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Phase I pharmacokinetic and biodistribution study with escalating doses of ^{223}Ra -dichloride in men with castration-resistant metastatic prostate cancer

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Abstract

Purpose— ^{223}Ra -Dichloride (^{223}Ra) is a novel bone-seeking alpha-emitter that prolongs survival in patients with castration-resistant metastatic prostate cancer. We conducted a study to better profile the pharmacokinetics, pharmacodynamics, and biodistribution of this agent.

Methods—Ten patients received either 50, 100, or 200 kBq of ^{223}Ra per kilogram of body weight. Subsequently, six of these ten patients received a second dose of 50 kBq/kg. Pharmacokinetics and biodistribution were assessed by serial blood sampling, planar imaging, and whole-body counting. Pharmacodynamic assessment was based on measurements of prostate-specific antigen, bone alkaline phosphatase, and serum N-telopeptide. Safety was also assessed.

Results—Pharmacokinetic studies showed rapid clearance of ^{223}Ra from the vasculature, with a median of 14 % (range 9–34 %), 2 % (range 1.6–3.9 %), and 0.5 % (range 0.4–1.0 %) remaining in plasma at the end of infusion, after 4 h, and after 24 h, respectively. Biodistribution studies showed early passage into the small bowel and subsequent fecal excretion with a median of 52 % of administered ^{223}Ra in the bowel at 24 h. Urinary excretion was relatively minor (median of 4 % of administered ^{223}Ra). Bone retention was prolonged. No dose-limiting toxicity was observed. Pharmacodynamic effects were observed (alkaline phosphatase and serum N-telopeptides) in a significant fraction of patients.

Conclusion— ^{223}Ra cleared rapidly from plasma and rapidly transited into small bowel, with fecal excretion the major route of elimination. Administered activities up to 200 kBq/kg were associated with few side effects and appeared to induce a decline in serum indicators of bone turnover.

Keywords

Bone metastases; Prostate cancer; ^{223}Ra ; Radium; Radionuclide therapy; Alpharadin

Introduction

Bone metastases are the primary cause of death and disability in patients with castration-resistant metastatic prostate cancer [1], causing pain, pathologic fractures, cord compression,

and marrow insufficiency, among other feared side effects of cancer [2]. A number of approaches that target the bone microenvironment have been evaluated to reduce the effects of bone metastases. In addition to treatments directed at the tumor itself, these include bisphosphonates, RANK ligand inhibitors, external beam radiation, and beta-emitting bone-seeking radiopharmaceuticals [3, 4]. None of these have been shown to prolong survival [5].

^{89}Sr -Chloride and ^{153}Sm -lexidronam are currently the only radiopharmaceuticals approved by the US Food and Drug Administration (FDA) for the palliation of bone pain. While some studies have shown a concurrent decrease in serum prostate-specific antigen (PSA) levels with the use of these agents [6], an improvement in survival has not been documented [7].

^{223}Ra -Dichloride (^{223}Ra) is a novel, bone-seeking alpha-emitter that accumulates in areas of increased bone turnover in bone metastases following i.v. injection, which is being developed to target metastatic bone disease [8–14]. Among its advantages are its availability from a long-lived $^{227}\text{Ac}/^{227}\text{Th}$ generator [15] and a physical half-life of 11.4 days, which allows for shipping to end users.

^{223}Ra has been shown to have a potent antitumor effect in animal models [12–14], which led to its evaluation in men with prostate cancer metastatic to bone [8, 10, 11]. These trials demonstrated palliation of bone pain, changes in bone alkaline phosphatase and PSA levels, and a favorable safety profile [10, 11]. A phase III study of ^{223}Ra in patients that enrolled men with progressive castration-resistant metastatic prostate cancer and pain showed that ^{223}Ra had reduced the risk of death relative to placebo [9].

