First Clinical Experience with α-Emitting Radium-223 in the Treatment of Skeletal Metastases

Sten Nilsson,1 Roy H. Larsen,2 Sophie D. Fosså,3 Lise Balteskard,4 Kari W. Borch,2 Jan-Erik Westlin,5 Gro Salberg,2 and Øyvind S. Bruland2,3

Abstract

Purpose: The main goals were to study the safety and tolerability of the α-emitter radium-223 (223Ra) in breast and prostate cancer patients with skeletal metastases. In addition, pain palliation was evaluated.

Experimental Design: Fifteen prostate and 10 breast cancer patients enrolled in a phase I trial received a single i.v. injection of 223Ra. Five patients were included at each of the dosages: 46, 93, 163, 213, or 250 kBq/kg and followed for 8 weeks. Palliative response was evaluated according to the pain scale of the European Organization for Research and Treatment of Cancer QLQ C30 questionnaire at baseline and at 1, 4, and 8 weeks after injection.

Results: Weekly blood sampling during follow-up revealed mild and reversible myelosuppression with nadir 2 to 4 weeks after the injection. Importantly, for thrombocytes only grade 1 toxicity was reported. Grade 3 neutropenia and leukopenia occurred in two and three patients, respectively. Mild, transient diarrhea was observed in 10 of the 25 patients. Nausea and vomiting was more frequently observed in the highest dosage group. Serum alkaline phosphatase decreased with nadir averages of 29.5% in females and 52.1% in males. Pain relief was reported by 52%, 60%, and 56% of the patients after 7 days, 4, and 8 weeks, respectively. 223Ra cleared rapidly from blood and was below 1% of initial level at 24 hours. Gamma camera images indicated, in accordance with pretreatment 99mTc-MDP scans, accumulation of 223Ra in skeletal lesions. Elimination was mainly intestinal. Median survival exceeded 20 months.

Conclusions: 223Ra was well tolerated at therapeutically relevant dosages. Phase II studies have therefore been initiated.

The morbidity associated with cancer affecting the skeleton is serious. Pain, pathologic fractures, hypercalcemia, and bone marrow insufficiency have a devastating effect on the patients’ quality of life. In particular, metastases in the vertebrae leading to spinal cord compression may be disastrous (1–6).

External radiotherapy is widely used to relieve pain from skeletal metastases (7, 8). However, lack of tumor selectivity limits its use as normal cells within the target volume receive the same radiation dose as the tumor cells. Because the radiosensitivity of tumor cells often is similar to that of the normal cells, the therapeutic index is generally low, ruling out the use of wide-field external irradiation in patients with widespread skeletal metastases. As an alternative, preferential irradiation at multiple metastatic sites can be accomplished by metabolically targeted radionuclide therapy by employing i.v. injected bone-seeking radiopharmaceuticals (9–11).

Clinical studies with bone-seeking compounds have thus far been conducted with low-linear energy transfer (LET) β-emitters and a conversion electron emitter (12, 13). These have been proven useful for pain palliation (9), and 89Sr (Metastron) and 153Sm-ethylene diamine N,N,N,N-tetra(methylene) phosphonic acid (153Sm-EDTMP; Quadramet) are approved for this indication. It has been difficult to show antitumor effects with these emitters though, and bone marrow toxicity has limited both the dosages that could be given and the use of repeated treatments. β-emitters have a relatively low radiobiological effectiveness and track lengths in tissues up to a few millimeters. In contrast, α-particles provide a much more densely ionizing type of radiation, classified as high-LET radiation (14). They yield a massive deposition of energy per unit track length and have a range of <100 μm. α-Particles induce predominantly nonrepairable DNA double-strand breaks, rendering cellular repair mechanisms ineffective against this type of radiation (15). This may be important as patients with skeletal metastases often have therapy-resistant disease. Because of the heavy damages created by high-LET radiation to the DNA, cell cycle dependency would be lower (16) and micrometastases with dormant clonogenic tumor cells residing in G0 could be eliminated.

