High-Linear Energy Transfer Irradiation Targeted to Skeletal Metastases by the α-Emitter ^{223}Ra: Adjuvant or Alternative to Conventional Modalities?

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Abstract The bone-seeking, α-particle-emitting radiopharmaceutical Alpharadin, $^{223}RaCl_2$ (half-life = 11.4 days), is under clinical development as a novel treatment for skeletal metastases from breast and prostate cancer. This article summarizes the current status of preclinical and clinical research on $^{223}RaCl_2$. Potential advantages of ^{223}Ra to that of external beam irradiation and registered β-emitting bone seekers are discussed. Published data of ^{223}Ra dosimetry in mice and a therapeutic study in a skeletal metastases model in nude rats have indicated significant therapeutic potential of bone-seeking α-emitters. This article provides short-term and long-term results from the first clinical single dosage trial. We also present data from a repeated dosage study of five consecutive injections of 50 kBq/kg body weight, once every 3rd week, or two injections of 125 kBq/kg body weight, 6 weeks apart. Furthermore, interim results are described for a randomized phase 2 trial involving 64 patients with hormone-refractory prostate cancer and painful skeletal metastases who received four monthly injections of ^{223}Ra or saline as an adjuvant to external beam radiotherapy. Lastly, we present preliminary dose estimates for ^{223}Ra in humans. Results indicate that repeated dosing is feasible and toxicity is low, and that opportunities are available for combined treatment strategies.

The clinical implications of skeletal metastases are serious. Pain, pathologic fractures, nerve entrapment, bone marrow insufficiency, and hypercalcemia have a devastating effect on patients' quality of life (1–5). Metastases in the vertebrae leading to spinal cord compression may be disastrous (6) and of particular concern in cohorts of cancer patients with a long expected survival (e.g., those with the diagnosis of skeletal spread as the first and sole metastatic event; ref. 7).

Radiotherapy

External beam irradiation relieves pain from single sites of painful skeletal metastases (6, 8–14). However, the lack of tumor-only selectivity limits its clinical usefulness because normal cells within the target volume receive the same radiation dose as the tumor cells. Skeletal metastases are usually multiple and distributed throughout the axial skeleton (15). When larger or multiple fields of irradiation are necessary (such as for multiple metastases in the vertebra and in the pelvis), bone marrow suppression increases and is visualized by a shift from active red to fibrous yellow bone marrow on magnetic resonance imaging in irradiated bones. Hence, wide-field external irradiation in patients with disseminated skeletal metastases is not frequently used and is also associated with significant acute gastrointestinal toxicity (16).

International consensus advocates the standard use of a single fraction (8.0 Gy) in most patients in whom the clinical indication is "pain relief" (8–10). Patients not responding or those with new pain arising at a previously irradiated site should be offered retreatment. Effective palliation may be achieved with localized radiation doses as low as 4.0 Gy (17). In contrast, when the aim is "local tumor control" in patients with solitary bony metastases and long life expectancy or when medullar compression is present, fractionated radiotherapy is advisable (3.0 Gy × ≥10) in selected cases (14). This seems also to be the case in patients with imminent fractures because remineralization is reported to be more favorable after fractionated irradiation (18).

Bone-Seeking Radiopharmaceuticals

Clinical experiences using bone-seeking radiopharmaceuticals have recently been reviewed (19, 20). Treatment with bone-seeking radiopharmaceuticals selectively delivers ionizing radiation to areas of amplified osteoblastic activity and will target multiple metastases simultaneously, symptomatic as well as asymptomatic foci (21). The target is Ca-OH-apatite in the metastasis. Currently, two principal chemical classes of therapeutic bone-seeking radiopharmaceuticals are available—cationic and anionic bone seekers (i.e., calcium analogues and

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phosphonates; refs. 22, 23). In the commercially available formulations, the radioisotopes involved are β-emitters. Strontium-89 dichloride (Metastron, GE Healthcare, Chalfont St. Giles, United Kingdom) is approved in the United States and in most European countries, and more recently, ^{153}Sm-EDTMP (Quadramet, Schering AG, Berlin, Germany and Cytogen Co., Princeton, NJ) has been approved.