^{223}Ra has a complex decay schedule in which four alpha particles are generated, resulting in high energy deposition (28.2 MeV), with 95 % of the energy from the alpha emissions. As the first three alpha emissions occur within 5 s of the initial decay of ^{223}Ra , significant translocation between organs in this time frame is unlikely, but could occur for the final α -emitting daughter ^{211}Bi that is produced following the beta decay of ^{211}Pb (36 min half-life). Mouse studies have demonstrated little redistribution of ^{223}Ra daughter away from bone [13]. An additional potential advantage of ^{223}Ra is the high linear energy transfer associated with alpha radiation, which results in a greater biologic effectiveness than beta radiation and gives rise to cytotoxicity that is independent of dose rate, cell cycle growth phase, and oxygen concentration [16]. ^{223}Ra , similar to other alkaline earth elements such as calcium, is absorbed into bone matrix at sites of active mineralization [17]. The range of the alpha particles ($< 100\ \mu\text{m}$) is much shorter than the beta particle ranges of ^{89}Sr and ^{153}Sm (0.7 and 0.33 cm, respectively) and sufficiently short that some portion of the trabecular marrow space will experience zero dose from ^{223}Ra distributed on trabecular bone surfaces. Consequently, less hematologic toxicity for a given bone surface dose would be expected in comparison with beta emitters [18].

The dosimetry of ^{223}Ra depends on its biodistribution and pharmacokinetics, as well as that of its radioactive progeny. Few pharmacokinetic and biodistribution studies in man have been reported, and most in only a small number of patients [8, 10, 11, 19–28]. In the current study detailed pharmacokinetics and biodistribution of ^{223}Ra were assessed by serial blood sampling, planar imaging, and whole-body counting in patients with castration-resistant

prostate cancer with bone metastasis. The potential translocation of radioactive progeny [primarily ^{211}Pb ($T_{1/2}=36$ min) and its alpha-emitting daughter ^{211}Bi ($T_{1/2}=2.2$ min)] was assessed using a multi-energy window imaging approach. We also report on the limited toxicity and pharmacodynamic effect.

Materials and methods

Design

Under the auspices of a protocol approved by the Institutional Review Board and an Investigational New Drug application approved by the FDA, ten patients in three cohorts received escalating activities of intravenous ^{223}Ra -dichloride after providing informed consent (trial registration ID, NCT00748046). This was a prospective, phase I dose escalation trial with the primary objective of determining the biodistribution, pharmacokinetics, and safety of ^{223}Ra -dichloride. Planned cohorts consisted of a minimum of three patients. If dose-limiting toxicity was observed in only one patient, up to three additional patients at the same activity level would be included. Escalation to the next level would not proceed if two of six patients had a dose-limiting toxicity. The maximum activity used in the current study was 200 kBq/kg and we did not seek to establish a maximum tolerated activity.

Patients

Patients with metastatic castration-resistant prostate cancer that had metastasized to bone were eligible. Patients were required to have at least two metastatic bone lesions documented by bone scan within 4 weeks of treatment, as well as evidence of disease progression as documented by a new lesion on bone scan, increase in size of target lesion on MRI/CT, or rising PSA (a minimum of three rising PSA values from a baseline obtained 1 week or more apart or two measurements 2 or more weeks apart). Patients had to have experienced failure of antiandrogen withdrawal and were required to maintain treatment to ensure castrate levels of testosterone. Other inclusion criteria were a Karnofsky performance status $\geq 60\%$ and life expectancy ≥ 6 months. Required laboratory parameters were white blood count (WBC) $\geq 3,000/\text{mm}^3$, absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, hemoglobin ≥ 10 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5\times$ upper limits of normal, and serum creatinine ≤ 2 mg/dl. Patients were excluded if they had predominantly visceral metastases, other active malignant disease, or other serious illness, or if they had received an investigational drug within 4 weeks of the ^{223}Ra , any chemotherapy, immunotherapy, or external radiotherapy in the previous 4 weeks, or prior hemibody radiotherapy or systemic radionuclide therapy within 24 weeks prior to administration of the study drug. Bisphosphonates were allowed if the dose had not changed in the previous 4 weeks.

Treatment

Cohorts were defined by activities of 50, 100, or 200 kBq/kg body weight (1.351, 2.703 or 5.405 $\mu\text{Ci/kg}$). Previous studies in Europe using activities ranging from 46 to 250 kBq/kg had demonstrated biologic effects and no dose-limiting toxicity [11]. A second administration of 50 kBq/kg was optional after the 6-week safety assessment if patients

showed treatment benefit, as judged by the referring physician, and there were no safety concerns and recovery of marrow function. Six weeks was selected as adequate time to observe for toxicity assessment from the first dose.

