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REVIEW ARTICLE

Imaging and dosimetry for radium-223: the potential for personalized treatment

GLENN D FLUX, PhD

Joint Department of Physics, Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK

Address correspondence to: Dr Glenn D Flux

E-mail: glenn.flux@icr.ac.uk

ABSTRACT

Radium-223 (^{223}Ra) offers a new option for the treatment of bone metastases from prostate cancer. As cancer treatment progresses towards personalization, the potential for an individualized approach is exemplified in treatments with radiotherapeutics due to the unique ability to image *in vivo* the uptake and retention of the therapeutic agent. This is unmatched in any other field of medicine. Currently, ^{223}Ra is administered according to standard fixed administrations, modified according to patient weight. Although gamma emissions comprise only 1% of the total emitted energy, there are increasing reports that quantitative imaging is feasible and can facilitate patient-specific dosimetry. The aim of this article is to review the application of imaging and dosimetry for ^{223}Ra and to consider the potential for treatment optimization accordingly, in order to ensure clinical and cost effectiveness of this promising agent.

INTRODUCTION

Prostate cancer is the most common male cancer in the UK, and the second most common male cancer worldwide.¹ The incidence of prostate cancer has increased by 155% in the past 40 years, in part due to increased detection from prostate-specific antigen testing, with the largest increase for males aged between 25 and 49 years. Diagnosis at Stage 4 occurs in 20–30% of cases when there may be bone involvement, in which case, life expectancy may be as low as 5 years.²

Radium-223 (^{223}Ra) dichloride, approved by the United States Food and Drug Administration in 2013, offers a novel therapeutic treatment option for castration-resistant prostate cancer that has metastasized to the bone. Although not the first radiotherapeutic used for this purpose, samarium-153 ethylenediamine tetra(methylene phosphonic acid) (^{153}Sm EDTMP) and strontium-89 (^{89}Sr) chloride have long been administered, as have phosphorus-32, rhenium-186 (^{186}Re) hydroxyethylidene diphosphonate (HEDP) and rhenium-188 (^{188}Re) HEDP.^{3,4} ^{223}Ra is the first alpha emitter to be approved and the first to demonstrate a survival advantage. A number of clinical studies of ^{223}Ra ^{5–8} culminated in a Phase-3 clinical trial of 921 patients to evaluate the survival advantage of ^{223}Ra in comparison with a placebo.⁹

In the UK, ^{223}Ra has become increasingly used following European Medicines Agency approval in 2013.¹⁰ From its

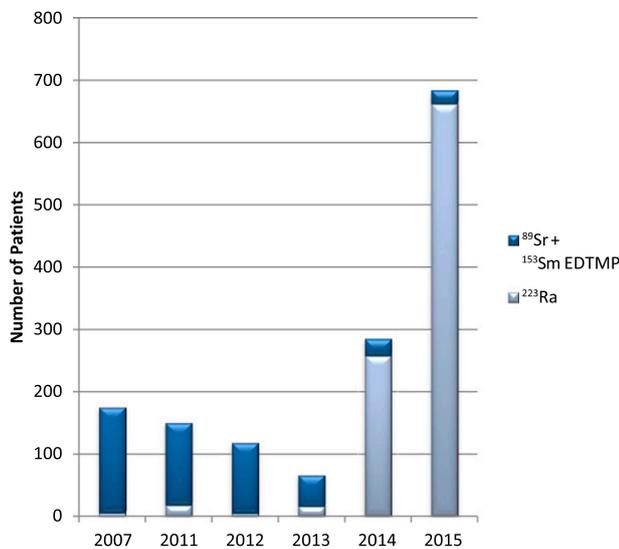
initial use in 2007,¹¹ ^{223}Ra was used in <5% of all treatments of bone metastases with radiopharmaceuticals in 2011 and 2012, but in 2015, it was used in >95% of treatments^{12,13} (Figure 1). The total number of patients with bone metastases treated with radiopharmaceuticals increased by nearly 400% from 2007 to 2015 due to ^{223}Ra .