Preclinical experimental data and dosimetric estimates have supported the hypothesis that bone targeted α-emitters can deliver therapeutically relevant radiation doses to bone
surfaces and skeletal metastases, at dosages that should be well tolerated by the bone marrow (17, 18). Initially, we studied the $^{212}$Bi complex of a bone-seeking phosphonate (19). However, because the time required to localize in the target tissue is substantial considering the short half-life of $^{212}$Bi ($t_{1/2} = 60$ minutes), and a less than ideal stability was obtained for the complex, a significant soft tissue exposure was seen (19). In a biodistribution and dosimetry study comparing bone-seeking $\alpha$-emitting $^{211}$At and $\beta$-emitting $^{151}$-bispophonate compounds, the bone surface to bone marrow dose ratio was strongly increased for the $\alpha$-emitter versus the $\beta$-emitter (17). The production and distribution limitations with short-lived $\alpha$-emitters like $^{211}$At ($t_{1/2} = 7.2$ hours), $^{212}$Bi ($t_{1/2} = 60$ minutes), and $^{213}$Bi ($t_{1/2} = 46$ minutes) make them suboptimal for clinical use and they are difficult to prepare at a commercial scale. A few $\alpha$-emitters with more suitable half-lives have recently been proposed as candidates to combat skeletal metastases: $^{225}$Ac ($t_{1/2} = 10.0$ days), $^{223}$Ra ($t_{1/2} = 11.4$ days), and $^{229}$Ra ($t_{1/2} = 3.7$ days) as well as $^{227}$Th ($t_{1/2} = 18.7$ days; ref. 20). These nuclides all decay via multiple steps. Hence, it is important to establish the fate of their radioactive daughters in vivo before they are tested clinically. To show sufficient selectivity for bone, Ac and Th require complexation to bone seeking $\alpha$-emitting elements (Sr, Ba, and Ra), $^{223}$Ra targets bone mineral without the need for a carrier agent. Due to some concern about the decay chain of $^{224}$Ra that includes a 56-second ($t_{1/2}$) $^{220}$Rn daughter which might escape from bone and also the significant half-life of another member of the decay series, $^{212}$Pb ($t_{1/2} = 10.6$ hours), this nuclide was not evaluated. Radium-223 ($^{223}$Ra) has a more short-lived radon daughter (i.e., $^{219}$Rn with $t_{1/2} = 3.96$ seconds) and was chosen for an extensive preclinical evaluation because its decay chain and half-life seemed well suited for biomedical application. The decay chain is as follows: $^{223}$Ra ($t_{1/2} = 11.4$ days) $\Rightarrow$ $^{219}$Rn ($t_{1/2} = 3.96$ seconds) $\Rightarrow$ $^{215}$Po ($t_{1/2} = 1.78$ milliseconds) $\Rightarrow$ $^{211}$Pb ($t_{1/2} = 36.1$ minutes) $\Rightarrow$ $^{207}$Bi ($t_{1/2} = 2.17$ minutes) $\Rightarrow$ $^{203}$Pb (stable). In one study, we evaluated the bone-seeking properties of $^{223}$Ra and compared it with that of the $\beta$-emitter $^{89}$Sr (18).

The biodistributions of the two radionuclides were studied in mice by determining their tissue content of radioactivity at injection day, days 1, 2, and 7 and thereafter weekly to 8 week after the injection of $^{223}$Ra. The injected activity was adjusted to each patient’s body weight. Five patients were enrolled at each dosage level; starting at 46 kBq/kg b.w. and then increasing to 93, 163, 213, and 250 kBq/kg b.w. At each dosage level, the results of the five patients would be considered before enrolling patients to a new dosage level. Based on this review one of the following options was available: (a) escalate to the next higher dosage; (b) repeat the same dosage, or the lower dosage, for three more patients; (c) discontinue the dosage escalation.

Approval was obtained from local ethics committees and all patients provided informed, written consent before entering the study.

Safety Assessment. Safety was assessed by evaluating all adverse events occurring after the injection and during the study period of 8 weeks. Serial laboratory tests, which included a complete blood count with differential and platelet count, and a serum biochemistry panel, were evaluated at injection days 1, 2, and 7 and thereafter weekly for 2 months. The National Cancer Institute of Canada Common Toxicity Criteria (version 2.0) were used to grade toxicity. Dose-limiting toxicity would be reached if one or more of the following changes had occurred during the 8-week period after study drug administration: platelets <20 × 10^9/L, or neutrophil granulocytes, <0.5 × 10^9/L. The dose escalation was to be terminated if patients experienced unacceptable toxicity, defined as observed dose-limiting toxicity in one of the five patients in a dosage level group, or two of eight patients in an extended group.