^{223}Ra -Dichloride (Alpharadin, Algeta ASA, Oslo, Norway) was provided by the manufacturer as a ready-to-use solution. Each vial contained 6.0 MBq and 6 ml of solution (0.162 mCi per 6 ml) at a specified reference date and time. On the day of use, the desired activity for each patient was drawn up in a syringe by volume and then measured in a radiation dose calibrator that had been previously calibrated with a known standard provided by the manufacturer [29]. Residual activity in the syringe was measured post-injection.

Endpoints

Pharmacokinetics and biodistribution of ^{223}Ra —Patients were injected through an indwelling peripheral intravenous catheter over approximately 2–5 min. Blood samples were collected from a vein in the arm opposite the injection site at baseline (preinjection), at approximately 1, 5, 15, 30, 45, 60, and 120 min post-injection, and at the times of imaging (nominally 4 h, 24 h, 48 h, 3–4 days, and 6–8 days post-injection). Whole blood and plasma samples were counted collectively for each individual patient after completion of all whole-body and imaging procedures. A predetermined amount of each blood or plasma sample (typically 500 μl) was pipetted in duplicate into separate tubes and measured in a calibrated sodium iodide well-type detector (Wallac Wizard, PerkinElmer, Inc., Waltham, MA, USA) alongside ^{223}Ra reference standards. The well counter energy window was set to its maximum extent (0–1,024 keV) to record all counts derived from parent ^{223}Ra and its progeny in radioactive equilibrium at the time of measurement. Counts were converted into % of injected dose per unit volume (%ID/L). Thereafter, bi-exponential clearance curves were fitted to the %ID/L values using SAAM II modeling software (v 1.1.1, University of Washington, Seattle, WA, USA). The bi-exponential fits were used to obtain pharmacokinetic parameters, including C_{max} , biologic $T_{1/2}$, volume of distribution, and clearance. Patient-specific whole blood and plasma volumes were estimated based on height and weight [30]. The total activity retained in whole blood or plasma was estimated by multiplying the appropriate volumes and concentrations.

The total activity in the whole body was quantified using a whole-body counter consisting of a single 5-in. sodium iodide crystal placed 3 m from the patient. Anterior and posterior counts were made in duplicate over 1-min intervals. Counts were also obtained for a ^{223}Ra reference standard at 3 m from the detector and room background. The geometric mean of the average background-corrected anterior and posterior counts was used to represent whole-body activity. Whole-body counts were acquired prior to voiding, immediately after voiding, and at each time the patient was scheduled for a gamma camera scan. The difference between the pre- and post-void whole-body measurements was used to estimate the amount of activity excreted in urine in the first void. In addition, an attempt was made to relate whole-body count reductions with the transit and elimination of ^{223}Ra through the bowel.

Sufficient data were collected to evaluate whole-body clearance in eight of ten patients treated and to estimate urinary excretion in six patients. Of the two exclusions, one patient was unable to undergo whole-body count measurements after 24 h post-administration

because of back pain. In the other case, the early whole-body count data were judged to be unreliable because of varying background counts resulting from a radiochemistry facility within the vicinity.

Anterior and posterior gamma camera spot images were obtained with the camera centered over the abdomen, including the upper abdomen and pelvis. In three patients, initial spot images were obtained prior to voiding at approximately 1 h post-injection. In seven patients, dynamic scans were started 5 min after the end of infusion for 60 min (one patient) or 40 min (six patients), consisting of frames of 10-min duration. Thereafter, spot images were obtained post-void at 1.5–3.7 h post-injection, 22.8 ± 2 h, 48 ± 12 h, 96 ± 24 h, and 144 ± 24 h. In addition, a whole-body scan (38–47 min acquisition) was also performed at 22.8 ± 2 h.

All imaging was performed with the same SKYLight JETStream gamma camera (Philips Healthcare, Milpitas, CA, USA) using a high-energy general purpose collimator with uniformity flood corrections turned off. Images were acquired simultaneously at each time point using five separate 20 % energy windows centered on 82, 154, 269, 351, and 402 keV, encompassing the main imageable photon emissions of ^{223}Ra and its progeny. Of these, the 351 keV window primarily reflects emissions from the decay of ^{211}Bi and its use enabled the degree of translocation of radioactive progeny to be assessed, as described below. For clinical review, the separate energy window images were combined (i.e., ^{223}Ra in combination with all daughter isotopes) and used to determine patterns of distribution of tracer. The spot images and whole-body scan were compared to each patient's most recent bone scan to identify sites of metastatic disease. Subsequently, the 351 keV energy window images (i.e., primarily ^{211}Bi) were compared with summed energy images to assess whether any redistribution of radioactive progeny occurred following ^{223}Ra decay. Specifically, the ratio of counts in the 351 keV energy window to those in the sum of the other four windows (primarily photon emissions from ^{223}Ra and its first daughter ^{219}Rn) were calculated for regions of interest (ROI) corresponding to bone, gut, kidney, liver, and a ^{223}Ra reference standard. An increase in this ratio for any ROI would indicate relocation of the ^{211}Bi daughter relative to the parent.

