Practical guide to the use of radium 223 dichloride

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Introduction: *Bone seeking radiopharmaceuticals have been used for decades in the palliation of pain from bone metastases emerging from prostate cancer. Recent clinical evidence has demonstrated an improved survival in men with metastatic castration resistant prostate cancer (CRPC) with radium 223.*

Material and methods: *A review of the literature was performed to identify the role of radiopharmaceuticals in the management of prostate cancer. We focused on prospective trials in order to identify the highest level of evidence describing this therapy. Further, we focused on providing a clinical guide for the use of radium 223.*

Results: *The phase III ALSYMPCA trial which compared radium 223 to placebo in men with symptomatic CRPC demonstrated a statistically significant improvement in median overall survival of 3.6 months and an improvement in time to first skeletal related event. There were higher rates of myelosuppression and diarrhea with radium 223, however, no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups.*

Conclusion: *Radium 223 is a safe and effective therapy in men with symptomatic CRPC providing a survival advantage on par with novel antiandrogens, CYP-17 inhibitors, and chemotherapy. Radium 223 has huge potential in combination strategies as well as for use earlier in the natural history of metastatic prostate cancer.*

Key Words: radium 223, castration resistant prostate cancer, alpha particle, radiopharmaceuticals

Introduction

Prostate carcinoma is the most common non-cutaneous malignancy diagnosed in US men and the second leading cause of cancer related death with approximately 29480 men succumbing to the disease in 2014.[1] Primary therapy for localized disease consists of either surgical resection or radiation therapy,[2] however, for patients with recurrent or metastatic prostate cancer, treatment consists of androgen deprivation therapy through depletion or blockage of circulating androgens.[3] While initially effective, most men develop resistance as manifested by either clinical, radiographic or most commonly biochemical progression (increase in prostate-specific antigen despite "castrate" [< 50 ng/dL] levels of testosterone).[4] The development of castration resistant prostate cancer (CRPC) signals an inappropriate reactivation of the androgen receptor (AR) axis resulting in growth and proliferation.[5] Further, targeting of the AR pathway, through either the disruption of adrenal production of androgens with abiraterone acetate,[6,7] or inhibition of ligand binding using the second generation antiandrogen enzalutamide,[8] results in increased survival for this population of men. Other Food and Drug Administration (FDA) approved modalities which have increased survival for men with CRPC include chemotherapy[9,10] and immunotherapy.[11]

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TABLE 1. **Physical characteristics of radiopharmaceuticals used in prostate cancer**

Radionuclide	Half-life	Decay particle	Tissue penetration
Radium 223	11.4 days	alpha	< 0.1 mm
Strontium 89	50.5 days	beta	5.5 mm
Samarium 153	1.9 days	beta, gamma	2.5 mm
Rhenium 186	3.8 days	beta, gamma	4.5 mm

Prostate cancer frequently metastasizes to the bone primarily within the axial skeleton (vertebral bodies, pelvis, ribs, and skull) but may also occur in the long bones.[12] Radiographically, osseous metastases are most often noted on ^{99}technetium methylene diphosphonate bone scintigraphy scans. However, newer modalities such as ^{18}sodium fluoride PET and ^{18}fluorodeoxyglucose PET are more frequently being utilized given their increased sensitivity for detection.[13]

Clinically, bone metastases are the primary cause of morbidity and mortality for men with metastatic CRPC,[14] with 80%-90% of patients eventually developing metastatic disease.[15] Bone lesions may cause pain or skeletal related events such as spinal cord compression, fractures, or hypercalcemia. Further, the extent of osseous involvement is associated with overall survival.[16] Given the systemic and complex nature of managing painful bone metastases, radiopharmaceuticals have emerged as a promising modality.

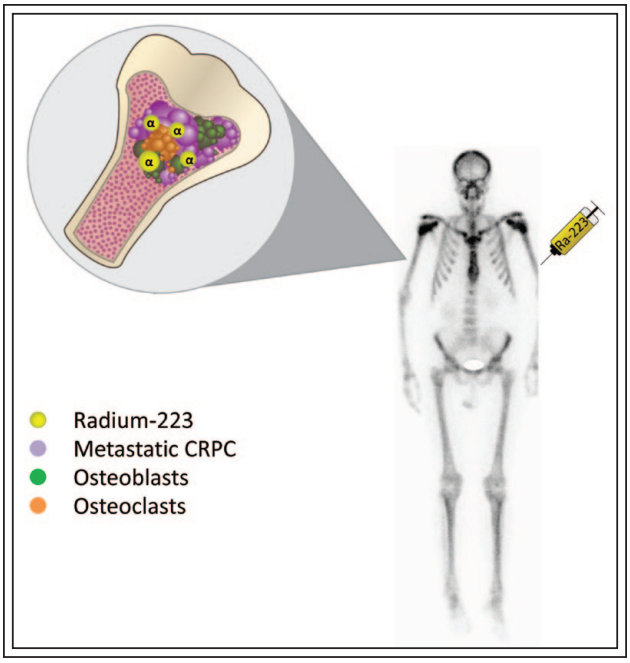

Figure 1. Overview schematic of radium 223 mechanism of action.