Adverse events and serious adverse events. An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational product. Only symptoms/signs that started or worsened in severity after study drug administration were recorded as adverse events in this study. Serious adverse events: adverse event was considered as serious if it was fatal, life threatening, disabling, or resulting in patient hospitalization or prolongation of hospitalization, as was occurrence of a secondary malignancy.

Patients and Methods

Patients. The study involved 25 patients with bone metastases, 10 females and 15 males (Table 1). Each of the patients received a single injection of $^{223}$Ra as part of a cohort dosage escalating study design. Eligibility criteria consisted of Eastern Cooperative Oncology Group performance status 0 to 2, ≥30 years of age, life expectancy of >8 weeks, and adequate bone marrow, liver, renal, and cardiac function. Most patients had relapsed with new foci in the skeleton after previous external beam radiotherapy. The patients were monitored closely at the injection days and 1, 2, and 7 and thereafter weekly to 8 week after the injection of $^{223}$Ra. The injected activity was adjusted to each patient’s body weight. Five patients were enrolled at each dosage level; starting at 46 kBq/kg b.w. and then increasing to 93, 163, 213, and 250 kBq/kg b.w. At each dosage level, the results of the five patients would be reviewed before enrolling patients to a new dosage level. Based on this review one of the following options was available: (a) escalate to the next higher dosage; (b) repeat the same dosage, or the lower dosage, for three more patients; (c) discontinue the dosage escalation.

Approval was obtained from local ethics committees and all patients provided informed, written consent before entering the study.
Table 1. Baseline demographic and disease characteristics of patients included in the phase I study of i.v. injected $^{223}$Ra

<table>
<thead>
<tr>
<th></th>
<th>Single dose (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n = 15)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>ECOG status, n (%)</strong></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>No. hot spots (n)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Platelets × 10^9/L</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>WBC × 10^9/L</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Granulocytes × 10^9/L</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>Serum alkaline phosphatase (units/L)</strong></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td><strong>QLQ pain, n (%)</strong></td>
<td>Not at all</td>
</tr>
<tr>
<td></td>
<td>A little</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Very much</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Important medical events that may not result in death, be life threatening, or require hospitalization, were considered serious adverse drug experiences when, based upon appropriate medical judgment, they could jeopardize the patient and could require medical intervention.

All adverse events reported by the patients or observed by the hospital personnel were recorded with duration, severity (mild, moderate, and severe), whether it was serious, any required treatment or action taken, outcome, relationship to study drug, and whether the adverse event caused withdrawal from the study.

The significance of adverse events was graded as mild, moderate, or severe using the following definitions:

- **Mild**: tolerable
- **Moderate**: interferes with patients normal activity
- **Severe**: incapacitating (causes inability to perform usual activity or at work)

In addition to the investigator’s own description of the adverse events, each adverse event was encoded by the sponsor, according to a dictionary of medical codes (WHO-Adverse Reaction Terminology).

Any serious adverse event was reported to the sponsor’s clinical safety officer immediately, recorded in the case report form, and monitored until the outcome was known. Serious adverse events were recorded if they occurred:

- Between the first administration of the study drug and the completion of the last follow-up evaluation at 8 weeks after study drug injection, whether or not considered related to the investigational product
- At any time after completion of the last follow-up evaluation, came to the investigator’s attention, and were judged to be related to the subject’s participation in the study.

**Blood clearance.** To determine the blood clearance profile for $^{223}$Ra, the 25 patients had blood samples of ~2 mL collected at 10 minutes and at 1, 4, 24, and 48 hours and 7 days post-injection. The weight of each blood sample was measured and the count rate per mL of blood was calculated (assuming 1 mL of blood equals 1 g). The radioactivity was measured in a NaI well-type counter. The activity level immediately after injection was calculated assuming that initially, 100% of the activity was in the blood and that the total blood weight represented 7% of the body weight. The data are presented as biological data (i.e., adjusted for the radioactive decay between the time of injection and the time of measurement).

**Gamma camera scintigraphy.** Besides the $\alpha$-particles, there are various other types of radiation emitted from the $^{223}$Ra-series. $^{223}$Ra itself has X-rays at 81 and 84 keV and gamma peaks at 269 and 154 keV and the $^{223}$Rn daughter, which has a very short half-life and may therefore be used to indicate the position of its mother nuclide, has a significant peak at 271 keV. Because of the low levels of injected radioactivity, the number of events is low, necessitating rather long acquisition times.