The intestinal uptake of ^{223}Ra was evaluated by ROI analysis of the whole body and spot images. The fraction of whole-body activity in the intestines at 24 h was estimated by the ratio of counts in an ROI drawn over the visible intestine to that in the whole body using the anterior whole-body scan (since intestinal activity was much better seen in the anterior view). The time course of intestinal uptake was derived from ROIs drawn over the visible intestine on the serial anterior spot images obtained on the day of injection and at 24 h. ROI count data were normalized by setting the intestinal uptake fraction from the 24-h spot image equal to that determined from the 24-h whole-body scan.

Safety—Any adverse event that occurred after the first ^{223}Ra injection and before 12 weeks after the last injection was recorded. Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [31]. Laboratory values were monitored closely during the treatment period (at baseline, 6 days, 2, 3, 4, 6, and 12 weeks) and at 6, 9, and 12 months as part of the safety assessment.

Conventional imaging—Bone scans were performed as per our clinical routine: patients were injected with 925 MBq (25 mCi) of ^{99m}Tc -methylene diphosphonic acid (MDP) and imaged approximately 3 h later.

Serologic—PSA, N-telopeptide, and bone alkaline phosphatase were determined at baseline and at 6 days, 3 weeks, 6 weeks, 12 weeks, and at 6 and 12 months after ^{223}Ra administration according to the study plan.

Statistical analysis

Descriptive statistics include either median or the mean $\pm$ standard deviation. Student's t test was used for paired comparisons. For group comparisons across the three cohorts, the Kruskal-Wallis one-way analysis of variance was used. All statistical analyses were performed with SigmaStat 3.5 (Systat Software Inc., Chicago, IL, USA).

Results

Patients

Eleven patients were registered to the study, ten of whom received ^{223}Ra -dichloride. Patient demographics, disease characteristics, and prior treatments are shown in Table 1. Six patients had received prior docetaxel. Nine of the ten treated patients had six metastatic bone lesions.

Treatment

Three patients were treated in the 50 kBq/kg (1.351 $\mu\text{Ci/kg}$) cohort, three in the 100 kBq/kg (2.703 $\mu\text{Ci/kg}$) cohort, and four in the 200 kBq/kg (5.405 $\mu\text{Ci/kg}$) cohort. Six patients (two in each dose cohort) received the second optional administration (50 kBq/kg) 6 weeks after initial treatment. Table 2 lists injected activity for each patient.

Endpoints

Pharmacokinetics and biodistribution—Over 98 % of the activity in whole blood was accounted for by that in plasma, indicating that there was no or minimal binding to cellular elements in blood. The average plasma to blood activity concentration ratio was 1.5 ± 0.1 ($n=9$). Pharmacokinetic parameters obtained from the bi-exponential fits of the plasma clearance data are shown in Table 3. The measured ^{223}Ra concentrations in plasma at the end of infusion (median 4.3 %ID/L; range 2.4–10) were significantly ($p<0.01$, paired t test) greater than the fitted C_{max} values (median 3.7 %ID/L; range 1.7–7.4). This indicates that the measured pharmacokinetic data contained an initial rapid clearance component that was suboptimally captured by a bi-exponential fit. The median volume of distribution (V_c) inferred from either curve-fitting or end-of-infusion measurements (27 and 23 L, respectively) were much larger than plasma volume inferred from patient height and weight (median 3.2 L). At the end of the infusion, a median of only 14 % (range 9–34 %) of the administered ^{223}Ra was present in plasma, indicating that the majority had already dispersed from the circulation. The total ^{223}Ra in plasma had decreased to a median of 2.0 % (range 1.6–3.9 %) after 4 h and 0.55 % (range 0.37–1.0 %) 24 h after administration.

Supplementary Fig. 1 in the “Electronic supplementary material” shows a summary chart of the plasma clearance of ^{223}Ra .