Personalized treatment planning is of increasing interest in molecular radiotherapy, for which the theragnostic potential of radiotherapeutics can be utilized and for which there is increasing evidence of correlations between absorbed dose and outcome.¹⁴ A fully individualized plan requires quantitative imaging, internal dosimetry, predictions of effectiveness and toxicity, and evaluation and optimization of the planning parameters available. Financial aspects must also be taken into account to demonstrate that the potential for patient benefit and cost-effective use of drugs would outweigh the increased costs associated with image acquisition and dosimetry. An European Union directive (Euratom 59/2013) mandates the same level of treatment planning and verification for radiotherapeutics as for external beam radiotherapy,¹⁵ and there are increasing calls to implement routine image-based dosimetry.¹⁶

IMAGING

^{223}Ra undergoes a complicated decay scheme, with a series of six daughter products, before decaying to stable lead. The total emitted energy is 28.2 MeV, of which 95% is from

Figure 1. Radiopharmaceutical treatments of bone metastases. ^{223}Ra , radium-223; ^{153}Sm EDTMP, samarium-153 ethylenediamine tetra(methylene phosphonic acid); ^{89}Sr , strontium-89. Adapted from Rojas et al.¹³



alpha emissions, 3.2% from beta particles and <2% from gamma emissions¹⁷ (Table 1). This results in a low signal which can present challenges for quantitative imaging, but nevertheless, introduces the potential for individualized biodistribution studies. Hindorf et al¹⁷ defined the imaging characteristics for ^{223}Ra , identifying three energy peaks as suitable for imaging of the 10 photon energies emitted with a probability >1%. Optimal energy windows were set at 82, 154 and 270 keV, each with a 20% width (Figure 2). Camera sensitivity was found to be 69, 31 and 34 counts per second (cps) MBq^{-1} from the three windows, respectively. Although the most abundant photon emissions at around 82 keV are potentially contaminated by the lead X-ray emissions from the collimator, this did not prevent quantitative imaging. The full-width half-maximum spatial resolution of the system was 11 mm at all peaks, although the scatter was at a minimum for the 82 keV peak. This spatial

resolution can lead to a marked partial volume effect for volumes <30 mm diameter. It was concluded that the 82-keV window is sufficient for quantitative imaging, with an effective mass attenuation coefficient of $0.071 \text{ cm}^2 \text{ g}^{-1}$. A phantom study with clinically relevant activities and volumes demonstrated that activity could be quantified to within 10% for a large 200-ml volume and within 40% for a 0.5-ml volume.

PHARMACOKINETICS AND DOSIMETRY

Internal dosimetry for the marrow and skeleton presents significant challenges due to microscopic energy deposition within the bone matrix.^{18,19} Although whole-body dosimetry can be assessed from either whole-body scans or from external retention measurements,²⁰ dosimetry for red marrow can be obtained from imaging and from blood sampling and should take into account the activity in the extracellular fluid, the blood, the bone marrow cells, the bone and major organs of uptake.²¹ Models to generate absorbed fractions for alpha particles in cortical and trabecular bones are necessary to consider dosimetry at a microscopic scale.^{22–25} Correlations between the absorbed dose delivered to the red marrow and toxicity have been found for treatments with ^{153}Sm EDTMP.²⁶

Of particular relevance to alpha emitters, a relative biological effect (RBE) may be applied to account for the biological effect of the high linear energy transfer (LET) radiation with a value of 5 recommended by the US Department of Energy.²⁷ For stochastic effects the International Commission on Radiological Protection (ICRP) recommends a radiation weighting factor of 20. Absorbed doses quoted in this review are for a RBE of 1, unless stated otherwise.