Published data indicate that, when using lower dosages aimed for pain palliation, the radiation dose levels to the skeleton may result in relatively few complications in patients with sufficient bone marrow function. On the other hand, associated bone marrow toxicity, often with delayed and unpredictable recovery, generally limits the usefulness of β-emitting radiopharmaceuticals when dosages are increased to deliver potential antitumor radiation levels (23).

Patients may benefit from a single i.v. infusion of 150 MBq (4 mCi) of Metastron [$^{89}SrCl_2$, physical half-life ($t_{1/2}$) of 50.5 days], and pain relief may occur within the first weeks and sometimes lasts for several months (24). Clinical phase 2 studies with ^{89}Sr have shown effective palliation of pain in most patients with metastatic prostate cancer. Initial reports showed palliative responses in up to 75% of the patients, with as many as 25% being able to stop taking analgesics (25, 26). Double-blind studies have compared radioactive and stable strontium and confirmed the therapeutic effect of Metastron. Effective pain palliation was, however, observed in a lower percentage of the patients than reported in the phase 2 trials (27). Conflicting data exist on a possible delay of new metastatic foci when Metastron is given as an adjuvant to external radiotherapy (27, 28). Two studies reported combination treatment with chemotherapy (29, 30).

Bone-seeking radiopharmaceuticals with shorter $t_{1/2}$s, such as ^{153}Sm-EDTMP (^{153}Sm, $t_{1/2}$ of 1.95 days) and $^{186/188}$Re-HEDP (^{186}Re, $t_{1/2}$ of 3.78 days or ^{188}Re, $t_{1/2}$ of 0.71 days), could facilitate more rapid bone marrow recovery (31–35), and repeated dosing seems feasible (36). The cross-irradiation of the bone marrow is, however, an ever-present concern with β-emitters.

Radiobiological Aspects

In contrast to the β-emitters, the α-particle emitters deliver a much more energetic and localized radiation, classified as high-linear energy transfer radiation (37). α-Particles are relatively heavy charged particles (helium nuclei with two positive charges) that produce densely ionizing tracks through tissue. α-Particles deposit a massive amount of energy per unit track length and have short ranges (<100 μm). α-Particle radiation induces predominantly nonreparable DNA double-strand breaks (38). This may be important because patients with skeletal metastases often have chemoresistant disease. In addition, micrometastases with dormant clonogenic tumor cells residing in cell cycle growth phase G_0 may be eliminated by high-linear energy transfer irradiation from α-emitters (37).

α-Emitters are more toxic and mutagenic than β-emitters when comparing effects on single cells. These adverse properties can be compensated for in targeted therapy because of the potential to irradiate much smaller volumes of normal cells when α-emitters are targeted against tumor cells (39). This feature helps treat skeletal metastases because the short α tracks cause smaller dose delivered from the bone surfaces to the bone marrow cells within the bone marrow–containing cavities (40). On the other hand, the spatial distribution of the hydroxyapatite target within an osteoblastic tumor (Fig. 1) would facilitate a volume distribution of the radionuclide and make it less likely that tumor cells evade the α-particles despite the limited track lengths.

Radium as a Targeting Moiety against Skeletal Metastases

Like cationic strontium, cationic radium is a natural bone seeker that has been used for targeting skeletal diseases, such as the use of ^{224}Ra for treating ankylosing spondylitis, characterized by elevated bone synthesis (41). Radium-223 is, in our view, the most promising radium isotope with favorable features for use in targeted radiotherapy. Radium-223 decays ($t_{1/2}$ = 11.4 days) via a chain of short-lived daughter radionuclides to stable lead, producing four α-particles (Table 1). In the decay of ^{223}Ra, 94% of the total decay energy is released as α-particles (Table 2). The noble gas first daughter ^{219}Rn has a $t_{1/2}$ of ~4 seconds, in contrast to the long-lived radon daughters from the other naturally occurring radium isotopes.

Radium-223 can be produced efficiently in large amounts. Sources of precursor ^{227}Ac ($t_{1/2}$ = 21.7 years) can be used as a long-term operating generator for ^{223}Ra (42, 43). Actinium-227 is produced by neutron irradiation of natural ^{226}Ra. Moreover, the $t_{1/2}$ of ^{223}Ra provides sufficient time for its preparation, distribution (including long distance shipment), and administration to patients. Its low γ-irradiation is favorable from the point of view of handling, radiation protection, and treatment on an outpatient basis (44).

