Radium-223 in Bone-Metastatic Prostate Cancer: Current Data and Future Prospects

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This article will describe the historic background of Ra-223; outline the clinical studies which led to phase III trials of this agent; highlight key results of these phase III studies; and explore possible future directions for use of Ra-223 and other alpha particles—both in prostate cancer and for management of other diseases.

History

Radium (Ra) and polonium (Po) were first described by Marie and Pierre Curie in 1898 while investigating the radioactive properties of a complex ore, “pitchblende,” which had radioactive emissions in excess of that explainable by the uranium content. They won the Nobel prize in physics in 1903 along with Henri Becquerel “in recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel”.[1] Marie Curie then went on to isolate and purify pure metallic Ra and received the 1911 Nobel prize in chemistry “in recognition of her services to the advancement of chemistry by the discovery of the elements Ra and Po, by the isolation of Ra and the study of the nature and compounds of this remarkable element”.[2] These discoveries set off a scientific odyssey that continues over a century later. Interestingly, sporadic medical use of Ra dates to the early 20th century, but its intravenous use as an anticancer agent is recent.

Radiobiology and Physics

The target of the intravenous bone-targeting radiopharmaceuticals such as Ra-223 and strontium-89 (Sr-89) is hydroxyapatite (Ca5[PO4]3OH), which is an essential and primary component of the inorganic bone matrix. In an osteoblastic metastatic lesion, the cancer cells are mixed in with hydroxyapatite, which is enriched in areas of newly formed bone.[3] Ra, barium (Ba), Sr, and calcium (Ca) are all elemental chemicals in the alkaline earth metal family on the periodic table, and each will localize to areas of osteoblastic metastases. Ra-226, which has a half-life of 1,590 years, is the most common naturally occurring isotope of Ra, however Ra-223 is the most useful for medical therapeutics due to its half-life of only 11.4 days. Although present naturally in small amounts, Ra-223 is manufactured for medicinal purposes by neutron bombardment of Ra-226. Ra-223 decays to a stable isotope of lead (Pb-207) after emitting four alpha particles through the following decay chain: Ra-223 (t½ = 11.4 days) to Rn-219 (radon) (t½ = 3.96 seconds) to Po-215 (t½ = 1.78 milliseconds) to Bi-211 (lead) (t½ = 6.1 minutes) to Bi-211 (bismuth) (t½ = 2.17 minutes) to Th-207 (thallium) (t½ = 4.77 minutes) to Pb-207 (stable).[4] Table 1 summarizes the details of Ra-223 decay.

Ra-223 is the first alpha emitter approved by the US Food and Drug Administration (FDA). The alpha particle consists of two protons and two neutrons, making it much larger than its decay cousins, the beta particle (electron) and gamma particle (photon), with a relative mass approximately 7,300 times greater than the beta particle. The beta particle is much faster than the alpha particle, with velocities around 90% of the speed of light compared with the velocity of 10% of the speed of light attained by the alpha particle.[5] The energy of the alpha particle is much higher, however, with initial energies ranging from 3–8 MeV compared with 0.01–2.5 MeV for various beta particles. The amount of energy that is transferred to a material by an ionizing particle is referred to as the linear energy transfer (LET). The LET of the alpha particle is between 100- and 1,000-fold higher than that of the beta particle, ranging from 25 to 230 keV/µm. Alpha particles have a higher energy level and a higher LET than beta particles, but the tissue penetration is only measured in microns—compared with millimeters for typical high-energy beta emission. Thus, Ra-223 delivers high-energy radiation...
to a small region, localizing the radiation to tumor-enriched osteoblastic areas as opposed to normal areas of bone or areas of marrow containing hematopoietic precursors. Ra-223 is dosed in the units kBq/kg of body weight; the Becquerel (Bq) is defined as the activity of a quantity of radioactive material in which one nucleus decays per second.