**Radionuclide production.** $^{223}$Ra was produced from $^{227}$Ac/227Th and purified using Ac-resin to immobilize $^{227}$Ac and $^{227}$Th as described (24) by Algeta ASA, Oslo, Norway. The product concentrate (i.e., dissolved $^{223}$RaCl$_2$) was tested for radionuclide purity by gamma spectroscopy before further use. A concentrate of the $^{223}$Ra in a NaCl/Na citrate mixture was transferred to a GMP radiopharmacy unit, The Isotope Laboratory at Institute for Energy Technology, Kjeller, Norway, where the sterile production was done. Isotonicity, pH, and activity concentration were adjusted and a sample kept aside for pathogen and pyrogen testing. The final product (Alpharadin) was filled in sterile vials that were subsequently capped with a sealed rubber membrane penetrable to syringes. The vials were labeled, placed in lead containers, and shipped to the hospitals.

**Pain assessment.** Pain was assessed in all patients as part of the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire (25) and the pain score was recorded at baseline and 1, 4, and 8 weeks following $^{223}$Ra administration and analyzed according to published guidelines (26), where pain relief was defined as a decrease in pain score >10. When pain score changed 10 points or less the pain was considered unchanged, whereas an increase in pain score of >10 was considered as pain progression.

**Results**

**Toxicity and adverse events.** Table 2 shows the maximum hematologic toxicity grading found in the various groups receiving $^{223}$Ra at various dosage levels. Dose-limiting hematotoxicity was not observed at any dosage level. Some reversible myelosuppression occurred, with nadirs 2 to 4 weeks after...
injection and complete recovery during the follow-up period. The neutrophils were more frequently affected than the platelets (Fig. 1). In general, there was a tendency towards increased myelosuppression at the higher dosage levels. Two patients experienced neutropenia of grade 3. Leucopenia grade 3 was seen in the same two patients (Table 2) in addition to a patient in dosage group 4. For platelets, only grade 1 toxicity was observed even at the highest dosage levels.

Seven of the 25 patients had a serious adverse event. Five of these were evaluated as a result of the patients’ condition or related to a different treatment. A breast cancer patient in dosage group 2 experienced an episode of supraventricular arrhythmia 1 week after 223Ra administration, during the initiation of external radiotherapy against newly diagnosed brain metastases. Normal sinus rhythm was successfully established by electroconversion. The causal relation to the study drug was considered uncertain, because the patient had previously experienced arrhythmia and electrocardiogram irregularities possibly resulting from previous cancer treatment. Another breast cancer patient was hospitalized with severe vomiting/nausea (Common Toxicity Criteria grade 3) and leucopenia (grade 3) after 223Ra administration. The patient recovered after treatment at the highest dosage level. The patient was hospitalized with severe vomiting/nausea (Common Toxicity Criteria grade 3) and leucopenia (grade 3) after the injection of 223Ra. The effect was stronger in the prostate cancer group versus the breast cancer group (Fig. 4). The reduction in alkaline phosphatase values after injection of 223Ra was observed in skeletal lesions similar to that seen in diagnostic 99mTc- methylene diphosphonate (99mTc-MDP) bone scans.

Clinical chemistry. Random variations in clinical chemistry variables were observed for some of the patients but without any noteworthy trend except for serum alkaline phosphatase. For all patients, there was a decline in alkaline phosphatase values after injection of 223Ra. The effect was stronger in the prostate cancer group versus the breast cancer group (Fig. 4). The reduction in alkaline phosphatase at nadir compared with baseline was 52.1 ± 14.8% (mean ± SD) and 29.5 ± 10.8% in the prostate and breast cancer groups, respectively, when data from all dosage levels were combined. The difference between the groups was significant (t test, P = 0.0028). The upper limit for the reference range was considered 276 units/L. In the 16 patients, 11 males and 5 females, with alkaline phosphatase above reference range, the mean reduction was 50.1 ± 17.2%, whereas for the patients with values below upper normal limit, the reduction was 30.6 ± 8.3% from baseline to nadir. There was a significant difference (t test, P = 0.0042) between the two groups. Of the 16 patients with elevated alkaline phosphatase, 11 had their levels reduced to within reference range during follow-up.

Pain score. Most patients reported pain palliation. Pain relief, defined as a change in pain score of >10 (26), was

<table>
<thead>
<tr>
<th>Table 2. Myelotoxicity after 223Ra treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
</tr>
<tr>
<td><strong>(CTC grade)</strong></td>
</tr>
<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>WBC</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

NOTE: Number of patients with myelosuppression at each dosage level, CTC toxicity grade 0, 1, 2, or 3 after a single dose of 223Ra. Highest CTC grade for neutrophils is grade 3 and for platelets grade 1.