α-Particles from the first three nuclides in the decay chain are emitted almost instantaneously (Table 1). They are therefore likely to contribute to the radiation dose in the vicinity of the site of ^{223}Ra decay. Hence, ^{223}Ra has the potential to deliver a therapeutically relevant tumor dose from a relatively small

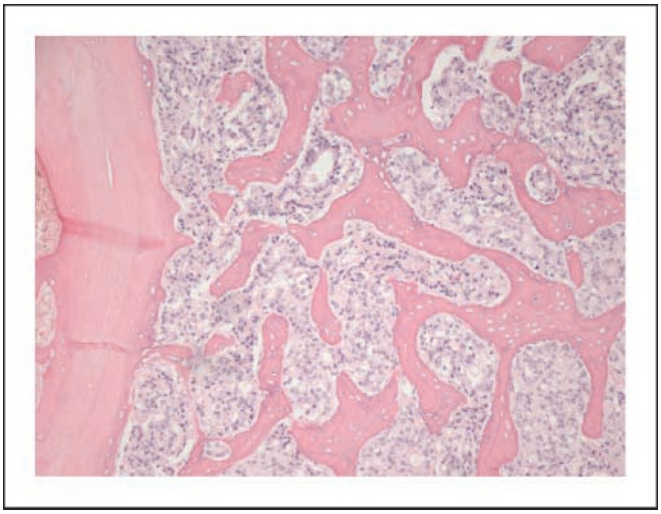

Fig. 1. Histologic section of an osteoblastic bone metastasis in a patient with prostate cancer. Note the presence of abundant woven bone distributed as a mesh in between cords of tumor cells. H&E staining. Magnification, ×200. Kindly provided by Dr. M. Roudier and Prof. R. Vessella (University of Washington Medical Center, Seattle, WA).

Table 1. Principle emissions of radium-223 and decay progeny (radon-219, polonium-215, lead-211, bismuth-211, and thallium-207)

Nuclide ($t_{1/2}$)	Decay	Yield/(Bq s)	Mean energy (MeV)	Dose constant Δ (Gy kg/Bq/s)
^{223}Ra (11.43 d)	α	0.525	5.72	4.80×10^{-13}
		0.242	5.61	2.17×10^{-13}
		0.095	5.75	8.74×10^{-14}
		0.091	5.54	8.07×10^{-14}
		0.023	5.43	2.00×10^{-14}
		0.009	5.87	8.45×10^{-15}
	X or γ	0.154	0.081	2.00×10^{-15}
		0.256	0.084	3.44×10^{-15}
		0.030	0.094	4.51×10^{-16}
		0.057	0.095	8.66×10^{-16}
		0.030	0.098	4.70×10^{-15}
		0.012	0.122	2.34×10^{-16}
		0.037	0.144	8.52×10^{-16}
		0.060	0.154	1.48×10^{-15}
		0.136	0.269	5.85×10^{-15}
		0.037	0.324	1.92×10^{-15}
		0.026	0.338	8.79×10^{-16}
		0.013	0.445	9.26×10^{-16}
^{219}Rn (3.96 s)	α	0.808	6.82	8.82×10^{-13}
		0.115	6.55	1.21×10^{-13}
		0.075	6.43	7.72×10^{-14}
	X or γ	0.099	0.271	4.30×10^{-15}
		0.065	0.402	4.25×10^{-15}
^{215}Po (1.78 ms)	α	1.000	7.39	1.18×10^{-12}
^{211}Pb (36.1 min)	β	0.997	0.449	7.16×10^{-14}
	X or γ	0.038	0.405	2.46×10^{-15}
		0.014	0.427	9.56×10^{-16}
		0.028	0.832	3.73×10^{-15}
^{211}Bi (2.17 min)	α	0.834	6.62	8.83×10^{-13}
		0.164	6.28	1.65×10^{-13}
	X or γ	0.008	0.071	9.02×10^{-17}
		0.013	0.073	1.52×10^{-16}
		0.130	0.351	7.30×10^{-15}
^{207}Tl (4.77 min)	β	1.00	0.491	7.86×10^{-14}
^{207}Pb	Stable			

NOTE: From Nuclide Explorer data sheets, Institute for Transuranium Elements, Karlsruhe, Germany. European Commission, Joint Research Centre, Program Version 1.00 (1999).

amount of administered activity without causing unacceptable doses to nontarget tissue.

