Radium-223 Chloride: Extending Life in Prostate Cancer Patients by Treating Bone Metastases

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Abstract
The treatment scope for patients with metastatic castrate-resistant prostate cancer (mCRPC) is rapidly expanding. On May 15, 2013, the U.S. Food and Drug Administration (FDA) approved radium-223 chloride (²²³RaCl₂) for the treatment of mCRPC patients whose metastases are limited to the bones. Radium-223 is an α-emitting alkali earth metal ion, which, similar to calcium ions, accumulates in the bone. In a phase III study (ALSYMPCA), mCRPC patients with bone metastases received best standard-of-care treatment with placebo or ²²³RaCl₂. At a prespecified interim analysis, the primary endpoint of median overall survival was significantly extended by 3.6 months in patients treated with radium-223 compared with placebo (P < 0.001). The radioisotope was well tolerated and gave limited bone marrow suppression. ²²³RaCl₂ is the first bone-targeting antitumor therapy that received FDA approval based on a significant extended median overall survival. Further studies are required to optimize its dosing and to confirm its efficacy and safety in cancer patients. Clin Cancer Res; 19(21); 5822–7. ©2013 AACR.

Introduction
Prostate cancer is the most prevalent and second deadliest cancer in men in the United States and Europe (1). Most morbidity and virtually all mortality from prostate cancer occur once the tumor has become metastatic and castrate-resistant (mCRPC; ref. 2). Therefore, research aimed at the development of novel therapies for prostate cancer has primarily focused on this patient group. Although a decade ago no therapy existed with a proven significant benefit on the median overall survival of mCRPC patients, patients now have the options to be treated with multiple life-extending therapies. These therapies consist of agents that selectively target the androgen pathway (abiraterone acetate, enzalutamide) and taxanes (docetaxel, cabazitaxel), which target microtubules (3–8). Furthermore, the immunotherapy sipuleucel-T has been approved for its use in asymptomatic or minimally symptomatic mCRPC patients (9, 10).

Prostate cancer primarily metastasizes to the bone (11). Bone metastases may lead to severe morbidity, such as bone marrow failure, pathological fractures, and spinal cord compression, reducing quality of life and potentially resulting in death (12, 13). Hence, specific treatment of bone metastases may significantly lower the burden of prostate cancer disease (14, 15). Multiple agents have been approved by the US Food and Drug Administration (FDA) for the palliative treatment of bone metastases in mCRPC patients, such as external beam radiotherapy and the α-emitting radiopharmaceuticals strontium-89 (1.5–2.2 MBq/kg) and samarium-153 (37 MBq/kg; Table 1). Such therapies result in symptomatic relief in more than half of patients (16, 17). However, the duration of response is limited; the effect of these treatments on overall survival has not been studied. Moreover, as surrounding tissue, including the bone marrow, can be damaged as well, significant adverse events such as bone marrow failure may occur in treated patients.

On May 15, 2013, the FDA approved radium-223 chloride (²²³RaCl₂; Xofigo, previously named alpharadin) for the treatment of bone metastases in mCRPC patients based on interim results from a phase III randomized clinical trial, the ALSYMPCA study (Alpharadin in the Treatment of Patients with Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer). This marks the first FDA-approved radionuclide that has been shown to extend overall survival in mCRPC patients in a phase III study. In this perspective article, we discuss the (pre-)clinical development of ²²³RaCl₂, focusing primarily on the most recent results from the ALSYMPCA study. Subsequently, we discuss the FDA approval and future implications this approval may have in clinical practice.

Radium-223 chloride
²²³RaCl₂ is a water-soluble radium salt. In ionic form, radium accumulates in bones at areas with increased bone turnover because of its chemical similarity to calcium ions; both are alkaline earth metals (18, 19). Radium-223 is an α-emitting radioisotope that decays via 7 daughter nuclides before it stabilizes as lead-207 (Fig. 1). During the decay
of each radium-223 isotope, 4 α-particles and 2 electrons (β-particles) are emitted (Table 1). Both α- and β-irradiation can induce local therapy by inducing damage in the surrounding tissue. Because of the size and high energy of α-particles, these particles are highly effective in inducing double-strand breaks in DNA within 100 μm. The half-life
of radium-223 is 11.4 days; the half-lives of its daughter nuclides range from seconds to minutes. These daughter nuclides do not have a chemical similarity to calcium ions. Therefore, the half-lives of radon-219 (4.0 seconds), bismuth-211 (2.1 minutes), and thallium-207 (4.8 minutes) seem to be long enough to allow diffusion from the primary accumulation site.

**Early preclinical and clinical studies**

In a preclinical study, nude rats with MT-1 human breast cancer xenografts were treated with pamidronate, a bisphosphonate used against skeletal complications of cancer, with or without radium-223 (18). Although all rats treated with pamidronate only had to be sacrificed within 21 days, 40% of rats treated with pamidronate and radium-223 at 10 or 30 kBq survived beyond 50 days. Compared with β-emitting particles such as strontium-89, rodents treated with radium-223 showed no signs of bone marrow suppression or other toxicities (20).