**Alkaline Phosphatase as a Biomarker**

As a bone-targeted radiopharmaceutical, Ra-223 has a clear and measurable impact on serum bone alkaline phosphatase, which is a secretory product of the osteoblasts. Thus, declines in circulating alkaline phosphatase (derived from osteoblasts) serve as a biomarker for Ra-223 action in bone, just as elevations in bone alkaline phosphatase serve as a biomarker for osteoblastic bone involvement. In a small randomized phase II trial, the median relative change in bone alkaline phosphatase 4 weeks after the final study injection was −65.6% in the Ra-223 group compared with −9.3% in the placebo group.[6] The prostate-specific antigen (PSA) response was not particularly brisk, however, with median relative change in PSA level of −23% in the Ra-223 group and 44.9% in the placebo group. Additionally, 35% of patients (11 of 31) had a confirmed > 50% reduction in PSA level with Ra-223, compared with 18% (5 of 28) in the placebo group. This difference was not significant ($P = .153$).

Similar results for alkaline phosphatase were seen in the phase III ALSYMPCA trial.[7] More patients in the Ra-223 group had normalization of the alkaline phosphatase level compared with the placebo group (34% vs 1%), and there was an increase in the time to first rise in the alkaline phosphatase level (7.4 vs 3.8 mo; hazard ratio [HR] = 0.17; $P < .001$) in these patients. Again it was demonstrated that Ra-223 does not seem to generate much of a PSA response, as only 16% of patients had a ≥ 30% reduction in the PSA level at 12 weeks. Thus, it is clear that alkaline phosphatase serves as a pharmacodynamic biomarker for Ra-223 in patients with prostate cancer metastatic to bone.

**Radiopharmaceuticals in Bone-Metastatic Prostate Cancer**

Sm-153 lexidronam (samarium) and Sr-89 are other radionuclides studied in the treatment of bone metastases from prostate cancer. Their effects have been found to be mainly palliative.[8,9] In a study by Tu et al, 72 patients with prostate cancer metastatic to bone who responded to induction chemotherapy were randomized to receive doxorubicin with or without Sr-89.[10] Although the study was limited by sample size and the use of older chemotherapy regimens, the results showed a survival advantage with use of Sr-89 (27.7 months in the doxorubicin + Sr-89 group vs 16.8 months in the doxorubicin-only group). This was the first study to suggest that radionuclides can affect the natural course of the disease, supporting the need for further research in this field.

**Phase I Studies**

In 2005, Nilsson et al studied the safety of Ra-223.[4] A total of 15 patients with prostate cancer and 10 patients with breast cancer, all with bone metastases, were given a single intravenous injection of Ra-223 in five different doses (46, 93, 163, 213, and 250 kBq/kg) and followed for 8 weeks. Ra-223 accumulated in the areas of bone metastases. Weekly blood work showed mild and reversible myelosuppression, with a nadir of 2–4 weeks. Transient gastrointestinal side effects were observed, especially with high dosages, as well as decreases in serum alkaline phosphatase and PSA in some patients. Ra-223 was cleared rapidly from the blood, mainly through fecal excretion. Pain palliation was achieved in some patients, although in a nonrandomized setting the meanings of pain decreases are not clear.

Another phase I trial studied the pharmacokinetics and pharmacodynamics of Ra-223.[11] A total of 10 patients with castration-resistant prostate cancer and bone metastases received a single dose of either 50, 100, or 200 kBq/kg; subsequently 6 patients received an additional dose of 50 kBq/kg. After intravenous administration, Ra-223 was rapidly eliminated from plasma into tissues, mainly bones and small bowel, with minimal biliary and renal excretion. Post-infusion, the proportion in plasma was 2% of the administered dose at 4 hours and 0.55% at 24 hours. In contrast, a median of 52% of the dose was present in the bowels by 24 hours after infusion, confirming fecal elimination of the majority of the administered dose. Urinary excretion accounted for 4% of the total administered dose. Bone uptake was persistent throughout the observation period of 7 days (and lasted up to 14 days in one patient). Declines in serum bone-turnover markers (alkaline phosphatase and N-telopeptides) were seen in the majority of patients. Ra-223 was well tolerated, with no
dose-limiting toxicity observed even at the 200 kBq/kg dose.