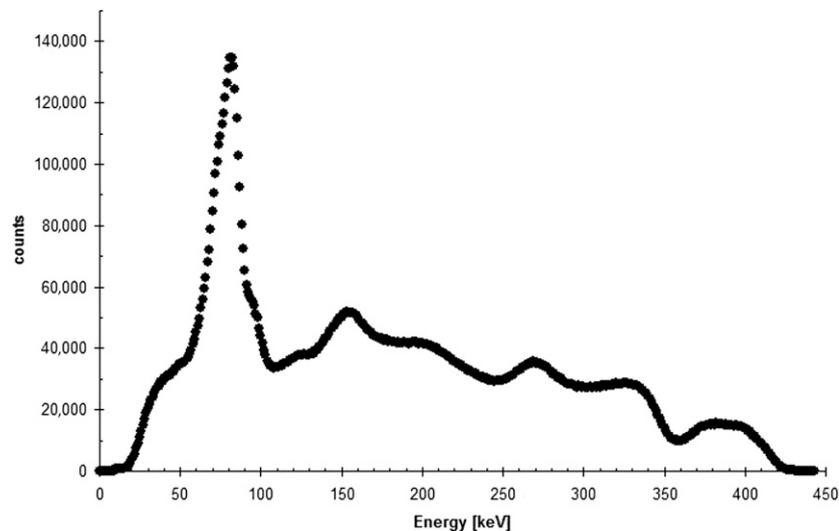
Absorbed doses were calculated according to the ICRP model for radium by Lassmann et al²⁸ using the DOSEAGE software. The ICRP biokinetic model^{29,30} considers that 25% of the administered radium localizes in the bone, with preferential uptake in osteoblastic activity. This can offer both an analgesic effect and potentially a degree of tumour control. Daughter products are also taken into account. The bone endosteum was calculated to receive the highest absorbed doses at $7.5 \times 10^{-7} \text{ Gy Bq}^{-1}$ for

Table 1. Decay chain for radium-223 (^{223}Ra). The relative proportions of the branched decay from bismuth-211 (^{211}Bi) are 0.997 and 0.003 for $^{211}\text{Bi} \rightarrow$ thallium-207 (^{207}Tl) and $^{211}\text{Bi} \rightarrow$ polonium-211 (^{211}Po), respectively

| Radionuclide | Mode of decay | Abundance | Half-life |
|---|---------------|-----------|------------|
| $^{223}\text{Ra} \rightarrow ^{219}\text{Rn}$ | α | 100% | 11.43 days |
| $^{219}\text{Rn} \rightarrow ^{215}\text{Po}$ | α | 100% | 3.96 s |
| $^{215}\text{Po} \rightarrow ^{211}\text{Pb}$ | α | 100% | 1.78 ms |
| $^{211}\text{Pb} \rightarrow ^{211}\text{Bi}$ | β^- | 100% | 36.1 min |
| $^{211}\text{Bi} \rightarrow ^{211}\text{Po}$ | β^- | 0.276% | 2.14 min |
| $^{211}\text{Bi} \rightarrow ^{207}\text{Tl}$ | α | 99.72% | 2.14 min |
| $^{211}\text{Po} \rightarrow ^{207}\text{Pb}$ | α | 100% | 0.516 s |
| $^{207}\text{Tl} \rightarrow ^{207}\text{Pb}$ | β^- | 100% | 4.77 min |
| $^{207}\text{Pb} \rightarrow -$ | Stable | - | - |

²⁰⁷Pb, lead-207; ²¹¹Pb, lead-211; ²¹⁹Rn, radon-219.

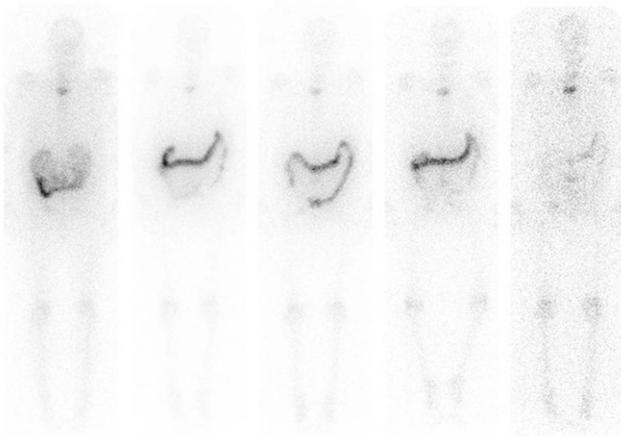
Figure 2. Energy spectrum for radium-223 (acquired for a standard, using medium-energy collimators on a Philips Forte camera).



alphas and $1.1 \times 10^{-8} \text{ Gy Bq}^{-1}$ for betas/gammas, with the red marrow receiving $7.2 \times 10^{-8} \text{ Gy Bq}^{-1}$ for alphas and $5.5 \times 10^{-9} \text{ Gy Bq}^{-1}$ for betas/gammas. The dose coefficients were also presented for radiation weighting factors of 5 and 20.

