A Phase 1, open-label study of the biodistribution, pharmacokinetics and dosimetry of Radium-223 dichloride (\(^{223}\)Ra dichloride) in patients with hormone refractory prostate cancer and skeletal metastases.

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Running title:

Dosimetry for $^{223}$Ra dichloride treatment
Abstract

The aims of this single site, open label clinical trial were to determine the biodistribution, pharmacokinetics, absorbed doses and safety from two sequential weight-based administrations of $^{223}$Ra dichloride in patients with bone metastases due to castration-refractory prostate cancer (CRPC). Methods Six patients received two intravenous injections of $^{223}$Ra dichloride, 6 weeks apart, at 100 kBq per kg whole-body weight. The pharmacokinetics and biodistribution as a function of time were determined and dosimetry was performed for a range of organs including bone surfaces, red marrow, kidneys, gut and whole-body using scintigraphic imaging, external counting, blood, faecal and urine collection. Safety was assessed from adverse events. (AE’s). Results The injected activity cleared rapidly from blood with 1.1% remaining at 24 hours. The main route of excretion was via the gut, although no significant toxicity was reported. The majority of the administered activity was taken up rapidly into bone (61% at 4 hours). The range of absorbed doses delivered to the bone surfaces from alpha emissions was 2331 - 13118 mGy/MBq. The range of absorbed doses delivered to the red marrow were 177 - 994 and 1 – 5 mGy/MBq from activity on the bone surfaces and from activity in the blood respectively. No activity limiting toxicity was observed at these levels of administration. The absorbed doses from the second treatment were correlated significantly with the first for a combination of the whole body, bone surfaces, kidneys and liver. Conclusions A wide range of inter-patient absorbed doses was delivered to normal organs. Intra-patient absorbed doses were significantly correlated between the two administrations for any given patient. The lack of gastrointestinal toxicity is likely to be due to the low absorbed doses delivered to the gut wall from the gut contents. The lack of adverse myelo-toxicity implies that the absorbed dose delivered from the circulating
activity may be a more relevant guide to the potential for marrow toxicity than that due to activity on the bone surfaces.

**Keywords**

Dosimetry, $^{223}$Ra, Biodistribution, Molecular Radiotherapy, alpha-emitter
Prostate cancer is the most common male cancer worldwide and one of the leading causes of cancer-related morbidity and death. Castration resistant prostate cancer (CRPC) has a poor prognosis with a median survival of approximately 2 years. The limited treatment options available have done little to change the overall prognosis and cytotoxic treatments are associated with substantial side effects. Approximately 90% of men with CRPC have radiological evidence of bone metastases which are the main cause of disability and death (1 - 4).

A number of beta-emitting radiopharmaceuticals, including $^{89}$Sr chloride, $^{186}$Re HEDP and $^{153}$Sm EDTP have been developed for palliation of bone pain due to metastases (5). These radiopharmaceuticals target the increased metabolism in areas of bone tumour and have demonstrated preferential uptake in metastases relative to normal bone. Alpha-emitting radiopharmaceuticals are increasingly under evaluation and offer highly localised cytotoxic effects due to their short range and high LET (6,7). $^{223}$Ra dichloride is a novel, bone-seeking alpha-emitter that has been administered to approximately 900 patients with bone metastases from CRPC in Phase I to III clinical trials worldwide (8–14). It has demonstrated an anti-tumour effect on bone metastases in animal models (15). $^{223}$Ra has a half-life of 11.4 days and decays via a chain of alpha and beta emissions into stable lead. Although the proportion of gamma emissions from each $^{223}$Ra decay is only 1.1%, scanning and counting of patients and samples was shown to be feasible in a preliminary study to establish the basic parameters required for quantitative patient imaging of $^{223}$Ra dichloride (16).
To date, only one study has reported the radiopharmacokinetics of $^{223}$Ra (12) based on clinical data and two studies have calculated absorbed dose estimates based on the ICRP model for radium (17,18). However, to our knowledge, dosimetry results from a clinical study have not yet been published.

The primary aim of this phase 1 open-label clinical trial was to determine the biodistribution, pharmacokinetics and dosimetry from two administrations of 100 kBq/kg $^{223}$Ra dichloride administered 6 weeks apart, based on the quantitative imaging methodology developed previously (16), external counting, and blood, urine and faecal collection.