In a phase I study, $^{223}$RaCl$_2$ was administered to 15 prostate and 10 breast cancer patients with bone metastases (21). Patients received a single i.v. injection of radium-223 with activities up to 250 kBq/kg. More than 50% of patients reported pain relief, although toxicity was low. Grade 3 leucopenia occurred in 3 patients, and the maximum-tolerated dose (MTD) was not established. Radium-223 accumulated in the skeleton, particularly in sites with metastases. In the blood, radioactivity levels diminished quickly: to 6% after 1 hour and to <1% 24 hours after injection. Recently, similar findings were presented from another phase I study (22). In this study, 10 mCRPC patients received radium-223 up to 200 kBq/kg, among which 6 patients received a second dose of 50 kBq/kg. The MTD was again not established, and radium-223 was rapidly cleared from the blood, primarily into the small bowel.

A subsequent phase II study compared treatment of 50 kBq/kg radium-223 with placebo treatment in 64 CRPC patients with painful bone metastases (23, 24). The median time to skeletal-related event was 14 weeks in the radium-223–treated group versus 11 weeks in patients treated with placebo ($P = 0.257$; ref. 23). Low toxicity of radium-223 was confirmed in this phase II study. None of the 33 radium-223–treated patients discontinued treatment because of adverse events. Grades 3 and 4 adverse events occurred in 3 (9.1%) and 0 (0%) radium-223–treated patients and in 1 (3.3%) and 1 (3.3%) placebo-treated patients, respectively. Severe nonhematologic adverse events occurred in 3 (9.1%) radium-223–treated patients and in 5 (16.7%) placebo-treated patients. In a follow-up report, 24 months after the first injection of study medication, no long-term treatment-related toxicity was noted (24). The median overall survival was 65 weeks in the radium-223–treated group, and 46 weeks in the placebo-treated group ($P = 0.056$).

**ALSYMPCA**

The ALSYMPCA phase III study was initiated in 2008, comparing the efficacy and safety of $^{223}$RaCl$_2$ with that of placebo (a saline injection) in patients with symptomatic CRPC with bone metastases (25). Patients needed to have at least 2 bone metastases, diagnosed by bone scintigraphy. Patients were eligible if they had previously received docetaxel, if they were unfit for docetaxel, if they declined therapy with docetaxel, or if docetaxel was not available. Patients were excluded if they had visceral metastases. Patients received an i.v. injection (50 kBq/kg) every 4 weeks for a maximum of 6 cycles.

In total, 921 patients were included at 135 study locations worldwide, primarily in North America, Australia, and Europe (26). Six hundred fourteen patients received radium-223, of whom 352 had received docetaxel before radium-223 treatment (57.3%). In the placebo group, a similar percentage had received prior docetaxel [56.6% (174 patients)]. Other baseline characteristics, such as age, disease stage, and baseline opioid use, were similar between the two treatment groups as well (25).

The primary endpoint of the ALSYMPCA study was overall survival. In general, the median overall survival in patients treated with radium-223 was extended by 3.6 months compared with placebo-treated patients ($P < 0.001$; ref. 25). For patients who had received docetaxel before participation in the ALSYMPCA trial, the median overall survival was 14.4 months in radium-223–treated patients versus 11.3 months in placebo-treated patients [HR = 0.71; 95% confidence interval (CI), 0.56–0.90; ref. 28]. For patients who had not received prior docetaxel, the median overall survival durations were 16.1 months and 11.5 months, respectively (HR = 0.74; 95% CI, 0.56–0.90; ref. 25).

The key secondary endpoint in the ALSYMPCA trial was time to symptomatic skeletal event (SSE), defined as the time to first use of external-beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fractures, spinal cord compression, or tumor-related orthopedic surgery. Imaging to assess for skeletal events was only performed when clinically indicated to avoid registration of asymptomatic fractures. Time to SSE was 15.6 months in radium-223–treated patients versus 9.8 months in the placebo-treated group ($P < 0.001$; HR = 0.66; 95% CI, 0.52–0.83; ref. 25). Time to initial opioid use and time to external beam radiotherapy were both increased in patients treated with radium-223 (HR = 0.670 and 0.621, respectively; ref. 27). Sixteen and 24 weeks after initiation of radium-223 treatment, patients had significantly less pain compared with baseline ($P < 0.001$ and 0.001, respectively).

Further analysis revealed that an increase in the levels of total alkaline phosphatase was associated with an increased risk for death in the patient population studied in the ALSYMPCA trial ($P < 0.0001$; ref. 28). In patients treated with radium-223, a ≥30% reduction in total alkaline phosphatase levels compared with the baseline was seen in 47% of patients versus 3% of placebo-treated patients (25).

In general, radium-223 was well tolerated by patients, with grade 3 or 4 adverse events occurring more frequently in the placebo-treated group (62%) than in patients treated
with radium-223 (56%). The only reported nonhematologic grade ≥3 adverse events that occurred more frequently in the radium-223–treated patient group were anorexia (2% versus 1%) and a decreased appetite (2 patients vs. 0 patients). Comparing grade ≥3 hematologic adverse events in the radium-223–treated group to the placebo group, anemia occurred in 13% and 13%, neutropenia in 3% and 1%, and thrombocytopenia in 6% and 2%, respectively (25). Analysis of these hematologic adverse events revealed that a baseline total alkaline phosphatase of ≥220 U/L strongly predicted anemia (29). Apart from the use of radium-223 instead of placebo, other baseline predictors for neutropenia and thrombocytopenia were prior docetaxel use and more than 6 bone metastases. However, prior external beam radiotherapy to the bone was associated with a decrease in anemia and neutropenia.

