients were randomized: 614 to the experimental radium-223 arm and 307 to the placebo arm; 43% had a World Health Organization (WHO) ladder for cancer pain score of 1 (mild pain, analgesic use, no opioid use), indicating that a significant proportion of ALSYMPCA patients with symptomatic disease did not use opioids. Additionally, 43% had no prior docetaxel therapy because of investigator or patient preference; hence, this segment of the trial population was chemotherapy naive.

In the ALSYMPCA trial, radium-223 treatment resulted in a 30% reduction in risk of death among radium-223 patients vs placebo. Median OS was 14.9 months with radium-223 and 11.3 months with placebo (hazard ratio [HR] = 0.70; 95% confidence interval [CI], 0.58-0.83). Additionally, radium-223 vs placebo significantly prolonged median times to first SSE (15.6 vs 9.8 months; HR = 0.66; 95% CI, 0.52-0.83; P < .001).17,18 Radium-223 was associated with an overall low incidence of grade 3 or 4 myelosuppression (thrombocytopenia, 6% vs 2% placebo; neutropenia, 2% vs 1%; and anemia, 13% vs 13%) and a low incidence of grade 3 or 4 gastrointestinal AEs (diarrhea, 2% vs 2% placebo; vomiting, 2% vs 2%; and constipation, 1% vs 1%).17

Radium-223 had a beneficial effect on delaying pain19 and preserving health-related QOL,17 with time to EBRT
for bone pain being significantly longer for radium-223 than for placebo (HR = 0.67; 95% CI, 0.53-0.85) and median time to initial opioid use being significantly longer for radium-223 than for placebo (HR = 0.62; 95% CI, 0.46-0.85). Finally, a significantly higher percentage of radium-223 than placebo patients had a clinically meaningful improvement in health-related QOL based on the Functional Assessment of Cancer Therapy–Prostate score (increased ≥10 points from the baseline) over the drug administration period (25% vs 16%; P = .02).

### Ongoing and Future Studies

A number of radium-223 clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) are ongoing. In ALSYMPCA, 574 (62%) patients have entered a 3-year follow-up (radium-223, n = 406; placebo, n = 168), evaluating the occurrence of treatment-related AEs, including acute myelogenous leukemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, and primary cancer in other organs. At 1.5-year post-treatment follow-up, 322 (79%) radium-223 patients and 145 (86%) placebo patients have withdrawn from the study, primarily because of death. During this period, 37 treatment-related AEs were reported in 25 of 404 (6%) radium-223 patients and 8 of 167 (5%) placebo patients; primary cancers in other organs occurred in 5 patients (2 radium-223 and 3 placebo patients). Myelosuppression incidence among radium-223 patients was ≤3%, with no reports of acute myelogenous leukemia, myelodysplastic syndrome, or primary bone cancer.20

Low myelosuppression rates and unique MOA of radium-223 have raised interest in combining radium-223 with other agents. A phase 2 trial investigating its combination with abiraterone or enzalutamide (NCT02034552) and a phase 3 trial with abiraterone and prednisone (NCT02043678) are ongoing. Additional radium-223 clinical trials include a phase 1 or 2 study evaluating safety and efficacy of radium-223 plus docetaxel in CRPC patients with symptomatic bone metastases (NCT01106352). Although the phase 2 segment is ongoing, phase 1 showed no AE-related radium-223 discontinuations or delays and no long-term toxicity during the 3-month follow-up, which began when the study treatment ended.21

A phase 1 or 2 study evaluating safety of retreatment with 6 additional doses is under way (NCT01934790). The short radium-223 half-life (11.4 days) and low myelosuppression rates during treatment permit administration of multiple doses at relatively short (4 week) intervals. Multiple doses may improve the radiation dose homogeneity, a factor likely to contribute to OS benefit.13 Early-access programs in CRPC patients with symptomatic bone metastases are assessing radium-223 acute and long-term safety, within and outside of the United States (NCT01516762 and NCT01618370). Future studies will explore radium-223 efficacy and safety in treating breast cancer (NCT01070485), osteosarcoma (NCT01833520), and other cancers associated with bone metastases.
Radium-223 Handling and Administration

