**Review Article**

**Ra-223 dichloride management in a Nuclear Medicine Unit: experience of a referral institution**

Giulia Anna Follacchio*, Viviana Frantellizzi, Francesco Monteleone, Giuseppe De Vincentis and Mauro Liberatore

Sapienza University of Rome, Department of Radiological Sciences, Oncology and Human Pathology, Nuclear Medicine Unit, 324, Viale Regina Elena, 00161, Rome, Italy

*Address for Correspondence: Giulia Anna Follacchio, Department of Radiology, Oncology and Human Pathology, Nuclear Medicine Unit, 324, Viale Regina Elena, 00161, Rome, Italy, Tel: +390649978590, Fax: +390649978592; Email: giuliaanna.follacchio@uniroma1.it

Submitted: 18 September 2017  
Approved: 26 September 2017  
Published: 27 September 2017

Copyright: © 2017 Follacchio GA, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Keywords:** Ra-223 dichloride; Targeted therapy; CRPC; Bone metastases; Radiopharmacy

**Abbreviations:** CRPC (Castration-Resistant Prostate Cancer), FDA (Food and Drug Administration), OS (Overall Survival), SSE (Symptomatic Skeletal Event), EDTMP (Ethylene Diamine Tetra Methylene Phosphonic acid), PSA (Prostate-Specific Antigen), ALP (Alkaline Phosphatase), ANC (Absolute Neutrophil Count), NIST (National Institute of Standard and Technology), BMF (Bone Marrow Failure)

**Abstract**

Ra-223 dichloride is a first-in-class alpha-emitting radiopharmaceutical recently introduced into clinical practice for treatment of men with Castration-Resistant Prostate Cancer (CRPC) and symptomatic bone metastases. Due to the proven benefit on Overall Survival and the favorable toxicity profile, Ra-223 therapy is gaining widespread use in both US and Europe. In this article, we describe the routine management of patients undergoing Ra-223 treatment in our Institution.

Currently, Ra-223 therapy is indicated for 6 intravenous injections (55 kBq per kg of body weight) administered every 28 days. In comparison to other radiopharmaceuticals, Ra-223 handling and administration do not need any additional training for authorized users. Due to the minimal external dose rate emission, Ra-223 dichloride can be delivered in an outpatient setting. Moreover, no particular precautions other than standard hygiene measures must be taken by patients’ family members or caregivers. Ra-223 therapy is associated to a favorable hematologic toxicity profile, while non-hematologic adverse events are generally mild and easy to manage.

Given the favorable toxicity profile of this treatment, clinical trials are currently ongoing to evaluate efficacy and safety of Ra-223 treatment in combination or sequence with recently approved drugs such as abiraterone acetate, enzalutamide and sipuleucel-T. In addition, the recent interest in Ra-223 bone lesion dosimetry could open the way to a dosimetric-based therapeutic approach with Ra-223. In this new scenario, results of these promising clinical trials may help clarifying the optimal sequencing of new therapeutic possibilities for metastatic CRPC and the appropriate eligibility criteria for Ra-223 treatment in oncologic patients.

**Background**

Prostate cancer is the most common male cancer and one of the leading causes of cancer-related morbidity and death [1]. In prostate cancer natural history, approximately 10% of patients will develop a castration-resistant disease, with a median survival of 2 years [2]. The majority of patients with metastatic Castration-Resistant Prostate Cancer (mCRPC) has a radiological evidence of bone metastases, which are the main cause of pain and disability, leading to a reduced quality of life. Moreover, in patients with mCRPC bone metastases are independently associated to mortality [3].

Over last years, several novel drugs for CRPC have been introduced, such as the new taxan agent cabazitaxel, immunotherapy (sipuleucel-T), RANK-L inhibitor denosumab, androgen biosynthesis inhibitors (abiraterone acetate) and androgen receptor antagonists (enzalutamide). These promising antitumoral agents have changed therapeutic management of CRPC patients, although there is still the need to define an
appropriate sequencing for their application in order to maximize patient benefit and minimize costs [4].