The current radiopharmaceutical agents used against metastatic prostate cancer include strontium-89, samarium-153, rhenium-186, and radium 223. The physical characteristics of these agents are shown in Table 1. Multiple randomized controlled trials have been conducted with these agents for the management of prostate cancer patients with bone metastases.[17-33] Historically, primary outcomes included pain response, decrease in analgesic consumption, and quality-of-life. Radium 223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone-metastatic CRPC.[32]

This review will provide an overview of radiopharmaceuticals in prostate cancer with a focus on the mechanism of action of alpha and beta emitters. Further, it will highlight radium 223, Figure 1, including the indications based on the clinical trials,[29-33] administration, and strategies to manage the side effects of therapy.

Alpha, beta, and gamma emission

Radioactive decay, also known as radioactivity, is the process by which the nucleus of an unstable isotope loses energy through emission of particles of ionizing radiation. Radiation may be emitted in the form of an alpha (α) or beta (β) particle, a gamma (γ) ray or any combination. An α particle consist of two protons and two neutrons, a β particle is a high energy electron, while a γ ray is described as ionizing electromagnetic radiation. Each type of radiation has different advantages and disadvantages.

Alpha particles have the shortest range of these particle types, resulting in a dense deposition of energy close to the origin of the particle emission. Thus, α particles provide more dense ionizing radiation over a shorter distance < 100 μm (approximately 2-10 tumor cell diameters), resulting in the induction of DNA double-strand breaks with minimized myelotoxicity.[30] Alpha particles can be stopped by a sheet of paper, eliminating the need for any radiation shielding. Radium 223, as an alpha emitter, administered intravenously requires no radiation safety precautions

such as particular sleeping arrangements, limited time or specified distance from children or pregnant women.

In contrast to alpha particles, β emitters have track lengths that consist of up to a few millimeters which results in collateral bone marrow toxicity. Further, β particles require increased shielding as they can penetrate paper, but can be stopped by a thin layer of high Z material depending on the energy of the particle. Consequently, β emitters are often stored in lead-shielded containers to reduce radiation exposure; however patients still have little to no radiation precautions or restrictions.

Bone physiology and cancer

Bone homeostasis is a complex cellular process consisting of osteoblasts, which function in bone production and mineralization, and osteoclasts, which function in bone resorption.[34] Bone matrix is initially organic osteoid whose calcium hydroxyapatite mineralization occurs through alkaline phosphatase function. Cancer cells cause inappropriate osteoblastic or osteoclastic activity resulting in either blastic or lytic lesions respectively.[35] Blastic function can be monitored clinically via alkaline phosphatase levels. The current radiopharmaceuticals either mimic calcium (radium, strontium) or bind as an attachment to the hydroxyapatite components of the bone matrix (samarium, rhenium).[36]

Current radiopharmaceuticals: indications and benefits

Strontium-89

Strontium-89 is a calcium analog approved by the FDA in 1993 for the treatment of painful bone metastases.[37] It decays as a pure β emitter with only 0.01% γ emission and is incorporated into bone when intravenously administered. Strontium has a 10-fold uptake increase into bone containing metastatic tumor as compared to normal healthy bone.[38] There have been multiple randomized trials evaluating the efficacy of strontium-89 with most focused on pain reduction. However, inter-study comparison is limited given the various grading systems utilized. A systematic review of strontium-89 reported a complete pain response varying from 8% to 77% with a partial pain response in 44% of patients.[39] In addition, use of analgesic decreased by 70%-80% and duration of clinical response varied from 3-6 months. The common toxicities include leukopenia, thrombocytopenia with nadir in counts occurring approximately 4-8 weeks post injection.