Phase II Studies

In a randomized, multicenter study by Nilsson et al, 64 patients with castration-resistant prostate cancer and painful bone metastases requiring external beam radiation therapy were assigned to receive four infusions of Ra-223 at 50 kBq/kg or placebo at 4-week intervals.[6] Serum bone turnover markers, including bone alkaline phosphatase (primary endpoint), decreased significantly in the Ra-223 group compared with placebo. The time to first skeletal-related event (SRE) was statistically similar in the two groups (second primary endpoint). There was a trend toward a survival advantage (65 weeks vs 46 weeks; \( P = .056 \)). Ra-223 was safe and very well tolerated, with no severe myleosuppression. No secondary malignancies were reported in a 2-year follow-up report of this study.[12]

Ra-223 showed a good safety profile across all doses in a randomized, dose-response, phase II trial.[13] A total of 100 patients with castration-resistant prostate cancer and painful bone metastases were each treated with a single infusion of Ra-223 at 5, 25, 50, or 100 kBq/kg. Pain was assessed by use of a visual analog scale and analgesic requirements. Patients were allowed to continue other cancer treatments. A statistically significant dose response was noted as early as week 2. At week 8, pain responses were more common with higher doses, as 40% of patients receiving 5-kBq/kg doses had a pain index ≤ 4, compared with 71% response in patients in the 100-kBq/kg arm. Of responders, 30% in the 5-kBq/kg group compared with 52% of patients in the 100-kBq/kg group reached pain index levels of 1–2, correlating with complete or marked pain response. Mean pain relief duration ranged between 28 and 44 days. Again, it is important to keep in mind the limitations of a nonrandomized study involving pain assessments.

Another dose-finding phase II trial included 122 patients with castration-resistant prostate cancer metastatic to bone.[14] They were assigned to receive infusions of Ra-223 at 25, 50, or 80 kBq/kg every 6 weeks for a total of three infusions. There was a statistically significant dose-response relationship for PSA and alkaline phosphatase. PSA decline of ≥ 50% was seen in 0% of the patients in the 25-kBq/kg group, in 6% in the 50-kBq/kg group, and in 13% in the 80-kBq/kg group (\( P = .0297 \)). Lower doses were associated with lower rates of alkaline phosphatase decline, and there was a plateau at the higher doses (16%, 67%, and 66% respectively; \( P < .0001 \)). SREs were similar between the treatment groups. Once again, Ra-223 was well tolerated. The most common adverse events were gastrointestinal and hematologic, and were mainly grade 1/2 when present.

Phase III Study

ALSYMPCA was an international, multicenter, randomized, double-blind, placebo-controlled phase III study.[7] A total of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases who received docetaxel, were unfit to receive docetaxel, or declined docetaxel were assigned in a 2:1 ratio to receive Ra-223 at 50 kBq/kg intravenously every 4 weeks for six doses, or to receive placebo in addition to the best standard of care. Best standard of care included nonexperimental hormonal therapies such as bicalutamide, dexamethasone, and flutamide, as well as bisphosphonates and external beam radiation therapy. Patients with visceral disease and lymphadenopathy > 3 cm in short axis diameter were excluded.

Several aspects of the inclusion/exclusion criteria are worth mentioning. The case report form did not distinguish between patients who refused docetaxel and those who were unfit for docetaxel; therefore, the group without prior docetaxel treatment was a heterogeneous group. Further, there was no clear definition of “unfit for docetaxel”; this was a physician judgment rather than an assessment based on protocol-specified criteria. The issue of “symptomatic” is also worthy of discussion. Although many of the patients were being treated with opiates (56%), a substantial minority (44%) were not. The protocol allowed patients taking regular acetaminophen or nonsteroidal anti-inflammatory drugs to be designated as symptomatic.

The primary endpoint was overall survival (OS); various secondary endpoints included time to first symptomatic skeletal events (SSE), time to alkaline phosphatase increase, and time to PSA progression. SSEs consisted of the need for external beam radiation or surgery to bone, spinal cord compression, and/or pathologic fractures. Unlike studies with zolendronate and denosumab, there were no prespecified skeletal surveys or other radiographic imaging procedures; thus, all pathologic fractures were clinically detected and not simply radiographic events.