Radium-223 is generally administered by radiation oncologists or nuclear medicine physicians certified to handle radioisotopes by their state Nuclear Regulatory Commission. It is provided as a ready-to-use solution for slow bolus IV injection (45-60 seconds, with a shielding container and decay correction table). The currently recommended and FDA-approved regimen is 6 doses of radium-223 50 kBq (1.35 mCi) IV per kilogram of body weight, administered at 4-week intervals. Radium-223 reaches its target rapidly after IV administration, with ~60% of injected activity taken up by the bone within 4 hours.

Alpha particles emitted by radium-223 are relatively large and easily shielded by skin. However, radium-223 should be handled and administered by trained personnel, taking appropriate radiation safety precautions to reduce or eliminate exposure risk. Radium-223 decays into a stable product and has to be discarded as fecal waste following standard universal precautions. Given the potential for bone marrow suppression (albeit lower than that with other radioisotopes approved for pain palliation of bone metastases), complete blood counts are taken before each radium-223 administration, and treatment discontinued with sustained bone marrow suppression. Before initial radium-223 administration, the hemoglobin, platelet, and absolute neutrophil counts should be ≥10 g/dL, ≥100 x 10^9/L, and ≥1.5 x 10^9/L, respectively, and hematologic evaluation should precede every subsequent dose. Subsequent radium-223 administrations require an absolute neutrophil count of ≥1 x 10^9/L and a platelet count of ≥50 x 10^9/L. Concomitant radium-223 with chemotherapy is not recommended (outside a clinical trial) because of potential additive effects on bone marrow.

UROLOGIST’S PERSPECTIVE

Radium-223 in the CRPC Treatment Paradigm

Radium-223 and several other approved agents prolonging OS in phase 3 trials have recently been incorporated with traditional palliative therapies into CRPC treatment guidelines (Fig. 2; Table 2). Sipuleucel-T is an autologous immunotherapy, administered IV, and recommended for asymptomatic or minimally symptomatic mCRPC patients. Cabazitaxel, an IV-administered cytotoxic chemotherapy, is recommended as an option for patients previously treated with docetaxel who have demonstrated disease progression. Abiraterone acetate, an androgen biosynthesis inhibitor orally administered in combination with prednisone, is a treatment option for patients with asymptomatic or minimally symptomatic mCRPC, both before and after docetaxel chemotherapy. Enzalutamide, an orally administered androgen-receptor signaling inhibitor, is also an approved option for CRPC patients in the prechemotherapy and postchemotherapy settings.

Radium-223, an IV-administered option for patients with CRPC with symptomatic bone metastases, may be considered either before or after docetaxel therapy. In the ALSYMPCA trial, 57% of patients had received prior docetaxel therapy, whereas 43% had not (due to ineligibility or patient refusal). Efficacy and safety in both populations were subsequently analyzed; radium-223 prolonged OS vs placebo, irrespective of prior docetaxel use. In patients with no prior docetaxel, median OS was 16.1 months with radium-223 vs 11.5 months with placebo (HR = 0.75; 95% CI, 0.56-0.99; P = .039); in patients with prior docetaxel, median OS was 14.4 months with radium-223 vs 11.3 months with placebo (HR = 0.71; 95% CI, 0.57-0.89; P = .003). The incidence of myelosuppression was low in both subgroups; however, patients with prior docetaxel had a significantly higher incidence of grade 3 or 4 thrombocytopenia with radium-223 vs placebo (9% vs 3%, respectively; P = .01).