Whole-body clearance typically showed a lag time before significant excretion was observed (Fig. 1, Table 4). The proportion of ^{223}Ra excreted through urine was relatively small (approximately 5 %); fecal excretion was the major route of elimination. In all patients, an initial major drop in whole-body counts was preceded by visualization of rectosigmoid activity. In nine patients at the time of whole-body imaging (nominally 24 h), a median of 52 % (range 40–61 %) of total ^{223}Ra present was in the large intestine. By the time of the last whole-body count (6–8 days), a median of 76 % (range 2–82 %) of the administered ^{223}Ra had been excreted from the body.

In patient 2 (see Table 4), there was little to no elimination by the time of the last measurement (6 days). However, the percentage of total activity in the gut at 24 h was similar to other patients and it is most likely that elimination was delayed by constipation.

Spot imaging showed small bowel visualization in the first 10 min, with no visualization of the biliary system. Activity moved from the small bowel into the large intestine, in a sequential manner where ascending, transverse, descending, and rectosigmoid colon were progressively seen in later images. Large intestine was not seen in the first hours (1.5–3.7 h) of imaging in any patient. Images of one patient are shown in Fig. 2. Decreases in whole-body counts correlated with removal of activity from bowel. The kinetics of bowel uptake in patients undergoing serial imaging is presented in Table 5, which shows increasing activity over the first 24 h. At 24 h, activity was seen in the large bowel and skeleton, with a small amount in soft tissues (Fig. 3). Activity in the kidneys was seen on the earliest posterior spot images in six patients but had resolved by 3.7 h (Fig. 4). There was immediate visualization of bone, which improved in contrast over time because of decreasing background. A small amount of liver uptake was noted in three patients in the early dynamic scans only. In those patients where the bladder was clearly in the field of view, no bladder activity was visualized at any time point.

ROI analysis of images of the final ^{211}Bi (351 keV) daughter relative to an image window containing the summed emissions corresponding primarily to the ^{223}Ra parent and first daughter ^{219}Rn generally showed similar distribution in bone and gut at all time points with a constant count ratio, suggesting equilibrium between parent and daughter and insignificant inter-organ translocation within the accuracy of the methodology used. Only at the earliest imaging time points (i.e., < 1 h) were there possible discrepancies in biodistribution with ^{211}Bi activity in the kidney higher than expected. This transient effect may possibly represent uptake of the radioactive progeny (^{211}Pb and/or ^{211}Bi) that are inevitably present at equilibrium levels in the primary injectate.

Safety—All ten patients reported at least one adverse event. In total, 74 of 148 adverse events were related to ^{223}Ra -dichloride. The adverse events are detailed in Supplementary Table 1 in the “Electronic supplementary material.” The most frequently occurring adverse events were leukopenia (7), diarrhea (6), anemia (6), blood calcium decrease (5), nausea (5), and fatigue (5). Grade 3/4 hematologic events were anemia (1), leukopenia (3), neutropenia

(1), and thrombocytopenia (1). The median time of onset for anemia and leukopenia was 11 days after injection and duration was approximately 2 weeks. Decrease in platelet count started at a median of 30 days and persisted through a median of 22 days. The median time of onset of diarrhea was 8 days, with a median duration of 13 days. Nausea, fatigue, and anorexia had a slower onset, with a median time to onset of 22, 25, and 23 days, respectively.

Serologic—Waterfall graphs of PSA, bone alkaline phosphatase, and serum N-telopeptides are provided in Supplementary Fig. 2A–C in the “Electronic supplementary material.” PSA decreases from baseline were observed in five of ten patients during the 12-week treatment period (two patients in the 100 kBq/kg dose group and three in the 200 kBq/kg dose group).

A decrease in mean and median values of bone alkaline phosphatase was seen across all dose groups during the treatment period; the mean percent change was $-27.6 \pm 19.6\%$ at week 3 and $-11.9 \pm 24.4\%$ at week 6. The nadir values were observed mainly 3–6 weeks after injection. Eight patients demonstrated a $>30\%$ decline and one had a $>50\%$ decline. Decrease of serum N-telopeptides was demonstrated in seven of ten patients during the 12-week treatment period; two patients demonstrated a $>30\%$ decline.