**MATERIALS & METHODS**

**Patient Population**

Six patients were enrolled onto the study. Patients were assessed within 2 weeks of $^{223}$Ra administration and were included if all the following criteria were satisfied: confirmed adenocarcinoma of the prostate; hormone refractory with evidence of rising PSA; serum testosterone level $\leq 50$ng/dl; skeletal metastases confirmed by bone scintigraphy; performance status ECOG 0-2; life expectancy $\geq 6$ months; neutrophils $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; haemoglobin $\geq 95$ g/L; normal total bilirubin; aspartate aminotransferase and alanine aminotransferase $\leq 2.5$ times the upper limit of the normal range (ULN); S-Creatinine $\leq 1.5 \times$ ULN and the patient was able and willing to comply with the protocol and gave informed consent.
Patients were excluded for any of the following reasons: they had received an investigational product in the 4 weeks before $^{223}$Ra administration or were scheduled to receive one during the study period; had received chemotherapy, immunotherapy or external radiotherapy (ER) in the 4 weeks before $^{223}$Ra or were recovering from adverse events due to prior therapy; had previously received more than one regimen of cytotoxic chemotherapy; had prior hemibody radiotherapy; required immediate radiotherapy; had prior systemic radiotherapy with $^{223}$Ra, $^{89}$Sr, $^{153}$Sm, $^{186}$Re or $^{188}$Re; commenced bisphosphonates within 3 months of $^{223}$Ra (unless dosage stable for $\geq 12$ weeks before $^{223}$Ra); had changes in systemic steroids within the week before $^{223}$Ra or during study period; other active malignancies (except non-melanoma skin cancer); visceral metastases from prostate cancer; lymph node metastases with short axis diameter $> 2$cm; bulky locoregional disease and any other serious illness or medical condition.

This clinical trial (NCT00667537) was approved by the appropriate ethics committees and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study subjects gave a signature of written informed consent.

Two intravenous (IV) injections of $^{223}$Ra dichloride were administered 6 weeks apart at an activity of 100 kBq per kg whole-body weight. Patients remained in hospital for approximately 48 hours following each administration at which time they were discharged.

**Data Acquisition**
The bio-distribution, pharmacokinetics and absorbed doses were determined from activity retention measurements in the whole-body, individual organs, blood, urine and faeces as described below. Safety was assessed from adverse events which were graded according to CTCAE version 3.0 (19).

**Blood Samples.** Approximately 3 ml blood was taken from a vein in the contralateral arm to the injection site. Samples were taken pre-injection, immediately post-injection, then at 15, 30 and 45 min and 1, 2, 4, 24, 48, 96 and 144 h post-injection. 1 ml of whole blood was taken from each blood sample. The sample was then centrifuged and 1 ml of plasma removed. The 1 ml blood and plasma samples were measured in an automatic gamma counter. A 1 ml calibration standard containing a known activity of $^{223}$Ra was counted with each set of samples.

**Urine and Faecal Collection.** A pre-injection urine sample and first void post-injection sample were collected separately. Thereafter total urine output was collected separately for the time periods 0 – 4 h, 4 – 8 h, 8 – 24 h and 24 – 48 h post-injection. All faeces excreted by each patient from injection to ~48 hours were collected. Gamma spectroscopy of samples of urine and faeces was performed using a whole-body counter, consisting of four 15 cm diameter x 10 cm thick NaI(Tl) detectors in fixed geometry located in a shielded room. Corrections were made for deadtime and sample volume.

**Whole-body Measurements.** Whole-body measurements of patients were performed on a low sensitivity whole-body counter that consisted of a single NaI detector, photomultiplier tube and pre-amplifier housed in a diverging lead collimator, suspended 2m above a bed. The counting
system had 1024 channels over an energy range of 2048 keV. Measurements were taken immediately post-injection, before first void, then at 1 h and thereafter every 2 h during the first day then at least twice daily until discharge. Subsequent measurements were taken at 96 and 144 h post-injection.

**Gamma Camera Imaging.** Scans were performed on the Philips Forte gamma camera using the medium energy general purpose collimator according to a protocol previously detailed (16). As there was an insufficient count rate to acquire SPECT data in a time-frame that was comfortable for the patient, whole-body and spot views were acquired for approximately 30 minutes each, using matrix sizes of 256 x 1024 and 256 x 256 pixels respectively. Imaging was performed using an energy window set at 82 keV with a 20% width to encompass counts from the 81 and 84 keV emissions from $^{223}$Ra. The first scan was acquired within 0 – 4 h post-injection, and subsequent scans were acquired at 24, 48, 96 and 144 h post-injection. All images were acquired post-void to reduce artefacts due to radioactivity in the bladder. The count rate for all measurements was sufficiently low (< 1 kcts/s over the entire spectrum counted by the camera) that no correction was required for detector dead-time for any scans. Quantification and attenuation correction were performed as previously detailed (16).