Abbreviation: CTC, Common Toxicity Criteria.

Blood clearance and gamma camera scintigraphy. The blood clearance profiles are shown in Fig. 2. Radioactivity levels at 10 minutes post-injection was 12% of the initial (estimated) values and further reduced to 6% at 1 hour and to <1% after 24 hours. It was indicated by scintigraphy (Fig. 3) that the radioactivity accumulated in the skeleton with a preference for the osteoblastic metastases. Clearing was predominantly by the hepatobiliary/intestinal route and presumably with some renal elimination (27). In the six patients where gamma-camera scintigraphy was done, accumulation of 223Ra was observed in skeletal lesions similar to that seen in diagnostic 99mTc- methylene diphosphonate (99mTc-MDP) bone scans.
observed in more than half of the patient population, for all
time points compared with the baseline. At the 1-week point,
52% reported improvement, 36% unchanged, and 12% worse
pain. At the 4-week point, 60% reported improvement, 20%
unchanged, and 20% worse pain. At the 8-week point, 56%
reported improvement, 24% unchanged, and 20% worse pain.
It should be noted that two of the patients had no skeletal pain
at baseline and were therefore limited to the unchanged or
worse pain categories. No clear dosage response relationship
could be observed. A transient increase in bone pain (i.e. a
“flare” response) was reported in seven of the patients during
the first week after treatment.

Discussion

The current study represents the first clinical trial exploring
targeted α-emitter therapy in cancer patients with skeletal
metastases. Two previous studies with such emitters have been
conducted with short-lived nuclides (i.e., 211At in brain tumors
and 213Bi in leukemia; refs. 28, 29). The current study
represents the first attempt to use an α-emitter with a half-life
of several days in cancer treatment. 223Ra can be produced in
clinically relevant quantity and quality via a generator system.
Sources of the precursor 227Ac (t1/2 = 21.7 years) can be used as
a long-term operating generator for 223Ra (24). 227Ac can be
produced by neutron irradiation of the relatively commonly available $^{228}$Ra. Moreover, $^{223}$Ra’s half-life provides sufficient time for its preparation, distribution, including long distance shipment, and administration to patients. The low intensity of gamma radiation is favorable with respect to handling, radiation protection, and treatment on an outpatient basis.

The clinical problem related to skeletal metastases is intricate with considerable morbidity. Hence, there is a great need for improvement in the treatment by including novel and preferentially targeted therapies. Skeletal metastases are usually caused by hematogenous spread of malignant cells. There is firm experimental evidence that initially such tumor cells attach themselves primarily to the endosteal bony surface, and that the interphase between bone and red bone marrow constitutes a favorable microenvironment for tumor cell proliferation. Here tumor cells are arrested in the red bone marrow sinusoid compartment within the axial skeleton. It is now appreciated that the release of bone-derived growth factors and cytokines from bone in the process of being resorbed can both attract cancer cells to the bony surfaces and facilitate their growth (30). Thus, the “seed and soil hypothesis,” originally launched by Paget (31), has received renewed attention (30). Because of the nature of developing skeletal metastases, it would be important to institute a therapy that delivers therapeutically effective radiation doses to multiple foci, including microscopic disease. When a macroscopic lesion is treated (e.g. by external beam radiotherapy), new foci often arise after short time, indicating the existence of microscopic metastases alongside with the macroscopic lesions in most patients.

Overall the myelosuppression observed in this study was mild with a tendency of increased toxicity with increasing dosages. Interestingly, it was seen that the toxicity profile for the blood producing cells after $^{223}$Ra treatment is different from that observed with the $\beta$-emitting nuclides. With $^{223}$Ra, the neutrophils were more easily affected compared with the thrombocytes, whereas for the $\beta$-emitters thrombocytopenia is often a clinically important toxicity. Other types of toxicity observed included diarrhea, nausea, and vomiting. These were generally mild and transient and were manageable.