Discussion

The major goal of this study was to better understand the pharmacokinetics and biodistribution of ^{223}Ra in patients with castration-resistant metastatic prostate cancer. New findings are the determination of early bone uptake and small bowel excretion based on early dynamic imaging; the demonstration of limited urinary excretion and lack of significant biliary excretion; the lack of significant organ redistribution of radioactive daughters; estimates of total bowel and urinary excretion; and determination of pharmacokinetic parameters.

After intravenous injection, ^{223}Ra clears rapidly from the blood with rapid transit into the contents of the small bowel. There was no evidence of reabsorption from bowel, but rather movement through large bowel followed by fecal excretion. Targeting to involved and normal bone was observed within 10 min of injection and persisted over the period of observation (approximately 7 days). A whole-body scan obtained 14 days after administration in one patient showed retention in bone with complete clearing of gastrointestinal activity. Notable was that even images acquired at the lowest administered activity (50 kBq/kg) were adequate to visualize biodistribution.

Several studies evaluating the route of radium excretion have shown it to be predominantly through bowel [32, 33], but this is the first to identify the small bowel as the main excretory organ. Nilsson et al. indicated that main clearing was by the hepatobiliary/intestinal route [10], which was not observed here. While some animal studies have shown activity in bile [34], others have not found significant excretion via this route [35]. It is clear from our studies that the intestinal route of elimination is directly through small bowel, since it was seen in the immediate post-injection images without ever seeing the typical pattern of biliary excretion. Although the greatest amount of excretion occurred within the first 10 min,

accumulation into the small bowel continued over the first few hours and most likely thereafter at low levels difficult to visualize. At 24 h predominant activity was in large bowel.

Activity in the soft tissues was difficult to quantify. Accumulation in the soft tissues outside the gut was visualized with a small amount of activity in the kidney and liver of some patients, but only at the very earliest time points (<4 h post-injection). The lack of visualization of the bladder and collecting system and the 4 % median excretion in pre- and post-void whole-body counts are consistent with minimal renal excretion. The faint uptake seen early in the kidneys most likely represents either accumulation in the renal parenchyma of a combination of coadministered equilibrium ^{211}Bi and/or ^{211}Pb or redistribution of ^{211}Bi and/or ^{211}Pb resulting from ^{223}Ra decays in blood. Kidney activity cleared rapidly and was not seen in images acquired later than 4 h post-injection. This is not surprising, since studies by Hursh et al. demonstrated that 94–97 % of filtered radium was reabsorbed [36]. Furthermore, a study by Lloyd et al. [38] of the pharmacokinetics of ^{226}Ra in beagles revealed low urinary excretion in the range of 6.5 % in the first 10 days and whole-body retention of 72.67 %, indicating that feces was the main route of excretion. Sansom and Garner found that ^{224}Ra administered orally to cows showed almost complete excretion through feces and very little excretion through urine (0.46 %), consistent with lack of reabsorption [37].

Our blood and plasma pharmacokinetic measurements showed very rapid clearance and confirm a previous report [10] suggesting that it is unlikely to contribute significantly to blood or bone marrow radiation dose. It is clear from our studies that association with cellular elements in blood is minimal. Overall Nilsson et al. also showed very fast clearance, with 6 % of the initial amount observed in blood at 1 h and less than 1 % at 24 h, in line with our findings of 0.56 % at 24 h. The volume of distribution of the central compartment (V_c) is much greater than plasma volume suggesting that the initial distribution is into body water.

Redistribution of daughters into the kidneys has been shown in dogs injected with ^{224}Ra and ^{225}Ra , possibly because of the longer $T_{1/2}$ of the daughters [38, 39]. In this study, once the ^{223}Ra had left the blood and entered the two main accumulation compartments (bone and gastrointestinal tract), the images of the ^{211}Bi daughter exactly reflected the images of the parents (^{223}Ra and first daughter ^{219}Rn). Only at the very earliest imaging time points did we see more activity in the kidneys than expected from the parent. These results alleviate concerns that the radioactive progeny of ^{223}Ra may leave bone or gut contents, enter the circulation, and accumulate in a potentially dose-limiting organ such as the kidney. No measurable kidney activity was observed after the first few hours post-injection. In contrast to previous work, the current study performed serial dynamic imaging, starting immediately post-injection which enabled us to demonstrate and quantitate early excretion directly through the small bowel rather than via the hepatobiliary route. Furthermore, we were able to estimate the amounts excreted through the gastrointestinal tract.