**Dosimetry**

Regions of interest (ROIs) were delineated on the images over bone uptake with reference to the $^{99m}$Tc MDP bone scans acquired at pre-treatment assessment. Activity in bone was calculated as the mean of the activity per unit mass in the right and left legs and skull, to avoid difficulties
in interpretation due to gut and lesion uptake in the torso. The activity in bone was assumed to be distributed on the cortical and trabecular bone surfaces, in a ratio relative to the total bone surface (38% on cortical bone surfaces and 62% on trabecular bone) (20,21).

The activity in the red marrow was calculated from the blood sample measurements assuming a blood to bone marrow activity concentration ratio of 1.0 (22). The red marrow absorbed dose from activity on the bone surfaces and from blood were calculated separately.

No specific uptake was seen in the kidneys on the whole-body scans. The cumulated activity in the kidneys was therefore calculated from the kidney mass and measurements of the concentration of activity excreted in the urine. The activity in the urine over the first collection period (0 to ~2 h after injection) was taken to be the activity measured at the end of this period. The activity in each subsequent collection was taken to be the average of the activity measured at the start and end of the collection period. The effective half-life following the last collection was extrapolated from the final data points. The cumulated activity in the bladder was calculated from the activity concentration determined from the collected urine.

The cumulated activity in the gut was derived from ROI’s drawn over the areas of gut uptake on the whole-body scans. In keeping with ICRP 100 the contribution of the alpha emission to the gut wall from the contents was taken to be 0 (23).

No specific uptake was seen in the liver on the whole-body scans. The activity in the liver was therefore estimated from the activity concentration measured in blood, under the worst-case assumption that the liver was entirely composed of blood. The blood activity concentration was multiplied by the mass of the liver to give an upper value of the activity in the liver at each time point.
The cumulated activity in the whole-body was calculated from the patient’s counts measured on the low sensitivity whole-body counter.

For imaged organs cumulated activities were calculated by trapezoidal integration. The activity at time zero was assumed to equal the activity at the first image. The effective half-life as determined from the last two gamma camera images was used for extrapolation from the last measurement to infinity.

The absorbed doses delivered to normal organs were calculated with Olinda / EXM with an alpha quality weighting factor of 1 (24,25). Patient-specific mass corrections were made to the Olinda S-values for whole-body, but not for other organs due to insufficient anatomical information for accurate mass determination. The total absorbed dose to the target region was calculated as the sum of the contributions from all source regions and included contributions from the decay of the daughter products of $^{223}$Ra.

**Statistical Analysis**

A statistical comparison was made between the intra-patient absorbed doses delivered at both administrations using the combined data from a representative organ for each method of data acquisition i.e. whole-body (external patient counting), liver (blood sampling), kidneys (excretion sample counting) and bone surfaces (quantitative imaging). A correlation coefficient and corresponding $P$-value were calculated. Bladder wall absorbed doses were excluded from the comparison as they were derived from the same sample measurements as the kidney doses (ie the activity concentration in urine). Similarly red marrow doses were excluded as they were derived
from bone surface uptake and blood activity measurements. No absorbed dose comparisons were made in the case of the gut as no correspondence was expected due to differing excretion patterns following each administration.

Statistical analysis was performed using GraphPad Prism. The D’Agostino-Pearson test was used for normality. A statistically significant $P$ value was considered to be $< 0.05$. Descriptive statistics are presented as either mean ± standard deviation where data are normally distributed or as median with the range otherwise. Mean or median absorbed doses are given as an average over all patients and both administrations.

RESULTS

Baseline and treatment characteristics for the six patients enrolled on the study are given in Table 1.

Pharmacokinetics and Biodistribution

The injected activity cleared rapidly from blood with 1.1% (range 0.6 – 5.1%) remaining at 24 hours.