Preparation of the radionuclide. Radium-223 may be produced from ^{227}Ac/^{227}Th and purified using Ac-resin to immobilize ^{227}Ac and ^{227}Th as described previously (42–44). According to current procedures used by Algeta ASA (Oslo, Norway),[5] the Alpharadin product concentrate (dissolved $^{223}RaCl_2$) is tested for radionuclide purity by γ-spectroscopy. The concentrate of ^{223}Ra in NaCl and Na citrate is transferred to a good manufacturing practices radiopharmacy unit, The Isotope Laboratory at Institute for Energy Technology (Kjeller, Norway), where the sterile production is done. Isotonicity, pH, and activity concentration are adjusted. Product is dispensed into vials, and the vials are autoclaved whereas a sample is kept aside for pathogen and pyrogen testing. The final product is shipped in sterile vials capped with a sealed rubber membrane penetrable to syringes.

Preclinical studies with ^{223}Ra. Animal data and dosimetric estimates have indicated that bone-targeted α-emitters can deliver therapeutic relevant radiation doses to bone surfaces and skeletal metastases at activity levels that should be acceptable in terms of bone marrow radiation exposure (39). In a previous study, we explored the bone-seeking properties of ^{223}Ra and compared them with those of the β-emitter ^{89}Sr. We found that ^{223}Ra and ^{89}Sr had similar bone uptake. Estimates of dose deposition in bone marrow showed that an advantage of α-particle emitters is bone marrow sparing (45).

A therapeutic study of ^{223}Ra in a nude rat skeletal metastases model showed a significant antitumor activity (46). In the same nude rat model, the tumor cells were resistant to high doses of cisplatin, doxorubicin, and an immunotoxin as well as to both pamidronate (Aredia) and ^{131}I-labeled bisphosphonate treatment, suggesting that ^{223}Ra is therapeutically more

[5] http://www.algeta.com.

Table 2. Summary of effective energy and dose constants for radium-223 and progeny for all emission combined

Nuclide	Effective energy*	Dose constant Δ (Gy kg/Bq/s)
^{223}Ra (11.43 d)	5.99	9.58×10^{-13}
	5.56†	8.90×10^{-13}
^{219}Rn (3.96 s)	6.95	1.11×10^{-12}
	6.72†	1.08×10^{-12}
^{215}Po (1.78 ms)	7.53	1.20×10^{-12}
	7.39†	1.18×10^{-12}
^{211}Pb (36.1 min)	0.518	8.29×10^{-14}
^{211}Bi (2.17 min)	6.75	1.08×10^{-12}
	6.57†	1.05×10^{-12}
^{207}Tl (4.77 min)	0.494	7.90×10^{-14}
Total	28.2	4.5×10^{-12}
	26.4†	4.2×10^{-12}

NOTE: From Nuclide Explorer data sheets, Institute for Transuranium Elements, Karlsruhe, Germany. European Commission, Joint Research Centre, Program Version 1.00 (1999). Branching of <1% is not considered.
*Includes α, β, photon, X-ray, and electron energies.
†Includes only α-particle energies.

effective and could have benefits in treatment-resistant skeletal metastases compared with these agents (46).

A biodistribution study of ^{223}Ra in a dog with bone cancer showed affinity for and stability within calcified tissues.[6] Radium-223, eliminated via intestinal clearance, resided in transit in the gut content, whereas the activity in intestinal walls was low and comparable with the other soft tissues. α-Track microautoradiography of canine specimens indicated a concentration of bone-seeking α-emitter on the bone surfaces of trabecular bone in a vertebra (Fig. 2A) and a very high accumulation in strongly osteoblastic bone matrix (Fig. 2B).

Clinical Evaluation of Alpharadin

The encouraging preclinical results have led to the initiation of a clinical development program for $^{223}RaCl_2$. Approval was obtained from the applicable institutional review boards, and all patients provided informed written consent before entering the clinical studies.