Samarium-153 lexidronam

Samarium-153, a β emitter with 28% γ emission, was approved by the FDA in the 1997 for the treatment of bone metastases. The radionuclide has a half-life of 1.9 days and is complexed with ethylene diamine tetramethylene phosphonate (EDTMP) which rapidly localizes to bone in association with hydroxyapatite. It has a five times greater affinity to tumor than normal bone. It is delivered intravenously and has a complete renal clearance within 6 hours of administration.[40] Multiple randomized phase III trials have consistently demonstrated an improvement in bone pain and reduced analgesic use.[24-26] As with strontium-89, myelosuppresion, particularly thrombocytopenia, is the most common side effect.

Rhenium-186 etidronate

Rhenium-186 hydroxyethylidene diphosphonate (HEDP) a β and γ emitter, has a half-life of 3.7 days. Its γ emission allows for bone metastases localization though imaging, making it both diagnostic and therapeutic. Rhenium has efficacy in pain reduction with thrombocytopenia and leukopenia being the most common toxicities.[27,28]

Comparison of beta emitters

These compounds have been compared in the management of patients with osteoblastic lesions to determine their relative efficacy. While all effective, there was no statistical significance between the various agents in terms of pain palliation, analgesic use, or bone marrow toxicity.[41-43]

Radium 223

Radium 223 was recently approved by the FDA in 2013 for the management of men with metastatic castrate resistant prostate cancer after the publication of a randomized phase III trial which showed an overall survival benefit.[32] Table 2 provides the indications, administration, and strategies to manage side effects. Radium 223, an alpha particle emitter, was originally selected given its half-life (11.4 days) that allowed convenient dosing, safe radon daughter isotope and high skeletal uptake in patients with osteoblastic metastases.[44]

The phase I dose escalation study of radium 223 consisted of 25 breast and prostate cancer patients with osteoblastic lesions who were injected with a single dose of the agent.[30] Pharmacokinetic studies demonstrated that within 24 hours < 1% of administered dose remained in circulation and was predominantly eliminated via the gastrointestinal tract. Pain relief was reported by 52%, 60%, and 56% of patients after either 1, 4, or 8 weeks respectively. Twenty-eight percent of patients

TABLE 2. **Administration and strategies to manage side effects of therapy for radium 223**

Indication	• Radium 223 is indicated for the treatment of patients with castration resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease
Administration	• Radium 223 is administered by slow intravenous injection over 1 minute • Prior to administration, the intravenous access line or cannula should be flushed with isotonic saline
Strategies to manage side effects	
Hematologic	• Hematologic evaluations should be performed at baseline and prior to every injection of radium 223 • Before the first administration ▸ absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L ▸ platelet count should be ≥ 100 x 10^9/L ▸ hemoglobin ≥ 10g/dL • Before subsequent administration ▸ ANC should be ≥ 1 x 10^9/L ▸ platelet count should be ≥ 50 x 10^9/L • If counts do not recover to the above values within 6-8 weeks of administration, despite supportive care, treatment should be discontinued • Supportive care includes transfusions and growth factors • Radium 223 should be discontinued in the event of life threatening complications despite supportive care for bone marrow failure • Patients are instructed to report signs of bleeding or infection
Non-hematologic	• Patients are instructed to remain well hydrated and to monitor oral intake • Patients are instructed to report signs of dehydration, hypovolemia, urinary retention or renal failure/insufficiency • Patients are instructed to follow good hygiene practices for at least 1 week post injection including: ▸ flushing the toilet several times after use ▸ promptly washing soiled clothing separately • Caregivers are instructed to use universal precautions including: ▸ hand washing ▸ using gloves and barrier gowns when handling bodily fluids ▸ patients are instructed to use condoms when sexually active and female partners are instructed to use birth control up to 6 months from last radium 223 injection

did experience a "flare" phenomenon. There was a significant decline in alkaline phosphatase amongst the prostate patient cohort. No dose limiting toxicities (defined as platelets < 20 x 10^9/L, or neutrophils < 0.5 x 10^9/L) were experienced. Myelosuppression was mild and reversible with a nadir 2-4 weeks after drug administration. However, nonhematologic toxicity consisting of transient diarrhea (40% of patients), fatigue (25% of patients), and nausea or vomiting (20% of patients) occurred.

The phase II double blind placebo control trial randomized 64 men with CRPC to receive four intravenous injections of either 50kBq/kg of radium 223 or placebo every 4 weeks. The primary endpoints were change in bone-alkaline phosphatase and time to skeletal related events (SREs).[29,45] At 4 weeks alkaline phosphatases levels were -65% in the radium 223 arm and +9.3% in the placebo arm ($p < 0.0001$). Time to skeletal related events was not statistically significant (14weeks versus 11 weeks, $p = 0.26$). There was a statistically significant change in time to PSA progression of 26 weeks versus 8 weeks and median change in relative PSA (-24% versus +45%). There was a trend to improvement in overall survival (65.3 weeks versus 46.4 weeks, $p = 0.066$), suggesting a potential survival advantage. Hematological toxicity was comparable in the two arms and noted only in the first 4 weeks of treatment with radium 223.