Specific uptake was seen on the gamma camera images in whole body, bone and gut (Figure 1). The majority of the administered activity was taken up rapidly into bone with 61 ± 10% in the bone on the first scan 4 hours post-injection.
Activity passed rapidly into the small intestine (SI). For all patients the maximum SI uptake had already occurred by the time of the first scan. 40% ± 19% of the administered activity was in the SI at 4 hours and all activity had cleared the SI by 72 hours. Maximum activity uptake in the ULI was 45% ± 16% at 24 hours, decreasing to 4% (range 0% – 18%) at 1 week. Maximum uptake in the LLI occurred at 24 – 72 hours with an uptake of 17% ± 11% at 48 hours decreasing to 6% ± 4% at 1 week after administration. Figure 2 shows an example of the transit of the activity through the gut.

Faecal excretion was the main route of elimination of activity from the body. Cumulative faecal excretion was 13 ± 12% at the time of discharge (~ 48 hours post-injection). Excretion of activity in the urine was significantly lower than that in faeces. At discharge cumulative urine excretion was 2% ± 2% of the injected activity and the rate of activity excretion was decreasing in all cases.

**Dosimetry**

The absorbed doses per injected activity delivered to each organ are summarised in Table 2 and displayed in Figure 3. It can be see that the whole-body dose delivered from the second administration is within 30% of that delivered from the first with the exception of two cases for which faecal excretion patterns differed. A statistical comparison between the intra-patient absorbed doses from the two administrations for the bone surfaces, kidneys, liver and whole-body resulted in a correlation coefficient of 0.99 ($P < 0.01$), indicating a significant correspondence between the absorbed doses delivered at the two administrations. In contrast, the inter-patient variability in the delivered absorbed doses per injected activity, varied from a
minimum of 150% for the liver absorbed dose to nearly 400% for the bone surfaces and red marrow.

**Safety**

All 6 patients experienced an AE during the study (see Table 3). The most frequently reported AEs were gastrointestinal (4 patients, 66.7%) and musculoskeletal and connective tissue disorders (3 patients, 50%).

**DISCUSSION**

The pharmacokinetic results of this trial demonstrated that the $^{223}$Ra dichloride was rapidly cleared from the blood and taken up into bone which supports previous findings ($^8,12$). The main route of excretion was via faeces. The mechanism of transport from the blood into the SI is not currently understood but clearly took place rapidly as the maximum uptake in the SI had already occurred by the time of the first scan 4 hours after administration as has been previously observed ($^12$). Subsequent activity levels in the SI fell sharply and activity appeared to pass into the LLI via the ULI.

It was assumed that the localisation of all daughter products followed that of the $^{223}$Ra. However, as stated in ICRP 67 (26) it is possible that $^{211}$Pb (with a half-life of 36 minutes) may localise to liver, although the gamma emissions from this daughter product are at the extreme of the range of the gamma camera. The potential for $^{211}$Bi (with a half-life of 5 minutes) to localise in liver
was explored by Carrasquillo et al (12) by imaging of the 351 keV emission with inconclusive results.

The biological effect of absorbed doses received from alpha particles is poorly understood in a therapeutic context (27). Thus, while radiation weighting factors ranging from 5 to 20 are often applied to evaluate stochastic risks due to the high linear energy transfer of the emissions, for this study no weighting factor was applied.

With the exception of the GI tract the mean absorbed doses for each organ presented in Table 2 vary by up to an order of magnitude. The absorbed doses previously calculated based on ICRP models (18) fall within these ranges except for the red marrow, bone surfaces and liver. Similar absorbed doses were delivered to the GI tract although the major contribution in (18) is from alpha irradiation, whereas this was set to 0 for this study according to the later ICRP model (23). The upper range of absorbed doses delivered to the red marrow and bone endosteum in this study are significantly higher (by up to a factor of 14) than those of (18). The absorbed dose to the liver was found to be significantly lower in this study.

In this study mild adverse myelotoxicity was seen for only one patient, although anaemia, leukopenia, neutropenia and thrombocytopenia have been reported in other studies (8-13). Adverse myelotoxicity has not been seen at a level that might be expected from the high total absorbed doses determined in this study. Absorbed doses are primarily delivered to the red marrow from circulating blood, and from uptake on the bone surfaces. However, alpha emissions will irradiate only a very small fraction of the red marrow due to their short range (28). The
absorbed dose delivered from the circulating activity may therefore be a more relevant guide to the potential for marrow toxicity than that due to activity on the bone surfaces. The large self-absorbed doses delivered to the bone surfaces are particularly of note and may prove in the long-term to be the cause of dose limiting toxicity.