Phase 1A. A phase 1 study of single-dosage administration of escalating amounts of ^{223}Ra in 25 patients with bone metastases from breast and prostate cancer was recently published (44). Dose-limiting hematologic toxicity was not observed. Dosages of 46, 93, 163, 213, or 250 kBq/kg were applied. Mild and reversible myelosuppression occurred with only grade 1 toxicity for thrombocytes at the two highest dose levels. Quality of life was evaluated at baseline and at 1, 4, and 8 weeks after injection, respectively. Pain relief was observed for all time points in >50% of the patients. Furthermore, a decline in total serum alkaline phosphatase >50%, accepted as a prognostic marker in metastatic prostate cancer, was observed among patients with elevated pretreatment values. Radium-223 was rapidly cleared from circulating blood; blood ^{223}Ra activity at 10 minutes after injection was 12% of its initial value. It was further reduced to 6% at 1 hour and to <1% at 24 hours after infusion. In patients where γ-camera scintigraphy was done, ^{223}Ra accumulated in skeletal lesions similar to patterns observed in diagnostic bone scans with ^{99m}Tc-MDP (44).

Phase 1B. A small phase 1B feasibility study that involved six patients with advanced prostate cancer has been completed (47). The main objective of the phase 1B trial was to evaluate the safety profile of repeated ^{223}Ra injections at two fixed dosage levels administered with 3- or 6-week intervals between injections. Prostate cancer patients with a previous diagnosis of skeletal metastases, with an Eastern Cooperative Oncology Group performance status of 0 to 2, ≥29 years of age, and a life expectancy of ≥8 weeks, and with adequate bone marrow, liver, renal, and cardiac function were eligible for the study. The patients were monitored closely at day 0, 1, and 2 and thereafter weekly for 2 months after the last injection.

Injected activity was adjusted according to body weight for all patients. Six prostate cancer patients were administered a total dosage of up to 250 kBq/kg body weight as a fractionated regimen either as two injections of 125 kBq/kg body weight with a 6-week interval (two patients) or 50 kBq/kg body weight dosages given five times with a 3-week interval (four patients).

The four patients in the 50 kBq/kg × 5 group did not experience any additional toxic effects compared with the single-injection phase 1A study related to repeated treatment. It seems that the hematologic profiles were smoothed out because of the fractionation schedule compared with a single dosage totaling the same as the five fractions combined. Because of nonskeletal disease progression, only one of the patients in the 125 kBq/kg × 2 group actually got the second dosage. Reversible myelosuppression occurred with nadirs 2 to 3 weeks after injection and complete recovery during the follow-up period. The thrombocytes revealed only grade 1 toxicity, whereas neutropenia of maximum grade 3 occurred in one of the patients. Few other adverse events were seen. Transient diarrhea was observed as well as nausea, both responding well to standard medication.

The main experience from the phase 1B study was that repeated administration of ^{223}Ra was well tolerated and that the time span between injections should be scheduled according to the dosages given, such that the blood cell count could normalize before a new injection is administrated.

Algeta ASA has requested that the clinical sites collect long-term safety data from patients who participated in the phase 1 study. The following data were collected at approximately 4, 6, 9, 12, 18, 24, 30, and 36 months after study drug injection: hematology (hemoglobin, platelet, and WBC counts) and selected serum biochemistry variables (creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and bilirubin).

Twenty of the 31 patients were alive 12 months after the first injection of ^{223}Ra in the phase 1 study. Nine patients were alive 2 years after, and 1 patient is alive 3 years after treatment. Clinical laboratory data were made available for 24 of the 31 patients. Data for 11 patients at 12 months, 5 at 18 months, 2 at 24 months, and 1 at 36 months were obtained. Several

[6] Unpublished data.