At the prespecified interim analysis, median OS was 14.0 months for patients treated with Ra-223 vs 11.2 months for those randomized to placebo (HR = 0.70; 95% confidence interval [CI], 0.55–0.88;
two-sided \( P = .002 \). The updated analysis performed after the initial interim analysis but before crossover reported a median OS of 14.9 months for the Ra-223 group compared with 11.3 months for the placebo group (HR = 0.70; 95% CI, 0.58–0.83; \( P < .001 \)). Importantly both the “prior docetaxel” group (HR = 0.71; 95% CI, 0.56–0.89) and the “no prior docetaxel” group (HR = 0.74; 95% CI, 0.56–0.99) had improved survival after treatment with Ra-223.

Secondary endpoints were met as well. Median time to first SSE was 15.6 months with Ra-223 compared with 9.8 months with placebo (HR = 0.66; 95% CI, 0.52–0.83; \( P < .001 \)). Time to increase in total alkaline phosphatase level and time to PSA progression were also significantly prolonged in the Ra-223 group. Furthermore, the rates of alkaline phosphatase response and PSA response (defined as ≥ 30% reduction from baseline) were significantly higher in the Ra-223 group. Table 2 summarizes primary and secondary endpoints.

Overall, in the Ra-223 arm had fewer adverse events than those in the placebo arm, however more diarrhea was noted in the Ra-223 group (25%, compared with 15% in the placebo group) but only 2% of the events in each arm were grade 3. Nausea was the second most common reported adverse event after bone pain, but its frequency was similar in both groups (36% vs 35%). Anemia was the most frequent hematologic adverse event, and was also seen equally in both groups (31%). Thrombocytopenia was more common in the Ra-223 group (12% vs 6% in the placebo group). Grade 3–5 thrombocytopenia occurred in 7% of patients in the Ra-223 group, compared with 3% in the placebo group. Neutropenia was rare in both groups (3% in the group treated with Ra-223 vs 1% in the placebo group). Prior docetaxel treatments were associated with more significant rates of adverse hematologic events.

A complete analysis of SSEs was published separately.[15] Ra-223 significantly prolonged the time to first SSE. It statistically significantly reduced the risk of external beam radiation therapy for bone pain and spinal cord compression, the two most common categories of SSEs. The risks of symptomatic pathologic bone fracture and the need for tumor-related orthopedic intervention were not statistically significantly different between the two groups. The effects of Ra-223 on SSEs were consistent irrespective of prior docetaxel use, baseline alkaline phosphatase level, or use of bisphosphonates. The multivariate analysis also indicated that bisphosphonate use (predominantly zoledronate) reduced the SSE rate independent of Ra-223. Table 3 summarizes the data regarding SSEs from the ALSYMPCA trial.

**Context and Future Potential**

Ra-223 is now FDA-approved for men with symptomatic bone metastases and castration-resistant prostate cancer. Many other agents are also approved in a similar therapeutic space, and treatment options currently include enzalutamide, abiraterone, docetaxel, and (to some extent) sipuleucel-T.[16] None of the new agents have been compared with one another, and no comparative trials of these agents are ongoing. For those metastatic castration-resistant prostate cancer patients with osteoblastic metastases and no visceral metastases, Ra-223 should be considered as one of the options for routine clinical care. Given that it was developed in an era without abiraterone or enzalutamide, the relationship between Ra-223 and these agents has yet to be defined. For patients with a high burden of soft tissue disease or visceral disease, Ra-223 may be viewed as poor therapeutic choice, whereas for those with a high burden of bone-metastatic disease, Ra-223 may be viewed as a better choice.

Little data exist for Ra-223 in terms of sequencing or concomitant use with the newer agents approved in the past 5 years, such as abiraterone, enzalutamide, cabazitaxel, or sipuleucel-T. There is no reason to believe that there would be safety issues regarding concomitant use of abiraterone or enzalutamide with Ra-223, and in fact, recent preliminary data suggest this is the case.[17] Whether or not there are additive effects or synergy between Ra-223 and the newer agents is a question being addressed by newer clinical trials. Specifically, large trials will investigate abiraterone/prednisone with or without Ra-223, as well as enzalutamide with or without Ra-223. The rationale for these trials is built on the facts that the mechanisms of action and the adverse event profiles of these treatments are distinct, and that various clinical and preclinical models indicate that hormonal therapies given in combination with radiation are more effective than either approach alone.