Calculations of the mean absorbed dose delivered to the walls of the SI, ULI and LLI were performed under the assumptions that all the activity was in the gut contents and that the contribution to the walls of the gut from alpha emissions was negligible, as stated by ICRP 100 (23). Although acute gastro-intestinal toxicity from $^{223}$Ra dichloride treatment has not been reported as a significant occurrence in other studies, diarrhoea has been reported and indeed one patient in this study experienced diarrhoea. If $^{223}$Ra is retained in the mucosa the absorbed dose delivered to the walls of the gut may not be negligible and the above assumptions would result in an under-estimate of gut doses (8-13).

Whole-body dosimetry can be calculated accurately, and has proven to be a reliable surrogate for the absorbed dose delivered to the red marrow in studies of $^{131}$I mIBG therapy (29). The relative simplicity of this procedure also facilitates its routine clinical use. However, a key assumption for organ level dosimetry is uniform distribution of uptake and only an average absorbed dose is calculated for a target organ. These assumptions are particularly erroneous for treatment with alpha emitters, and whole-body dosimetry may prove to be of limited value. Further studies are required to investigate this.
Inter-patient comparisons indicate that a wide range of absorbed doses are delivered from weight-based administrations of activity while intra-patient results show that the absorbed doses delivered from a second administration closely follow those delivered from the first in the majority of cases. Taken into consideration with the generally low toxicity profile of the studies performed to date, this implies that the option of personalised treatments could be explored.

CONCLUSION

This dosimetry study of $^{223}$Ra dichloride has demonstrated a range of absorbed doses delivered to critical organs. Biodistribution, pharmacokinetics and absorbed doses are largely consistent over two administrations for any given patient, which would facilitate personalised treatments.

DISCLOSURE

Christopher C. Parker consults for Bayer Healthcare Pharmaceuticals and Algeta ASA. Valerie J. Lewington consults for Bayer Healthcare Pharmaceuticals. Research funding from Bayer Healthcare Pharmaceuticals and Algeta ASA is disclosed. All other authors declare no conflict of interest.

Acknowledgements

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REFERENCES


Figure 1: Whole-body anterior images for patient 3 acquired at A) 4, B) 24, C) 48, D) 72 and E) 144 hours post administration.
Figure 2: Activity retention curves in the SI, ULI and LLI for patient 1 for A) administration 1 and B) administration 2.
Figure 3: Absorbed dose (in mGy/MBq) for A) Bone surfaces, B) Red marrow from blood, C) Kidneys, D) Bladder Wall, E) Liver, F) Whole-body.
## TABLE 1: Patient data

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<th>3</th>
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<td>63</td>
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<td>72.5</td>
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<td>74.5</td>
<td>97.6</td>
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<td>2</td>
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</table>

* Extent of disease (EOD) grading system: 0 = normal or abnormal because of benign bone disease; 1 = fewer than six metastatic sites; 2 = 6 to 20 metastatic sites; 3 = more than 20 lesions but not a superscan; 4 = superscan.
**TABLE 2**: Mean residence times and absorbed doses delivered from both administrations

<table>
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<tr>
<th></th>
<th>Mean residence time (h)</th>
<th>Mean alpha absorbed dose (mGy/MBq)</th>
<th>Range (mGy/MBq)</th>
<th>Mean beta + gamma absorbed dose (mGy/MBq)</th>
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<td>2 – 15</td>
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<td>408</td>
<td>177 - 994</td>
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<td>2331-13118</td>
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<td>&lt;1</td>
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<td>UB Wall</td>
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<td>Number of Patients (%)</td>
<td>Highest CTC Grade (number of patients)</td>
<td>Relationship to $^{223}$Ra dichloride: Term (number of patients)</td>
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<td>----------------------------------------</td>
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<td>1 (16.7)</td>
<td>2 (1)</td>
<td>Unlikely (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>1 (16.7)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (16.7)</td>
<td>-</td>
<td>Possible (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No CTC grade reported, severity was recorded as mild, defined as transient and easily tolerated.
† One patient died approximately 1 year after the first administration, due to disease progression.
CTC=Common Toxicity Criteria.
A Phase 1, open-label study of the biodistribution, pharmacokinetics and dosimetry of Radium-223 dichloride (223Ra dichloride) in patients with hormone refractory prostate cancer and skeletal metastases

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