The initial clinical study with ^{223}Ra -dichloride was a phase I dose escalation trial in patients with breast or prostate cancer. Escalating doses of up to 250 kBq/kg body weight were

administered. The main adverse events observed were transient diarrhea in 40 % (10 of 25) of the patients enrolled, bone pain including flare, fatigue, nausea, and vomiting. A trend toward myelosuppression was observed at the higher doses but was not dose limiting, with no grade 3 or higher thrombocytopenia and only one grade 3 neutropenia [10]. A more recent study in which doses ranging from 5 to 100 kBq/kg were administered also showed safety and good patient tolerance [8]. Our study confirmed that ^{223}Ra was well tolerated with no dose-limiting toxicity. Hematologic toxicity was seen, but mostly grade 1 and 2. Diarrhea was reported in six of ten patients, probably related to bowel transit of ^{223}Ra . Based on our data, we speculate that diarrhea may be the result of small bowel radiation dose during excretion.

Consistent with work by others, patients receiving ^{223}Ra have marked changes in markers of bone turnover, with fewer patients demonstrating changes in PSA. Interpretation of efficacy findings is limited because of the small numbers of patients. However, it is already known that, despite the paucity of patients with significant PSA declines, treatment with ^{223}Ra significantly prolongs survival and can reduce bone pain [8, 9].

Although the study was designed using the 3+3 approach to dose escalation typical of phase I oncology trials intended to determine the maximum tolerated dose, this was not an objective of the study which required only administration of an activity sufficient to obtain adequate gamma camera imaging in an adequate number of patients. Thus, although one dose-limiting toxicity was observed at our maximal activity of 200 kBq/kg, only one additional patient was enrolled since all ongoing or planned clinical trials with ^{223}Ra use an activity of 50 kBq/kg. It was agreed, therefore, that further characterization of the 200 kBq/kg level was not warranted and the study was stopped without expanding the final dose cohort.

Conclusion

In summary, we demonstrated that the main route of excretion is early uptake in the small bowel followed by eventual fecal clearance and little urinary excretion. No significant organ redistribution of the radium daughters was observed in this study. We confirmed that ^{223}Ra blood clearance is very rapid. As in previous studies ^{223}Ra activities of up to 200 kBq/kg were generally well tolerated, with no dose-limiting toxicity. Furthermore, evidence of pharmacodynamic effects was noted in alkaline phosphatase and serum N-telopeptides.

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Fig. 1. Decay-corrected percentage of ^{223}Ra retained in the whole body (initial pre-void counts taken as 100 %) in patients ($n=8$) over a period of approximately 1 week post-administration

Fig. 2.

Serial dynamic images of anterior abdomen/pelvis obtained after intravenous administration of 7,585 kBq (0.205 mCi) of ^{223}Ra -dichloride (patient 4). The images show prompt uptake throughout small bowel with mild uptake in liver and no gallbladder visualization. The uptake in small bowel, although showing some changes, persists for 232 min. The activity moves intraluminally into ascending and transverse colon (1 day), then into descending colon (2 days), and there is significant clearing from bowel by 6 days. The volume-rendered contrast CT shows bowel loops that correspond to the early ^{223}Ra -chloride images. A $^{99\text{m}}\text{Tc}$ -MDP bone scan is available for reference. There is prompt uptake in the bone metastasis that persists and improves in contrast over time. Small amount of liver uptake is noted in the early dynamic images, but resolves in the later images

Fig. 3.

Whole-body bone scan in *left panel* shows multiple metastatic disease to bone. ^{223}Ra whole-body bone scan in *right panel* was taken 1 day after injection. Although ^{223}Ra images have lower counts and are noisier than the bone scan, they clearly show focal accumulation in the most obvious bone metastasis, e.g., left distal femur, right femur, left proximal humerus. In addition, excretion into the ascending and transverse colon is noted

Fig. 4.