The use of Ra-223 in combination with docetaxel has been reported; while these agents clearly can be administered in various ways, the dosages of each agent must be modified, and use of docetaxel and Ra-223 together outside the setting of a clinical trial is not advised.[18]

The question of optimal dose and duration of Ra-223 has not been addressed. The q4wk dosing for a
total of six doses in the ALSYMPCA trial was effective in prolonging survival, but no published studies compare six doses vs treatment with more than six doses. It was observed that the safety profile of Ra-223 was excellent. Perhaps there is a more intense or prolonged dosing plan that would represent a more optimal regimen. Such questions can only be answered by additional clinical trials.

If Ra-223 is effective for patients with castration-resistant bone-metastatic disease, what about newly diagnosed patients with bone-metastatic disease? Additional trials are being designed to address this issue. It has been fundamentally established in many studies that hormonal therapy and external beam radiation therapy are important (with a potentially synergistic therapeutic effect) when given together in patients with localized disease.[19] In many ways, the proposed Ra-223 studies in hormone-sensitive disease (and the administration of Ra-223 in combination with agents such as abiraterone/prednisone or enzalutamide) are extensions of this concept.

Intermediate clinical endpoints for use in studies of Ra-223 are under discussion and evaluation. The effects on both conventional bone scan imaging and PSA effects in prostate cancer patients do not fully reflect the activity of Ra-223, and trials dependent on those endpoints would likely have terminated development prematurely. The serum alkaline phosphatase endpoint needs further exploration and validation as a predictor of survival, but this simple measurement has previously been linked to survival in studies with agents such as docetaxel.[20]

The relative lack of PSA effects with Ra-223–based therapy, despite a survival improvement, is intriguing. The strong alkaline phosphatase effects are compatible with a bone stromal effect out of proportion to the direct antitumor effect. It has long been known that there is a “vicious cycle” of interactions between the bone and tumor, a cycle that results in positive feedback interaction between tumor cells and their microenvironment.[21] It is conceptually possible, but hard to prove, that Ra-223 effects are predominantly mediated by radiation of the microenvironment rather than being direct tumor effects.

Many patients beside prostate cancer patients have bone metastases, and the mechanism of action of Ra-223 is such that almost any osteoblastic bone-forming tumor would potentially be susceptible to treatment with this agent. Trials in other tumors are being conducted, and overviews on this topic have been published.[3] Osteosarcoma is a bone-forming tissue that might be a potentially appropriate target for Ra-223 isotopes. Breast cancer trials are ongoing.

Multiple myeloma is an osteolytic tumor when it affects the bone, and most would consider it to be a poor Ra-223 target; interestingly, however, after successful treatment with agents such as bortezomib, the bone healing that occurs is associated with increased bone formation, a rise in alkaline phosphatase levels, and increased Ra-223 uptake on bone scans. All of these parameters are associated with osteoid formation and the deposition of hydroxyapatite. Of note, the bone-seeking radiopharmaceutical Sm-153 lexidronam has been used as a salvage therapy with some success in multiple myeloma.[22] Given that conventional bone scans can readily detect areas of osteoblastic activity, these scans could also potentially serve as a predictive biomarker for Ra-223 action.

Currently, alpha particle therapy is limited to one agent and one disease. Given the potent and desirable properties of alpha particles with regard to the induction of DNA strand breaks, one can readily envision targeted alphas being used in many diseases. Although targeted radiopharmaceuticals such as I-131 tositumomab and Y-90 ibritumomab have been commercial failures, they are scientific successes. More work in the targeted delivery of isotopes needs to be performed and in our opinion represents a promising area for additional therapeutic advances.

**Financial Disclosure:** Dr. Sartor is an investigator and consultant for Bayer. The other authors have no significant financial interest or relationship with the manufacturers of any products or providers of any service mentioned in this article.
Table 3: Summary of Symptomatic Skeletal Events (SSEs) From the ALSYMP...

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