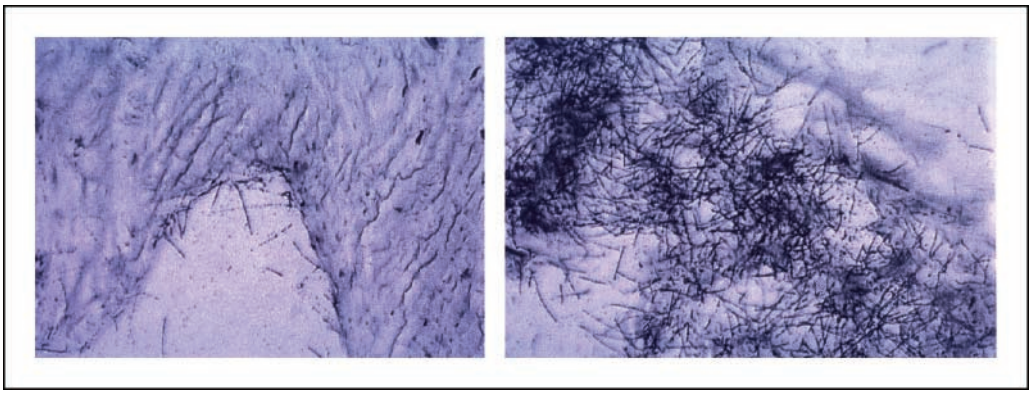

Fig. 2. Microautoradiography from a dog injected with an α-emitting bone seeker. Distribution of α-particle tracks in normal spongious bone (*A, left*) and an osteoblastic zone (*B, right*).

patients received other cancer therapies after the phase 1 study. There were no patients with severe or persistent myelosuppression, signs of myelodysplasia or diagnosed leukemia. No trends were reported that indicated late gastrointestinal toxic effects on kidney or liver function, as observed from the creatinine, transaminases, lactate dehydrogenase, and bilirubin values.

Phase 2. Interim data from a phase 2 randomized trial of external beam radiation plus either saline injections (four times with 4-week intervals) or four times repeated ^{223}Ra (50 kBq/kg given at 4-week intervals) have recently been presented (48). Adjuvant ^{223}Ra treatment resulted in a statistically significant decrease in bone alkaline phosphatase from baseline compared with placebo. The mean change for the external radiation plus ^{223}Ra group (33 patients) was $-58 \pm 37\%$ versus $+47 \pm 107\%$ in the external beam radiation plus saline group (29 patients). In the external radiation plus ^{223}Ra group, 15 of 31 patients had a prostate-specific antigen decrease of >50% from baseline compared with only 5 of 28 patients in the group receiving external radiation plus saline. We observed a favorable adverse event profile and minimal bone marrow toxicity for patients who received ^{223}Ra (48).

These results showed that administration of ^{223}Ra after external radiation was well tolerated. We observed that treatment substantially influenced bone alkaline phosphate levels and other bone markers, and we observed a favorable trend for prostate-specific antigen response among the ^{223}Ra versus saline groups. Minimal bone marrow toxicity after repeated doses was encouraging and justifies further clinical development of ^{223}Ra as a targeted agent for the treatment of bone metastases.

Equivalents dose for ^{223}Ra. The clinical dosimetry data are at the moment relatively limited for ^{223}Ra. Table 3 presents some newly estimated equivalent dose for i.v. injected $^{223}RaCl_2$. A quality factor of 5 is assumed for therapeutic dose levels of α-particles. The data represent an injected dosage of 50 kBq/kg of body weight. It is assumed that the daughter radionuclides decay within the same volumes as the parent. The absolutely largest value is seen for the skeletal surface. It should be noted that the data are calculated based on the ICRP-67 model (50), which reflects the distribution kinetics of adults without bone metastases. In these subjects, the total skeletal uptake would approximate 30% of the injected ^{223}Ra. In subjects with significant volumes of osteoblastic tumors in the skeleton, the overall skeletal uptake of bone-seeking radionuclides is generally elevated and therefore the uptake of ^{223}Ra in prostate or breast cancer with skeletal involvement more likely would be between 40% and 60% of administered activity and with a concomitant reduction in normal tissue exposure.

As for the red bone marrow, the α-particle radiation dose distribution would be between 0% and 100% of the bone surface dose with significant volumes of the bone marrow–containing cavities receiving almost no α-particle dose similar to the distribution profiles in a previously published animal model (45).

Table 3. Estimated equivalent dose after i.v. injection of a dosage of 50 kBq/kg of ^{223}Ra

Target organs	Dose equivalents (Sv)
Adrenals	5.60×10^{-2}
Urinary bladder	5.70×10^{-2}
Brain	5.55×10^{-2}
Breast	5.55×10^{-2}
Gall bladder	5.60×10^{-2}
Heart wall	5.55×10^{-2}
Kidneys	5.60×10^{-2}
Liver	6.35×10^{-1}
Muscle	5.60×10^{-2}
Ovaries	5.65×10^{-2}
Pancreas	5.60×10^{-2}
Testes	5.55×10^{-2}
Thyroid	5.55×10^{-2}
Bone surface	13.05
Stomach	5.60×10^{-2}
Small intestine	5.65×10^{-2}
Upper large intestine	1.68×10^{-1}
Lower large intestine	3.67×10^{-1}
Skin	5.55×10^{-2}
Spleen	5.55×10^{-2}
Thymus	5.55×10^{-2}
Uterus	5.60×10^{-2}
Expiratory tract	5.55×10^{-2}
Lung	5.55×10^{-2}
Colon	2.54×10^{-1}
Thoracic lymph node	5.55×10^{-2}
Esophagus	5.55×10^{-2}
Gonads	5.65×10^{-2}
Remainder	5.60×10^{-2}