Representative biodistribution images. Serial posterior images following injection of 4,366 kBq (0.118 mCi) of ^{223}Ra -dichloride show initial accumulation in bone metastasis and normal bone that persists over time, compared to posterior $^{99\text{m}}\text{Tc}$ -MDP bone scan spot image of the same region. Early images will often show some mild uptake in the kidneys that decreases rapidly and is barely seen at 4 h and not seen beyond 1 day

Table 1

Patient characteristics

Characteristic	Patients (n=10)
Median age, years (range)	69.3 (57.9–80.9)
Extent of disease in bone, <i>n</i> (%)	
< 6 metastatic sites	1 (10 %)
6–20 metastatic sites	5 (50 %)
> 20 sites but not a superscan	3 (30 %)
Superscan	1 (10 %)
Prior/current treatment, <i>n</i> (%)	
Currently on bisphosphonate therapy	8 (80 %)
Median no. (range) of prior hormonal regimens	6 (2–9)
Prior radiation therapy	8 (80 %)
Primary only	2 (20 %)
Brachytherapy	2/10 (20 %)
Primary and metastatic	4 (40 %)
Metastatic only	2 (20 %)
Prior chemotherapy (docetaxel)	6 (60 %)
Median no. of prior chemo regimens	1 (0–2)
Median Gleason score at diagnosis	8 (7–9)
Gleason score at diagnosis	
7	3 (30 %)
8	5 (50 %)
9	2 (20 %)
Median baseline serum PSA level, ng/ml	114 (3.6–400)

Table 2

Individual activity per treatment of patients in the three cohorts

Patient	Initial treatment kBq (μ Ci)/kg body weight	Total activity first treatment kBq (μ Ci)	Total activity second treatment (50 kBq/kg) kBq (μ Ci)
1	50 (1.351)	4,588 (124)	4,514 (122)
2	50 (1.351)	4,366 (118)	4,292 (116)
3	50 (1.351)	3,774 (102)	nt
4	100 (2.703)	7,585 (205)	nt
6	100 (2.703)	8,251 (223)	4,144 (112)
7	100 (2.703)	8,288 (224)	4,366 (118)
8	200 (5.405)	13,320 (360)	nt
9	200 (5.405)	14,763 (399)	3,737 (101)
10	200 (5.405)	16,835 (455)	nt
11	200 (5.405)	24,272 (656)	6,216 (168)

Patient 5 gave consent but was not injected with ^{223}Ra

kBq kilobecquerel, *μ Ci* microcuries, *kg* kilogram, *nt* not treated

Table 3

Plasma pharmacokinetic parameters

Parameter	Activity levels, median			Combined		
	50 kBq/kg	100 kBq/kg	200 kBq/kg	Median	Mean±SD	
No. of patients	3	3	4	10	10	
C_{meas} (%ID/L)	4.9	4.3	4.3	4.3	5.5±2.6	
C_{max} (%ID/L)	3.9	2.4	3.8	3.7	3.8±1.7	
$T_{1/2 \text{ fast}}$ (h)	0.5	1.3	0.8	0.8	0.9±0.4	
$T_{1/2 \text{ slow}}$ (h)	20	22	16	19	22±11	
V_c (L)	26	41	27	27	32±14	
AUC (%ID h/L)	18	14	15	14	16±5	
Clearance (L/h)	5.5	7.3	6.9	7.1	6.7±1.8	

SD standard deviation, *ID* injected dose, C_{meas} %ID/L measured immediately after injection, C_{max} %ID/L intercept at $t=0$ (the time of injection) from fitted curves, $T_{1/2 \text{ fast}}$ and $T_{1/2 \text{ slow}}$ biologic clearance half-times for bi-exponential fits, V_c apparent volume of distribution of central compartment, *AUC* area under the decay-corrected time-activity curve, *Clearance* volume cleared of administered material per unit time

Table 4

Estimated urinary and fecal excretion based on whole-body decay-corrected measurements and imaging

Patient	Percent of injected activity (%ID) excreted in urine, first void	Fraction (%ID) in large intestine at ~24 h (time of whole-body scan)	Whole-body excretion	
			Time (days)	Total percent excreted (%ID)
1	4	43	7.3	45
2	–	61	5.9	2
3	11	43	7.2	75
4	–	52	7.0	76
6	–	49	–	–
7	8	58	6.9	77
9	5	59	7.8	78
10	2	40	7.0	66
11	2	53	6.0	82
Median	5	52	7.0	76
Mean±standard deviation	5 %±3	51 %±8	6.9±0.6	63 %±27

Table 5

Fraction of injected activity in the intestine over time

Time	Uptake in intestine %ID $\pm$ standard deviation
10 min	23.7 $\pm$ 3.2
20 min	25.3 $\pm$ 3.1
30 min	26.5 $\pm$ 3.4
40 min	28 $\pm$ 3.3
2.7 $\pm$ 0.7 h	39.6 $\pm$ 5.9
22.8 $\pm$ 2.2 h	50.8 $\pm$ 7.5