Review Article

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. UROLOGY ■: ■—■, 2015. © 2015 Elsevier Inc.

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 interventional therapies, 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.[3] 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.[7] 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 RADIUM-223

Mechanism of Action

Radium-223, an alpha-emitting radiopharmaceutical, mimics calcium in forming complexes with the bone mineral hydroxyapatite, which specifically targets bone metastases.[8,9] Radium-223 preferentially targets new bone

Financial Disclosure: *Neal D. Shore has had a consultant or advisory relationship with Astellas, Bayer, Bayer AS (formerly Algeta ASA), Ferring, Janssen, Dendreon, Pfizer, BN Immunotherapeutics, Medivation, Millennium, and Sanofi.*

Funding Support: *This study is supported by Bayer HealthCare Pharmaceuticals, Inc, Whippany, NJ.*

From the Department of Urology, Carolina Urologic Research Center, Myrtle Beach, SC

Address correspondence to: Neal D. Shore, M.D., F.A.C.S., Department of Urology, Carolina Urologic Research Center, 823 82nd Parkway, Myrtle Beach, SC 29572. E-mail: nshore@gsuro.com

Submitted: October 13, 2014, accepted (with revisions): November 27, 2014

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 radioisotopes[11]; 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 radiopharmaceuticals that use beta and gamma isotopes (Fig. 1).[8,10]

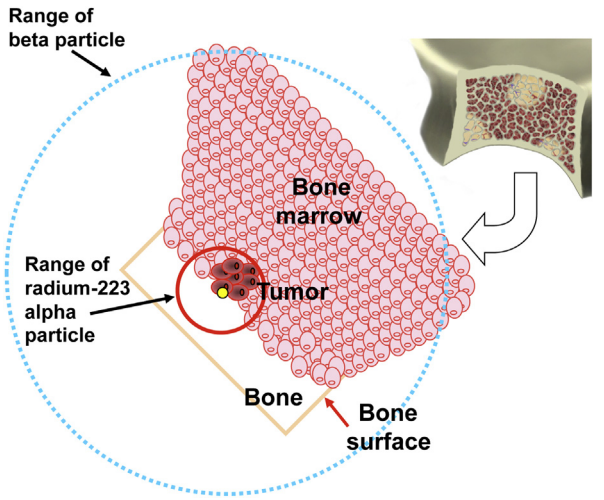

Figure 1. Radium-223 mechanism of action. (Color version is available online.)

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 to 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 symptomatic 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 pain[19] and preserving health-related QOL,[17] with time to EBRT