NOTE: The data represent ^{223}Ra in equilibrium with the daughter radionuclides and were calculated according to the ICRP-67 recycling model for radium. A quality factor of 5.0 for α particles was assumed.

Table 4. Characteristics of some bone seekers used clinically in patients with skeletal metastases

Radiopharmaceutical	Physical $t_{1/2}$ (d)	Average particle energy (MeV) per decay	Range in tissue (mm)	Bone surface to red bone marrow dose ratio
Metastron ($^{89}SrCl_2$)	50.5	0.58	2.4	1.6*
Quadramet (^{153}Sm-EDTMP)	1.9	0.22	0.55	4.4†
Alpharadin ($^{223}RaCl_2$)	11.4	27.4‡	<0.1	10.3§

*Based on values presented in prescribing information at:http://www.cytogen.com/professional/quadramet/pi.php.
†Based on values presented in prescribing information at:http://www.amershamhealth-us.com/shared/pdfs/pi/Metastron.pdf.
‡Including daughter nuclides.
§Average ratio estimated based on the ICRP-67.

Comparison of properties of Alpharadin, Metastron, and Quadramet. Characteristics of Metastron, Quadramet, and Alpharadin are compared in Table 4. Radiation doses following i.v. injection of ^{89}Sr result in the delivery of low dose rates. Absorbed doses in the range of 20 to 40 Gy were deposited as a continuously declining dose rate during 16 weeks to 1 year (51, 52). This low dose rate suggests a minimal tumoricidal effect. The higher dose rate and the shorter range of Quadramet less energetic electrons may improve its therapeutic index compared with that of Metastron (Table 4). To our knowledge, however, no comparative studies have been reported.

Discussion

Because of the dynamic nature of the developing skeletal metastases, therapy must deliver effective radiation to multiple foci and also to microscopic disease. When a macroscopic lesion is treated by external beam radiotherapy, new foci often arise after a short time, showing the existence of microscopic metastases alongside the macroscopic lesions. After the ^{223}Ra treatment, a strong and consistent effect on the alkaline phosphatase levels occurred, showing a particularly strong decrease in patients with elevated levels before treatment (44). This observation showed that the areas mostly affected by ^{223}Ra were the regions with an elevated bone metabolism, a common feature of developing skeletal metastases, and in particular for prostate cancer metastases (Fig. 1).

The myelosuppression observed after ^{223}Ra treatment was minimal and seems different from that observed with the β-emitting nuclides (44, 48). With ^{223}Ra, the neutrophils decreased more than thrombocytes, whereas for β-emitters, thrombocytopenia could also be dose limiting. It seems that, with α-emitters, the endosteal bone surface receives high radiation doses, whereas large fractions of the marrow are spared.

An important question is to what extent ^{223}Ra is carcinogenic. It is well known that bone cancer did occur in subjects exposed to ^{226}Ra (52–55). However, at intermediate dose levels (below 20 Gy to the bone for ^{226}Ra), no significant increase in cancer was observed in humans (56). For several decades, injections of ^{224}Ra ($t_{1/2}$ = 3.2 days) were used to treat ankylosing spondylitis (56, 57). Radium-224 was recently reintroduced and reapproved for ankylosing spondylitis in Germany (41). For ^{224}Ra, long-term follow-up of patients receiving moderate levels revealed no significant difference in overall cancer incidence or life expectancy compared with a control population (56, 57).

Because repeated dosing is the common way to use therapeutics in oncology, this may be warranted with bone-seeking radiopharmaceuticals. This article presents our first clinical experiences with repeated injections of ^{223}Ra in patients with bone metastases from prostate cancer. It is plausible to use repeated treatment also for ^{223}Ra for two reasons. First, the range of the radiation is short and therefore repeating the treatment could improve dose homogeneity in the target. Second, the bone metabolism in normal bone and calcified metastases is a dynamic process where the absorptive and resorptive zones change position over time, which would likely affect the microdistribution of the bone-seeking compound over time.