In a Phase-1 pharmacokinetic and biodistribution study, Carrasquillo et al³¹ performed an activity escalation study at 50, 100 and 200 kBq kg^{-1} of ^{223}Ra in 10 patients. Rapid clearance of the ^{223}Ra from the blood was found, with faecal excretion as the major route of elimination. Urinary excretion was minor. Few side effects were observed.

The biodistribution, pharmacokinetics and dosimetry of ^{223}Ra were further studied in a Phase-I trial of ^{223}Ra administered at 100 kBq kg^{-1} to six patients treated twice, 6 weeks apart.³² Dosimetry was evaluated from image data obtained according to the criteria determined by Hindorf et al¹⁷ from external whole-body counting,²⁰ from blood sampling and from faecal and urinary excretion data, using the OLINDA/EXM software.³³ The

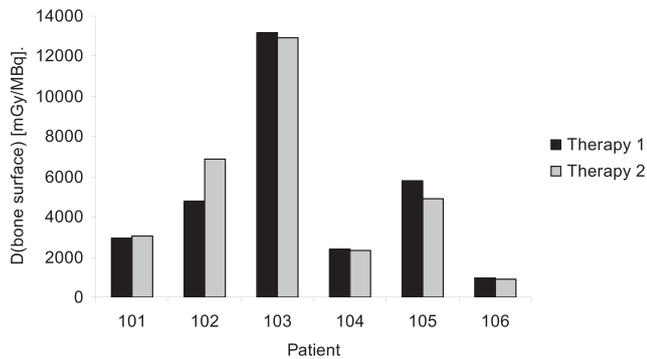
Figure 3. Anterior scans of radium-223 at days 0, 1, 2, 3 and 6 following administration of 55 kBq/kg .

study confirmed that activity was quickly cleared from the blood and that the main route of excretion was *via* the gut (Figure 3). As predicted by the ICRP modelling study,²⁸ the bone surfaces were observed to receive the greatest absorbed dose. Of particular note was that the range of absorbed doses delivered to bone surfaces was extremely large, ranging from 2.3 to 13.1 Gy MBq^{-1} from alpha emissions and 9–51 mGy MBq^{-1} from beta/gamma emissions. However, patients exhibited similar biodistribution and pharmacokinetic profiles for both ^{223}Ra administrations (Figure 4). A lack of either severe gastrointestinal or severe myelotoxicity was assumed to be due to the very short path length of the alpha particles that do not uniformly irradiate the intestinal walls from the gut contents or the marrow from bone surfaces.

A Phase-1 study was performed in Japan according to similar image acquisition parameters, as for the study by Chittenden et al³⁴ for six patients who were administered a single injection of either 50 or 100 kBq kg^{-1} . The absorbed doses delivered to osteogenic cells were found to be lower than that for the Chittenden et al study, at a mean of 0.76 Gy MBq^{-1} . This may be due to the fact that two patients were considered as outliers due to the number or size of metastatic burden, although with the low numbers of patients recruited in each study, the values can only give an indication.

Pacilio et al³⁵ performed tumour dosimetry on 24 lesions in a cohort of 9 patients. Patients were given six administrations of 50 kBq kg^{-1} at 4-week intervals. Tumours received absorbed doses ranging from 0.2 to 1.9 Gy. Whole-body planar imaging was performed for up to 24 days post-administration according to the recommendations of Hindorf et al,¹⁷ as outlined above. The potential benefit of incorporating data acquired from technetium-99m ($^{99\text{m}}\text{Tc}$) methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) bone scans was explored to facilitate delineation of target volumes following co-registration of the bone scans with the radium scans. A correlation between uptake on both imaging modalities was seen, indicating that the bone scans could provide an indication of ^{223}Ra uptake. A Monte Carlo study with SIMIND³⁶

Figure 4. Absorbed doses delivered to bone surfaces from six patients treated twice with 55 kBq kg⁻¹ radium-223 with a 6-week interval.



and experimental measurements found good agreement with Hindorf for the spatial resolution. A mean absorbed dose of 0.7 Gy (range 0.2–1.9 Gy) was delivered to lesions. Notably, this trial included scans at later time points than those in the previous studies. The low count rate of ²²³Ra, in combination with the relatively long half-life, necessitates optimization of scan time points.