In the ALSYMPCA trial, both radium-223 and the placebo control-arm patients were allowed concomitant BSOC at the time of the trial enrollment (eg, local EBRT, glucocorticoids, antiandrogens, ketoconazole, or estrogens); the options were equally distributed between the 2 treatment arms. Since its availability as part of an
### Table 2. AUA recommended CRPC therapeutic options

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AUA, American Urological Association; OS, overall survival; PSA, prostate-specific antigen; SRE, skeletal-related event; SSE, symptomatic skeletal event; other abbreviations as in Table 1.

* Taken from 2014 Update of the AUA Guideline for castration-resistant prostate cancer.

† Index patient profiles: 1, asymptomatic nonmetastatic CRPC; 2, asymptomatic or minimally symptomatic, metastatic CRPC without prior docetaxel chemotherapy; 3, symptomatic, metastatic CRPC with good performance status and no prior docetaxel chemotherapy; 4, symptomatic, metastatic CRPC with poor performance status and no prior docetaxel chemotherapy; 5, symptomatic, metastatic CRPC with good performance status and prior docetaxel chemotherapy; and 6, symptomatic, metastatic CRPC with poor performance status and prior docetaxel chemotherapy.
Patient Selection

Urologists should have a defining role in the early identification of CRPC patients and subsequently in their careful evaluation for all approved mCRPC therapies including radium-223; thus, they should have timely discussions with patients regarding the most suitable and preferred treatment options, based on the published data and recent NCCN and AUA guidelines. Given the expanding and aging male population, as well as the lengthening survival of CRPC patients, there is ongoing interest in maintaining the QOL metrics throughout the course of CRPC disease progression. This discussion is increasingly common in urologic practices caring for advanced prostate cancer patients. Urologists evaluating and managing mCRPC patients should be well versed in their comprehension of the level-1 evidence within the peer-reviewed literature, as well as the AUA and NCCN guideline recommendations for mCRPC patients. Interestingly, the recently updated AUA guideline defines “symptomatic” more narrowly than the ALSYMPCA inclusion criteria. The currently approved mCRPC treatment options improve OS via distinct MOAs, and a given therapeutic may also have specific and unique side effects. In the absence of unforeseen accessibility or financial considerations, it should become increasingly more likely that a mCRPC patient will receive most, if not all, of these CRPC therapies as he progresses through his disease course (Table 2); this emphasizes the importance of further establishing the ideal sequencing and combinatorial strategy for the individual patient.

Appropriate radium-223 candidates may have minimally symptomatic or symptomatic mCRPC (requiring nonopioid or opioid analgesic medications), no lymph nodes >3 cm in diameter, and no concomitant visceral metastases. In the ALSYMPCA trial, 42% and 45% of radium-223 and placebo patients, respectively, had a WHO ladder for cancer pain score of 1 (requiring nonopioid analgesic medications), and 56% and 55%, respectively, had a baseline WHO ladder score of 2 or 3 (requiring opioid analgesic medications).19 Radium-223 may be administered with no required preadministration or postadministration medications; there is no food requirement other than an enhanced hydration recommendation, and there has been a demonstrated low incidence of severe AEs (Table 2).17 Radium-223 has been combined with other traditional nonchemotherapeutic antineoplastic agents as demonstrated with the concomitant BSOC administration in the ALSYMPCA trial. Even though there are no FDA-labeled contraindications for its use with denosumab, abiraterone acetate and prednisone, or enzalutamide, these combinatorial strategies and their associated safety profiles are still under investigation. Radium-223 may be considered both before and after docetaxel chemotherapy.20