We conclude that use of ^{223}Ra in single dose or repeated regimens and also after external beam irradiation seems to be safe. This finding suggests that ^{223}Ra should be further evaluated in future therapeutic studies aimed at showing delayed disease progression and improved survival in patients with skeletal metastases.

Open Discussion

Dr. Vessella: Typically, α-emitters have a relatively short half-life. What is the half-life of radium-223?

Dr. Bruland: 11.4 days.

Dr. Weilbaecher: Are you concerned that the α-emitter can hurt the bone?

Dr. Bruland: Yes, indeed we are concerned about that. Fortunately, we have found support for this strategy in the literature. In a previous study, the investigators gave radium-224 to relieve the pain from ankylosing spondylitis. More than a thousand German patients were given repeated injections, and they have been followed up for decades for long-term bone marrow failure, myelodysplastic syndromes, leukemia, and all other kinds of secondary cancers. There were no worrisome conclusions from their trials. Of course, we know that the stromal lining cells might be affected and that our alkaline phosphatase decline is a mixture of targeted killing of normal osteoblasts and reactive osteoblasts within the metastasis and also may be directly from the prostate cancer cells themselves.

Dr. Boyce: Are you implying that tumor cells may be making the bone in some of these osteoblastic metastases?

Dr. Bruland: I think that the answer is yes—not necessarily bone, but alkaline phosphatase.

Dr. Guise: Leland Chung has proposed an osteomimetic theory of cancer cells that can produce bone. *In vitro*, some of

the cancer cells can express proteins that osteoblasts express. Whether or not that's actually happening *in vivo* is not clear.

Dr. Bruland: It's a mixture. At the Davos meeting on cancer-induced bone disease, Dr. Roudier showed histomorphometric pictures of skeletal metastases in patients with prostate cancer. She showed that the bony phenotype was entwined as a mesh between the tumor cells. It's not only the rim surrounding the metastases, but woven bone was distributed throughout the entire lesion in many cases.

Dr. Vessella: That's true, but our general consensus is that so far prostate cancer cells do not make bone directly. There are spindle cells or other types of cells involved where the osteomimetic factors play a role, but the prostate cancer cells themselves don't make woven bone.

Dr. Bruland: This is what we are looking more carefully into by analyzing the prostate-specific antigen response data.

Dr. Boyce: As a pathologist, I don't recall ever seeing morphologic evidence of tumor cells making bone matrix in the absence of osteoblasts being associated with the matrix. I'm certainly familiar with tumor cells having the ability to express BMPs, for example, where you may or may not have the outcome of bone matrix formation. For example, in mixed salivary tumors, where cartilage can be formed, the salivary epithelial cells can express BMPs and induce the myoepithelial support cells to start to elaborate cartilage, because they change the phenotype. I'm skeptical of the notion that tumor cells themselves *in vivo* will make bone matrix under most circumstances.

Dr. Berenson: There are emerging data to suggest a big differential effect on the tumor cell versus the normal hematopoietic cell population. These may be ideal for combinatorial therapy with some of the new agents, particularly the NF-κB inhibitors.

Dr. Bruland: The most important finding is that the low bone marrow toxicity observed with radium-223 seems to make it feasible to do combination treatment with docetaxel, a drug that we know works in prostate cancer. With regard to combination with bisphosphonates, that's an open question. Other targeted agents are also a possibility. The Achilles heel of this type of bone-targeted radionuclide treatment is, however, the phenotype and the homogenicity of the hydroxyapatite present within the small clusters of tumor cells.

Dr. Berenson: The Mayo Clinic has some fairly compelling data to suggest that radiopharmaceuticals are useful.

Dr. Powles: With regard to single-fraction pain relief, osteoclasts are very radiosensitive. I'd always thought osteoclasts were a key figure in mediation of tumor-induced pain. What's interesting is that the pain relief is more than you would anticipate if you were just hitting inflammatory cells. If that's the case, it must also be blocking osteoclast recruitment at that site.

Dr. Bruland: It's correct that we think they are much more radiosensitive than osteoblasts, but the literature is scarce.

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