The absorbed doses delivered to bone surfaces from the most common radiotherapeutics for typical administrations are listed in Table 2.

EFFECTIVENESS

Pre-clinical studies found anti-tumour activity in rats.³⁷ A Phase-1A study of single activity administrations ranging from 46 to 250 kBq kg⁻¹ in patients with bone metastases from both prostate and breast cancer found pain relief in >50% of patients and a decline in alkaline phosphatase, although whether this correlated with the higher activity administrations was not reported.⁶ The Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial demonstrated an increased survival of 3.6 months, with minimal toxicity.⁹ Unfortunately, as no dosimetry was performed for these patients, there is as yet no evidence for correlations of absorbed dose with outcome.

TOXICITY AND RISKS

Considerations of marrow toxicity are complicated. The high LET of alpha particles and short path length (approximately 80 μm)

induces a high cell kill in adjacent cells, but spares normal tissues beyond.^{38,39} Uptake of ²²³Ra on the bone surfaces will therefore not irradiate the marrow cavities uniformly. The largest uniform contribution to the absorbed dose delivered to the red marrow will be from the distribution of the radiopharmaceutical in blood following administration. This may account for a lack of expected toxicity. However, it has been observed that there is a spatial gradient of haematopoietic stem and progenitor cells with a larger concentration closer to the bone²⁴ so that the radiosensitive cells of interest may receive higher absorbed doses. Uptake and marrow distribution will vary widely from patient to patient.

In a clinical Phase-1 trial, a single administration of up to 250 kBq kg⁻¹ was given to 25 patients. Only grade 1 toxicity for thrombocytopenia was observed.⁶ In the Japanese study, thrombocytopenia was reported for 20% of EOD4 (“superscan” patients, as defined by intense uptake in the skeleton with little or no activity in the soft tissues) as opposed to 6% of patients receiving a placebo.³⁴

The package insert for Xofigo⁴⁰ states that 2% of patients administered with ²²³Ra on the ALSYMPCA trial experienced bone marrow failure (54% of whom required blood transfusions) or ongoing pancytopenia and that there were two deaths due to bone marrow failure. Four percent of patients receiving Xofigo (as opposed to 2% of those given a placebo) permanently discontinued therapy. Thrombocytopenia is cited as “very common” with an incidence of >1 in 10 patients. There has been no testing of the potential concomitant effects of toxicity for patients who subsequently receive chemotherapy.

To date, there have been no systematic studies to evaluate mid- to long-term risks associated with ²²³Ra due to the expected latency period, although in pre-clinical studies osteosarcomas were found in rats at clinically relevant administered activities.⁴⁰ The issue of potential secondary malignancies for patients undergoing molecular radiotherapy has not been addressed but may become more relevant as trials promise increased survival. This may become particularly relevant for patients undergoing treatment for bone metastases from breast cancer.⁴¹

In the absence of long-term outcome data, it is interesting to note cases of toxicity from other radium products that have been used

Table 2. The mean absorbed doses delivered to the bone surface and red marrow from commonly used radionuclides for typical administrations

| Target Volume | Total absorbed dose (Gy) | | | | |
|---------------|-------------------------------|--------------------------------|--------------------------------|---------------------------------------|---|
| | ⁸⁹ Sr ^a | ¹⁵³ Sm ^b | ¹⁸⁶ Re ^c | ²²³ Ra (ICRP) ^d | ²²³ Ra (measured) ^e |
| Bone surface | 2.6 | 17.6 | 1.8 | 17.3 | 54–303 |
| Red marrow | 1.7 | 3.9 | 1.7 | 1.7 | 4–23 |

²²³Ra, radium-223; ¹⁸⁶Re, rhenium-186; ¹⁵³Sm, samarium-153; ⁸⁹Sr, strontium-89.

Values are based on administration levels in Lassmann and Nosske,²⁸ Chittenden et al³² and Bodei et al.⁷⁰

^aFixed activity of 150 MBq.