An important observation made was that after the $^{223}$Ra treatment, a consistent reduction of alkaline phosphatase levels occurred, showing a particularly strong decrease in patients with elevated levels before treatment. Prostate-specific antigen responses as well as reductions in alkaline phosphatase levels have previously been reported after treatment with $\beta$-emitting bone seekers in prostate cancer patients (32, 33). The data from those studies indicate a less pronounced reduction in average values of alkaline phosphatase compared with this study. Recent published data indicate that a treatment that reduces alkaline phosphatase levels (32) or prevents increases in bone-related alkaline phosphatase levels (34) could increase time to progression in prostate cancer patients. Future studies would have to resolve if such a correlation exists for $^{223}$Ra therapy. Anyway, the consistent reduction in alkaline phosphatase levels seen with $^{223}$Ra suggest that the areas most strongly targeted by $^{223}$Ra would be the regions with an elevated bone metabolism, as is often seen in the zones of developing skeletal metastases. This is visualized by $^{223}$Ra-scintigrams showing a preferential uptake in the skeletal lesions previously diagnosed by $^{99m}$Tc-MDP bone scan. Thus, we conclude that $^{223}$Ra shows a significant targeting of skeletal metastases.

Radium solutions have previously been given to humans for other purposes. From about 1940 to 1980, several thousand German patients with noncancerous diseases have received $^{224}$Ra against ankylosing spondylitis or bone tuberculosis (35, 36). $^{224}$Ra ($^{224}$SpondylAT, Altmann Therapie GmbH & Co., Salzgitter, Germany) has recently been reintroduced in Germany as a therapy in ankylosing spondylitis (37). To our knowledge, $^{223}$Ra has previously been given to only one human subject. This was in a tracer study comparing different alkaline earth elements involving
a single healthy subject (27), where $^{223}$Ra distribution was compared with those of $^{133}$Ba, $^{85}$Sr, and $^{47}$Ca, given successively. It was found that $^{223}$Ra had longer whole body retention and a higher degree of intestinal elimination compared with the other alkaline earth radionuclides. The significant intestinal clearance of $^{223}$Ra was confirmed by the gamma scintigraphy in the present study.

Intestinal clearance could potentially be a problem because intestines in general is considered sensitive to radiation. There are some distinct advantages with $\alpha$-emitters considering their intestinal clearance. Assuming that the radioactivity is mainly located in the intestinal content, the dose delivered to the intestinal wall will penetrate <100 $\mu$m into the wall. Data from two dogs injected with $^{223}$Ra and evaluated by biodistribution measurements 24 hours after injection revealed that the radioactivity was principally located in the intestinal content and not in the intestinal wall (data not shown). Assuming a similar relation in humans, only a few cell layers will be exposed to the $\alpha$-particles leaving the deeper intestinal tissue unharmed. This is in agreement with the dose distributions described by Lassmann et al. (38) for $^{224}$Ra in humans. It seems, although that with $^{223}$Ra, the irradiation of the inner surfaces of the intestines causes some temporary irritation, manifested as transient diarrhea, in about 40% of the patients. It was a slight tendency towards more intestinal toxicity at higher dosages. None of the more severe side effects associated with many chemotherapeutic drugs (e.g. mucositis), severe vomiting and hair loss, was observed with the exception of a breast cancer patient in the highest dosage group that experienced leucopenia grade 3 and severe vomiting. It is recommended to do thorough evaluation of gastrointestinal toxicity (e.g., by using the NIH scale for reporting adverse responses) in future studies.

As for long-term effects including carcinogenesis on the intestines in humans, $^{224}$Ra data may be useful as an indicator. $^{224}$Ra and $^{223}$Ra delivers a similar dose to the intestines because (i) the excretion half-life is significantly shorter than the physical half-lives for both nuclides and (ii) although the decay chains for $^{224}$Ra and $^{223}$Ra produces different isotopes, they produce for each step the same elements with the same mode of decay and would release a similar amount of $\alpha$-radiation. With

Fig. 3. Gamma scintigrams of $^{99m}$Tc-MDP (top) and $^{223}$Ra (bottom) in a patient with skeletal metastases.
224Ra, there exists data from long-term follow-up on German ankylosing spondylitis patients, which were compared with data from ankylosing spondylitis patients receiving nonradioactive conventional treatments. Late effects from the α-particle exposure have been evaluated extensively (36, 39). As with other types of treatments inducing DNA damage, an increased risk of late cancer has been observed. Cancer forms observed include sarcomas to the bone, breast cancer, and connective tissue tumors. Late cancer was mainly seen in individuals treated when they were children or juveniles involving high-dosage regimens (39). There was no significant increase in overall risk for cancer among individuals treated when they were adults (39). No increased intestinal carcinogenesis was reported in 899 patients treated with high dosages of 224Ra (39) or 649 patients treated with moderate dosages of 224Ra (36), after follow-up for several decades. These data support the hypothesis that α-emitters, which clear via the intestinal tissue, irradiate sufficient volumes of proliferating cells in the intestines to cause any significant carcinogenesis.