In this evolving scenario, a first-in-class alpha-emitting radionuclide, Ra-223 dichloride, has been recently approved for the treatment of men with mCRPC with symptomatic bone metastases and no known visceral metastases. FDA approval of Ra-223 came in May 2013 as a result of the findings of the international, randomized, double-blind Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) Phase III trial that evaluated efficacy on Overall Survival of Ra-223 treatment versus placebo in patients with mCRPC [5].

Ra-223 is a short-lived (half-life 11.4 days) alpha emitter, which decays to stable lead through a cascade of short-lived alpha-emitting and beta-emitting progeny. Thanks to its analogy to calcium, Ra-223 targets areas of increased bone turnover delivering high-energy, short-range alpha particles. Ra-223 emits predominantly alpha-particle radiation (95.3% of total emitted activity), 3.6% of beta particles and 1.1% of gamma rays. Alpha particles are responsible for double stranded breaks in cell DNA, causing a local cytotoxic effect [6,7]. Notably, alpha-particle radiation has a very short penetration range (<100 μm), so there is limited damage to the bone marrow [8-10]. Results of the ALSYMPCA trial have shown a significant impact of Ra-223 therapy on Overall Survival (OS) and a delay in median time to the first Symptomatic Skeletal Event (SSE), associated to a relevant bone pain palliation. In addition, Ra-223 treatment was characterized by a low toxicity profile in terms of both hematologic and non-hematologic adverse events, which were mild to moderate in intensity [5].

Survival benefit distinguishes Ra-223 from other bone-targeted therapies, such as local radiation, radioisotopes Sr-89 and Sm-153-EDTMP, zoledronic acid and denosumab, which have demonstrated to be effective on bone pain palliation but have not shown an improvement in Overall Survival [11].

To date, Ra-223 benefits and recommendations for use are included in all major European and North American treatment guidelines for CRPC [12-18]. Since its introduction in Italian pharmacopoeia in May 2015, Ra-223 therapy is gaining widespread use in clinical practice. Currently, Ra-223 dichloride therapy is addressed to patients with Castration-Resistant Prostate Cancer with symptomatic bone metastases and no evidence of visceral disease (excepted for malignant lymphadenopathies not exceeding 3 cm in short-axis diameter). The approved dose regimen of Ra-223 consists in an activity of 55 kBq per kg of body weight administered in 6 intravenous injections at 4-weeks intervals [19]. This paper describes a single-center clinical experience in the routine management of Radium-223 treatment.

Patient referral and management

Italian law states that a nuclear physician (or a radiation oncologist in structures not equipped with a nuclear medicine department) would administer Ra-223 and that this would take place within a licensed Nuclear Medicine or Radiology department. Italian regulation requires that the Nuclear Medicine department would have obtained permission for detention of the alpha-emitting radiopharmaceutical Radium-223.

Patients eligible to receive Radium-223 are generally referred from medical oncologists, radiation oncologist or urologists to an authorized Nuclear Medicine department for consultation and administration. In our routine practice, once the patient has been referred to the Nuclear Medicine unit for Ra-223 therapy, he undergoes a first clinical evaluation to assess the clear eligibility to treatment. During consultation, the patient is extensively informed on the aim of Ra-223 therapy and about possible treatment-related adverse events. Informed consent form is then obtained from the patient.
In order to be eligible to Ra-223 therapy, the patient must present adequate hematologic parameters (Hb≥10 g/dl, Absolute Neutrophil Count≥15x10^9/L, Platelets≥100x10^9/L). Ra-223 hematologic toxicity profile is highly favorable due to the very short penetration range of alpha particles, which results in a limited irradiation of normal bone marrow [5,8-10,20]. Hematologic evaluation must be repeated before subsequent Ra-223 cycles, where ANC should be ≥10x10^9/L and Platelets ≥50x10^9/L. In our routine activity, complete blood counts are obtained on the 10th and 24th day after Ra-223 injection; in this last blood sample PSA and total Alkaline Phosphatase (t-ALP) are also evaluated.