^bAdministered activity of 37 MBq kg⁻¹, based on a 70-kg male.

^cAdministered activity 1295 MBq.

^dSix administrations of 55 kBq kg⁻¹, based on a 70-kg male.

^eSix administrations of 55 kBq kg⁻¹, based on a 70-kg male.

medicinally or for other purposes. Radium-224 was used to treat tuberculosis and ankylosing spondylitis in children and adults after World War II but was found to cause bone sarcomas and severe non-skeletal effects.^{42–44} The example of the “radium dial painters”, who ingested ²²⁶Ra from licking paint brushes whilst painting watch dials, is of particular interest. In this case, a retrospective analysis found a threshold skeletal absorbed dose of 10 Gy to the skeleton for the induction of bone sarcomas from ²²⁶Ra⁴⁵ (Figure 5). In a study of 1634 dial workers, there were no cases of sarcoma below this threshold, whereas sarcomas were induced in 64 of the 264 cases who received >10 Gy. Although the challenges of retrospective dosimetry in a population, for whom dosimetry was not performed, render a degree of uncertainty on the actual value of the dose threshold, it is of note that this value is of the order of that seen in the clinical studies reported above.

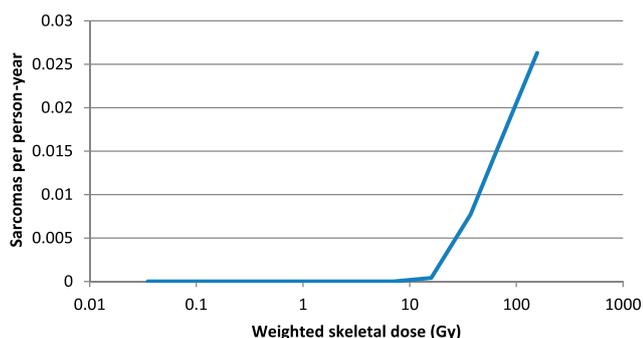
TREATMENT PLANNING

Treatment planning for molecular radiotherapy must operate with a different set of parameters than those used for external beam radiotherapy (EBRT). For a given radiotherapeutic, these parameters comprise the level and frequency of administrations. The prediction of an absorbed dose delivered from a first administration requires a study with either a low level administration of the radiotherapeutic or a surrogate tracer.

Adaptive treatment planning could consist of an initial nominal administration of ²²³Ra (currently 55 kBq kg⁻¹), with dosimetry obtained from a series of quantitative scans acquired over a suitable time period, accounting for effective decay, to determine the biodistribution and retention. Subsequent administrations would be tailored to the individual patient, taking into account the absorbed doses delivered to healthy organs, particularly the gut, red marrow and bone endosteum. Blood sampling could also provide useful dosimetric information.

Murray et al⁴⁶ demonstrated that baseline standardized uptake value (SUV) from a fluorine-18-fluoride scan correlated with ²²³Ra uptake and with the absorbed doses subsequently delivered. Response, as measured by a decrease in SUV, was seen as a function of the baseline SUV. Chittenden et al³² found a correlation between the absorbed doses delivered to the normal organs of the same patient, including bone surfaces, from two consecutive administrations of ²²³Ra despite a wide interpatient

Figure 5. Incidence of bone sarcomas as a function of the absorbed dose to the skeleton. Adapted from Rowland.⁴⁵



variation, indicating that an adaptive planning strategy may be investigated.

The rationale for repeated treatments is worthy of investigation. In EBRT, fractionation of treatment is based on differential sparing in late responding normal tissues relative to tumours. However, high LET radiation is not expected to exhibit this effect and *in vitro* experiments have shown that in human kidney cell lines, there is no tissue-sparing effect from administration of activity in two or three fractions.^{19,47} Nevertheless, marrow recovery benefits from an interval between treatments and continued administrations may prolong palliative effects.