Preclinical data have indicated that 223Ra treatment has antitumor activity against skeletal metastases and could cause life extension (21). Prolongation of life span for breast or prostate cancer patients after treatment with single-agent β-emitting bone-seekers is questionable. The Trans-Canada study failed to show benefit in terms of increased survival after treatment with 89Sr (40). Later studies in prostate cancer patients have, however, indicated some survival benefit from bone-seeking radionuclides. Recently, Palmedo et al. reported increased survival with repeated treatment over single-dose treatment with the β-emitting bone seeker 188Re hydroxyethylenediphosphonate in patients with hormone-refractory prostate cancer (41). In a randomized phase II trial in androgen-independent prostate cancer which disease were stabilized or responding to induction chemotherapy, there was a significantly prolonged survival in patients given 89Sr in combination with doxorubicin versus doxorubicin alone (42). The survival of patients in the current study has been followed for >20 months and the median survival for the 25 subjects included is beyond 20 months relative to the time of administering the 223Ra. This is promising compared with what has been reported previously for similar patient groups in Scandinavia (33). However, because no control group was included in the current phase I study, firm conclusions cannot be drawn regarding potential survival benefits following 223Ra treatment. A placebo-controlled study to evaluate if life prolongation from 223Ra occurs in patients with skeletal metastases is therefore warranted.

The pain score data in this study were quite encouraging because in general more than half of the patients reported improved pain scores compared with baseline values. The pain scores improved already at 1 week posttreatment versus baseline and the fraction of patients reporting pain relief lasted throughout the study period of 8 weeks. This indicates that 223Ra may produce pain relief similar to that of the β-emitting bone seekers. However, it should be noted that the study was without a control group and not designed specifically for studying pain relief and the patients’ quality of life. In the current study, neither the consumption of analgesics nor activities of daily living were measured. This might be a confounder. Thus, there is a need to do a designated pain palliation study with 223Ra using more advanced reporting schemes and pain assessment should be included as one of the study variables in future studies with 223Ra.

The dosimetry of the α emitter 223Ra (and daughters) is likely to be different from that of 89Sr and 153Sm-EDTMP. The human dosimetry of 223Ra will have to be studied in future investigations, but estimates based on animal data (18) suggest a significant reduction in bone marrow dose for a given dose to the skeletal surfaces from 223Ra compared with the β-emitters.

In conclusion, 223Ra was well tolerated at therapeutically relevant dosages by prostate and breast cancer patients with skeletal metastases. Because of the mild myelotoxicity, the generally weak side effects, and the encouraging pain scores found in this phase I study, 223Ra could be a valuable alternative to the currently used palliation agents. The median survival of the patients in the current study was promising, suggesting that the issue of survival should be addressed in randomized controlled studies. We have therefore initiated further clinical studies with this novel α-emitter including a randomized placebo-controlled phase II study in prostate cancer patients with symptomatic bone metastases.

Acknowledgments

We thank Dr. Darrell R. Fisher (Pacific Northwest National Laboratory, Richland, WA) for providing 226Ra used in reactor production of 227Ac and for helpful discussions; Professor Peter Strang (The Karolinska Hospital, Sweden) for helpful discussions; and Lars Johansson (The Karolinska Hospital); Erik Traasdal (The University Hospital of Tromso, Tromso, Norway); and Magne Aas (The Norwegian Radium Hospital, Oslo, Norway) for providing nuclear medicine services including acquisition of gamma camera images; the Algeta production team and the IFE GMP production facility for preparing the study product.

References


Fig. 4. Serum alkaline phosphatase level at baseline (normalized to 100%) and after 223Ra administration. Point, mean for breast cancer (○, n = 10) or prostate cancer (■, n = 15); bars, ± SD.
Bone-Seeking Radionuclide Therapy

First Clinical Experience with α-Emitting Radium-223 in the Treatment of Skeletal Metastases


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/11/12/4451

Cited articles
This article cites 36 articles, 12 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/11/12/4451.full#ref-list-1

Citing articles
This article has been cited by 16 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/11/12/4451.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.