Patient Monitoring and Education

Urologists should have a pivotal role in the monitoring and treatment selection for their CRPC patients. The careful monitoring of patients transitioning from nonmetastatic to asymptomatic mCRPC will identify patients who may benefit from approved CRPC therapies that can extend OS. Unfortunately, most mCRPC patients will eventually develop bone-related symptomatology, becoming appropriate candidates for a course of radium-223. The ideal radium-223 patient selection will have symptomatic bone metastases, yet no visceral metastases or malignant lymphadenopathy exceeding 3 cm. As a course of radium-223 therapy requires a 6-month interval (each cycle is administered on an every 4-week basis), there should be a careful evaluation and consideration of the potential timing of future chemotherapy administration. Concomitant administration of a novel oral hormonal agent, as discussed earlier, remains under investigation. Serum biomarkers are often used to monitor CRPC treatment efficacy; the Prostate-Cancer Working Group (PCWG2) recommends basing the decision to discontinue treatment on clinical symptomatology and therapeutic tolerability, as well as radiographic progression, not solely on PSA kinetics.29 Docetaxel, abiraterone acetate, and enzalutamide may be associated with a PSA response, as their MOAs will impact the androgen receptor and subsequent PSA gene transcription. Other approved CRPC therapies with alternative MOAs not directly influencing the androgen receptor, such as sipuleucel-T, radium-223, zoledronic
acid, and denosumab, are much less likely to significantly affect PSA kinetics.\textsuperscript{23,30,31}

As radium-223 is a first-in-class alpha-emitting radiopharmaceutical with a unique MOA distinguishing it from beta-emitting radiopharmaceuticals, patients and caregivers require education regarding radium-223 efficacy and safety. Urologists should communicate that although radium-223 provides relief of bone pain in some patients, pain palliation should not be used as a marker for efficacy, as pain palliation was not a primary end point in the ALSYMPCA trial.\textsuperscript{17} Clinicians should plan for the patient to receive all 6 cycles of radium-223, which is the recommended treatment course to achieve OS benefit.\textsuperscript{22} Therefore, patient disease volume and performance status relating to all CRPC options should be considered. On choosing a course of radium-223 therapy, patients will require a complete blood count within 1 week before each administration to establish acceptable hematologic status; fecal matter and other body waste should be handled with standard universal precautions.\textsuperscript{22} There are no patient restrictions regarding nonsexual contact with caregivers and others after a radium-223 treatment.

**Radium-223: A Multidisciplinary Therapy**

Urologists, in solo practice or as part of a multidisciplinary team, can now offer CRPC patients another treatment option in addition to immunotherapy, novel hormonal agents, and cytotoxic chemotherapies. With a dedicated and comprehensive understanding of these agents’ efficacy and safety, urologists can effectively manage advanced prostate cancer, collaborate with other specialists, and educate patients to make informed decisions in a timely and beneficial manner during their CRPC course of care.

Urologists may work in tandem with medical oncologists and radiation oncologists to discuss with patients the advantages and disadvantages of an oral hormonal therapy, chemotherapy, immunotherapy, or radiopharmaceutical. If radium-223 therapy is initiated, urologists can coordinate the administration with a nuclear medicine radiologist or a radiation oncologist while monitoring patients during and after the therapeutic course.

**CONCLUSION**

For urologists dedicated to CRPC patient care, radium-223 is an important therapeutic option for treating patients with symptomatic bone metastases. Radium-223 prolongs OS, delays time to first SSE, and is associated with a beneficial effect on pain and QOL.\textsuperscript{17} The safety profile has been established, specifically demonstrating a low incidence of myelosuppression ($\geq 3\%$).\textsuperscript{20,22}

Current challenges to the successful incorporation of radium-223 into the CRPC treatment paradigm include the timing of sequential and combination therapy with other approved CRPC options. Although radium-223 provides pain palliation in some patients, this is not a surrogate measure for efficacy and should not prompt discontinuation in the absence of an analgesic effect. Once initiated, the full 6-cycle radium-223 course should be administered to potentiate the survival benefit. In the ALSYMPCA trial, radium-223 was administered along with the BSOC at each center; however, its role in combination therapy with other newly approved CRPC therapies has not yet been established. Future and ongoing studies will explore the combination of radium-223 with currently available CRPC agents. Finally, as radium-223 becomes incorporated into the CRPC treatment discussion, logistic workflow can be established to facilitate interdisciplinary treatment among medical oncology, radiation oncology, nuclear medicine, and urology clinics.

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**References**