A single study has investigated the reproducibility of imaging and dosimetry in up to six sequential treatments for four lesions in two patients using planar whole-body scans with three energy windows centred at the peaks identified above.⁴⁸ In one patient, the uptake was imaged at between 30.0 and 34.5 counts/pixel/hour over the six cycles in one lesion and from 27.8 to 36.5 counts/pixel/hour in the second lesion. The half-life in the first lesion varied from 1.8 to 3.6 days and from 3.0 to 4.5 days in the second lesion. Variations in effective half-life resulted in a two-fold difference in the absorbed dose delivered to the different lesions, and a two-fold difference in the absorbed dose delivered to the same lesion over six cycles. A similar result was seen for the second patient. The authors conclude that owing to these variations in biokinetics and dosimetry of different patients and of different lesions, individualized treatment planning using dosimetry is necessary. This may be aided by correlations between uptake of ^{99m}Tc-MDP and ²²³Ra,³⁵ as has also been seen for ¹⁵³Sm EDTMP and ¹⁸⁶Re etidronate.^{26,49,50} ^{99m}Tc DMSA uptake has also been shown to correlate with that of ¹⁸⁸Re DMSA.⁵¹

COSTS

Inevitably, a cost resource would be associated with the routine introduction of imaging and dosimetry. However, the cost of ²²³Ra, as for other emerging commercial radiotherapeutics, is in line with conventional cancer drugs and significantly greater than that for ¹⁵³Sm or ⁸⁹Sr for a full course of treatment. The cost of extra scans for dosimetry is therefore relatively low.

It follows that imaging and dosimetry calculations would be cost effective in the short term if unnecessary treatments could be identified and prevented, beyond that possible with diagnostic ^{99m}Tc-MDP or fluorine-18-fluoride imaging. This would enable alternative treatment strategies to be identified. Of particular relevance for this treatment is that the treatment course of 6 months is longer than that for many radiotherapeutics. As yet, there have been no studies to report the percentage of courses of ²²³Ra that are completed. The cost benefit would also be seen in the longer term if it were possible to deliver effective treatments in a shorter time frame that would mitigate further treatments. This hypothesis could also be tested in clinical trials. The cost of ²²³Ra relative to more established radiopharmaceuticals has a significant impact on the justification of resources for dosimetry although the health economics of radiopharmaceutical treatments,

imaging and dosimetry have yet to be evaluated. Costs for imaging and dosimetry should therefore be considered in relation to patient benefit, the overall cost of the treatment and in relation to corresponding costs incurred for treatment planning for EBRT.

DISCUSSION

The challenges of dosimetry

The nature of alpha irradiation in a clinical context is not clearly understood. It has been noted that such irradiation from internal sources lies at an extreme from uniform irradiation from gamma rays⁵² and raises conceptual and practical challenges for dosimetry. Of particular relevance is the short range high LET that can necessitate the use of a relative biological weighting factor.

There are a number of complications and confounding factors that impede the accuracy with which dosimetry may be performed. These include the low gamma yield that produces poor qualitative information in comparison with conventional bone-seeking diagnostic agents, although it may be argued that for well-defined volumes of uptake, the reproducibility of quantitative information, as shown by phantom measurements and by the consistency of sequential measurements, can inform an individualized approach to treatment. The non-uniform cellular distribution of target cells and of ²²³Ra uptake and irradiation complicates interpretation of the macroscopically averaged absorbed dose in terms of the biological effect, and similarly, there are as yet no definitive evidence-based values for the RBE applicable in the context of therapy. This will only become apparent in time following investigative clinical trials and collection of absorbed dose–effect data. Nevertheless, preliminary evidence suggests that this is an area that is worthy of investigation, with a view to improving the palliative and therapeutic use of ²²³Ra, possibly in conjunction with other radiotherapeutics and “cold chemotherapeutics”.

The role of mean dosimetry can be questioned for alpha emitters, due to the high LET, culminating in the Bragg peak, and the short range that will result in a very localized deposition of energy.⁵³ Nevertheless, macroscopic mean dosimetry is feasible in a clinical setting with patient-specific data, whereas microscopic considerations are necessarily limited to models with limited applicability to a given patient. The role of dosimetry is yet to be determined.⁵⁴

Uncertainties

The challenges faced with quantitative imaging and dosimetry for ²²³Ra, although more pronounced, are not exclusive to alpha emitters. The most widely used radiopharmaceutical in molecular radiotherapy, iodine-131, also presents significant challenges due to the high-energy gamma emissions and the high activities administered. This incurs camera deadtime,⁵⁵ which is not applicable to ²²³Ra. The various issues will undoubtedly continue as long as gamma cameras are designed exclusively for low-activity imaging of ^{99m}Tc.⁵⁶ Similarly, although the heterogeneous absorbed dose distribution at a microscopic scale is critical to the relevance of alpha emitters,^{57–59} this characteristic

is also highly relevant for beta emitters, that can have a mean path length of far <1 mm.