FDA approval

Interim results from the ALSYMPCA phase III clinical trial led to approval of radium-223 by the FDA for the treatment of mCRPC patients who have symptomatic bone metastases and no visceral metastases. It was recommended to be administered at 50 kBq/kg every 4 weeks with a maximum of 6 doses, which is equal to the treatment regimen in the ALSYMPCA trial. This approval makes radium-223 the first agent available for mCRPC patients that significantly increases overall survival by exclusively treating bone metastases.

Despite its decision to approve radium-223, the FDA required four additional studies, besides final analysis of ALSYMPCA study results (30). Noncompliance to this decision, or negative results, could result in the FDA revoking the approval.

As mentioned previously, no MTD for radium-223 has been established (21, 22). Results from phase I studies suggested concentrations higher than 50 kBq/kg could be administered to patients with relatively few changes in the toxicity profile of the agent. Two recent phase II studies confirm that treatment up to 100 kBq/kg has similar toxicities compared with radium-223 at 50 kBq/kg, although the efficacy of radium-223 is increased (31, 32). Therefore, the FDA required a randomized phase II study to further assess the efficacy and safety of radium-223 in CRPC patients with bone metastases at concentrations higher than 50 kBq/kg. If these results suggest a beneficial risk–benefit profile for higher doses, an additional phase III study will be required to confirm the optimal activity level.

The FDA required the company to perform three studies to further assess the safety of radium-223: an observational study in 1,200 CRPC patients with bone metastases, evaluating the long-term safety of radium-223 administered at the recommended dose; a randomized clinical trial in CRPC patients with bone metastases and no visceral metastases to further assess the safety of radium-223, particularly for enhanced assessment of the effect of radium-223 on healthy bone marrow and secondary malignancies, such as acute myeloid lymphoma and myelodysplastic syndrome (33), and finally, an assessment of the short- and long-term safety of a radium-223 rechallenge, for which the company was required to perform a study in which CRPC patients with bone metastases were re-treated with radium-223.

Discussion

With the FDA approval of 223RaCl2 for CRPC patients with symptomatic bone metastases regardless of prior chemotherapy, the treatment scope for mCRPC patients has further expanded. By excluding patients with visceral metastases, the most rational step for oncologists would be to use radium-223 primarily as a first-line therapy in mCRPC patients. That said, a subpopulation may also be eligible for radium-223 treatment as second-line therapy or later.

Considering the results of radium-223 treatment in the robustly designed and well-conducted ALSYMPCA trial, it is expected that the approval and consequently clinical use of radium-223 will expand beyond the United States in the near future. In addition, radium-223 may improve the quality of life and survival for patients with other tumor types who suffer from bone metastases. However, such expansions require additional clinical investigations. Finally, the FDA approval of radium-223 as the first metastasis-targeting agent based on an improved median overall survival confirms that selectively treating metastases may be an effective strategy in patients with advanced solid tumors for whom palliative treatment is the only option, strengthening the development of such agents.

A major limitation of the ALSYMPCA phase III study is that the group of patients selected for this study may not correspond to the patient population in clinical practice that will receive radium-223 treatment. Patients with visceral metastases were excluded from participation in the trial. Considering that β-emitting radionuclides, such as samarium-153, have been shown to induce pain relief in patients with advanced prostate cancer, further research is required to address whether radium-223 provides clinical benefit for patients with visceral metastases (16, 17). Based on the approval of radium-223, physicians may decide to administer this agent to this group of patients as well, although its efficacy has not been proven. Furthermore, patients were excluded from the ALSYMPCA study when docetaxel was available, patients were fit for (and willing to receive) docetaxel treatment and had not received docetaxel before. Nevertheless, the FDA does not exclude this group of patients for radium-223 treatment in its approval letter. Until the required postmarketing studies have been conducted that will indicate whether mCRPC patients eligible for docetaxel treatment will also benefit from radium-223, its clinical benefit in this patient group remains uncertain.

Currently, no long-term follow-up is known for patients in the ALSYMPCA trial, limiting the toxicity profile of the drug. Although the high number of therapeutic emissions in the decay process of radium-223 may yield a strong therapeutic effect, the daughter nuclides, which do not have affinity to the bone, may diffuse throughout the body and cause damage in healthy tissue. Although no bone marrow...
suppression was seen in the short term, it will be important to follow patients over time to ensure that there are no long-term harmful effects from radium-223 treatment. Most of the FDA’s postmarketing requirements therefore focus on drug safety, particularly on the long-term effects of radium-223 treatment and safety of radium-223 rechallenge at a later stage.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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Conception and design: M.D. Wissing, H. Gelderblom
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.D. Wissing
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