The phase III placebo controlled trial randomized 922 men with symptomatic bone-metastatic CRPC using a 2:1 ratio to receive six injections every 4 weeks of either radium 223 (50 kBq/kg) or placebo.[32] Entry criteria included at least two bone metastases without visceral metastases and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was overall survival, with secondary endpoints of time to first SRE, time to alkaline phosphatase progression, alkaline-phosphatase response, alkaline-phosphatase normalization, time-to-PSA-progression, safety, and quality-of-life. The study was designed with 90% power to detect a hazard ratio for death of 0.76 at 5% significance level. The trial was halted at interim analysis after 809 patients (541 on radium 223 and 268 on placebo) had been randomized. The two arms were well balanced in terms of baseline demographics. At interim analysis, 50% of the patients receiving radium 223 had received all six injections in comparison to 35% of placebo while 21% and 19% were still undergoing therapy. Median survival was significantly increased from 11.2 months to 14.0 months with a hazard ratio of 0.695 in favor of radium 223.

Subset analysis revealed that the survival advantage was primarily seen in those patients who had not previously received docetaxel (hazard ratio 0.611; 95%CI: 0.423-0.883) as opposed to those who had received docetaxel (hazard ratio 0.755; 95%CI: 0.565-1.009) and those with ECOG performance of 0-1 (hazard ratio 0.691; 95%CI: 0.535-0.892) as opposed to those with a score ≥ 2 (hazard ratio 0.731; 95%CI: 0.398-1.343). Use of concurrent bisphosphonate did not impact the survival advantage. In addition, there was significant improvement in median time to SRE (13.6 months versus 8.4 months), time to alkaline phosphatase progression, and time to PSA progression (hazard ratio 0.671) favoring the treatment arm.

Adverse events (AEs) were determined for any man who received > 1 injection in 762 patients. AEs were observed in 88% of the radium 223 patients and 94% of placebo-treated patients. Serious AEs were higher in the placebo group (43% versus 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% versus 20%). Grade 3/4 hematologic toxicities were comparable between the two arms (neutropenia 3% versus 1%, thrombocytopenia 6% versus 2%, anemia 13% versus 13%). Nonhematologic Grade 3/4 toxicities included bone pain (21% versus 26%), nausea (2% in either cohort), diarrhea (2% in either cohort), vomiting (2% in either cohort), fatigue (5% versus 6%), and bone pain (21% versus 26%). A statistically higher percentage of patients had meaningful improvement in quality-of-life with radium 223 over placebo.

Assessment and management

Prior to initiation of radium 223 therapy, baseline hematologic evaluation must be performed at which the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L, platelet count of ≥ 100 x 10^9/L, and hemoglobin ≥ 50 x 10^9/L. Before subsequent treatments, the ANC should be ≥ 1 x 10^9/L, and platelet count of ≥ 50 x 10^9/L. If recovery to the values mentioned above does not occur within 6 to 8 weeks after administration, despite supportive care, radium 223 should be discontinued. Further, in patients with life threatening complications from bone marrow failure should have their treatments halted.

Given, that radium 223 is excreted via the intestinal system, which can manifest as diarrhea, nausea or vomiting, careful monitoring of the patient's oral intake and fluid status is crucial to prevent dehydration. There are no contact restrictions for patients receiving radium 223 and patients are instructed to follow good hygiene during the 6 months of therapy and 1 week after completion of treatment to minimize radiation exposure to household members and caregivers.

Future directions

Radium 223 is the first radiopharmaceutical to provide a prolongation in overall survival in men with castration resistant prostate cancer. The safety profile of radium 223 is encouraging, in comparison to the β emitters, which may allow for increased dosing (phase I study planned), integration with myelosuppressive chemotherapy (NCT01106352, phase I/IIa study of safety and efficacy of radium 223 with docetaxel in patients with bone metastasis from castration resistant prostate cancer), or novel AR targeting agents (phase I study planned with enzalutamide and abiraterone acetate). The long term safety data of radium 223 are still unknown and are of particular importance when considering integration of this agent in the setting of non-metastatic or micro-metastatic disease especially in terms of potential secondary malignancy. However, this agent provides another beacon of hope in the management of this disease.

Disclosure

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