There are a number of sources of uncertainty inherent in the calculations of absorbed doses. The uncertainty regarding this value may make direct comparisons with other radionuclides challenging, although as a systematic factor it does not impede treatment planning. Similarly, the absorbed dose calculated for the endosteal layer is dependent on the thickness of this layer, as the absorbed dose delivered is inversely proportional to the mass. This has been quoted as between 10 and 50 μm .¹⁹ Again, this introduces only a systematic error that does not prevent treatment planning. The increasing use of ²²³Ra, with standardized administrations, offers the possibility to recruit a large patient cohort.

Harmonization of imaging, dosimetry and reporting

In addition to the need for harmonization of performing and reporting imaging and dosimetry,⁶⁰ there is also a requirement for standardization of trial methodologies, reporting of trial outcomes and response criteria. Although using similar methodology, lower absorbed doses were reported for the Yoshida et al study³⁴ than for the Chittenden et al study,³² possibly due to exclusion of the outliers in the former case that exhibited large tumour burdens. However, such “superscans”, expected in 10% of patients,⁸ do not constitute a contraindication for treatment.

Although there are no defined criteria by which to measure response,⁶¹ imaging of ²²³Ra offers the potential to evaluate response predictively according to tumour burden as has been demonstrated for ¹⁸⁶Re HEDP⁶² and for whole-body diffusion-weighted MRI.^{63,64}

Future prospects

The role of ²²³Ra as part of a multimodality approach to the patient pathway has yet to be investigated thoroughly. Alpha therapy is possibly best used as an adjunct to chemotherapy due to its strength at targeting microscopic deposits. The radiobiological considerations of alpha emitters offers the potential for concomitant administrations of complementary beta-emitting radiotherapeutics such as ¹⁸⁸Re HEDP, ⁸⁹Sr chloride, ¹⁵³Sm EDTMP or lutetium-177 prostate-specific membrane antigen for which dosimetry is feasible.^{3,65–68}

Treatment strategy is primarily pain relief, and although this mechanism is poorly understood,⁴ it can be linked to survival. ⁸⁹Sr chloride, ¹⁵³Sm EDTMP, ¹⁸⁶Re HEDP and ¹⁸⁸Re HEDP have similarly all been shown to have palliative effects, although no survival studies at the scale of the ALSYMPCA trial have been performed. The aim of treatment calls into question the treatment regimen itself. If pain palliation is the primary aim, it may be beneficial to administer lower levels of activity over a prolonged period. If an anti-tumour effect is intended, higher activities would be given, taking normal tissue toxicity into account.

SUMMARY

Dosimetry is increasingly used for all forms of treatment with radiotherapeutics that deliver radiation treatment. In the case

of external-beam radiotherapy or brachytherapy, a lack of dosimetry-based personalized treatment planning and verification would be considered unsafe practice. Patients undergoing radiopharmaceutical treatment for bone metastases may receive higher absorbed doses to bone surfaces or marrow where the uptake is high, and those patients with a favourable prognosis may be exposed to unwarranted long-term risks.

There is now a pressing need for larger multicentre trials to investigate the dosimetry and to optimize treatment regimens. There is as yet little evidence for the absorbed doses delivered to metastatic deposits throughout the full course of six administrations or that the absorbed doses delivered to organs at risk over six administrations remain the same as those measured from one or two administrations.

^{223}Ra is at the forefront of the resurgence of radiopharmaceuticals for cancer treatment.⁶⁹ The potential for patient benefit as well as for adverse effects and the substantially increased costs relative to more established agents accentuates the need to ensure maximum effectiveness and cost benefit of clinical implementation. It is likely that the application of imaging and dosimetry to facilitate personalized treatment planning will help to ensure successful clinical and commercial results that will have a strong bearing on the continued development of other radiotherapeutics.

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