Non-hematologic adverse events such as diarrhea, fatigue and nausea are more commonly observed, and are mild to moderate in intensity. A bone pain flare phenomenon can be experienced by patients shortly after Ra-223 injection, but it is generally limited in time (2-3 days). These adverse effects are all easily manageable with symptomatic and supportive treatments. As assessed in Ra-223 biokinetics studies, this radiopharmaceutical is mainly excreted through gut, so a variable degree of intestinal inflammation is expected [21]. For this reason, eligible patients must not present a condition of chronic Inflammatory Bowel Disease. Within one month before first Ra-223 treatment, baseline burden of bone disease is evaluated with a whole-body Tc-99m diphosphonate bone scan. Pain score is evaluated with Brief Pain Inventory (BPI) 0-10 Numeric Rating Scale at baseline and after each Ra-223 administration. To further evaluate patient response and Quality of Life endpoints, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLC-C30) and the bone metastasis module (QLQ-BM22) are submitted to patients at baseline and after each treatment and analyzed according to published guidelines [22]. Edmonton Symptom Assessment System (ESAS) is used with the same timing to evaluate clinical response to treatment [23].

At the time of the first clinical evaluation in the Nuclear Medicine facility, patients generally underwent different anti-neoplastic treatments. ALSYMPCA trial showed that Ra-223 produced a survival benefit in both chemo-naïve patients and in the docetaxel pre-treated subgroup. These findings were further validated in a prespecified subgroup analysis of ALSYMPCA patients that confirmed the highly favorable safety profile of Ra-223 verifying the low incidence of myelosuppression, irrespective of previous docetaxel use [24]. In our clinical experience, there is a quite balanced proportion between chemo-naïve population and patients pre-treated with docetaxel. In our centre, regular communication between referring physicians and the treating nuclear medicine physicians have been established to keep all parties informed of patients’ progress. Furthermore, a dedicated Ra-223 telephone line has been activated to allow patients to connect to the nuclear medicine physicians.

Radiopharmaceutical ordering

As assessed by Italian Drug Agency AIFA, Ra-223 must be administered in a public hospital facility. Pharmaceutical reimbursement to hospital is assured by Italian National Healthcare System.

In our centre routine, every single Ra-223 treatment is ordered approximately 14 days before the scheduled treatment date. Ra-223 activity is required as a patient-specific dosage unit according to patient's weight. The drug dose is shipped to the licensed user from the production site in Norway. The shipping time is about 10-14 days. At the time of shipment from the manufacturer, the vial contains 14 MBq of Ra-223. The shipping box arrives with a glass vial containing 6 ml of Ra-223 dichloride solution for injection stored in a lead container, shipping documents and a table for decay correction according to physical decay of the radionuclide. Ra-223 dichloride comes in a ready-to-use glass vial as a sterile, non-pyrogenic, clear and colorless solution for intravenous administration. Notably, it doesn’t require any kit preparation.
prior to administration. The drug product has a shelf-life of 28 days from production
day and must be stored at room temperature in its lead container. It must be placed in
a secure facility with limited access until administration.

**Radiopharmaceutical preparation**

The accurate measurement of Ra-223 activity is assured by calibration of dose
calibrators using a National Institute of Standard and Technology (NIST) reference
standard which is provided to authorized users by Bayer Healthcare. In 2015, primary
NIST dose calibrator standards for Ra-223 have been revised due to erroneously
activity readings, about 10% lower than expected [25]. Updated secondary NIST
reference standards have been introduced into clinical practice from January 2016
[26]. Each center must determine the Ra-223 dial setting on their own dose calibrator.
For the routine accuracy check, the reference source is placed in the dose calibrator
and the activity is recorded. Values should be within the allowable tolerance of 10%
Radiopharmaceutical preparation should be carried out within a shielded contained
workstation equipped with laminar air flow, under aseptic conditions. To assist
department workflow, one defined day each week is dedicated to Ra-223 treatment.
When feasible, two staff members should be present at the time of injection, to allow one
staff member to prepare the injection while the other takes care of the patient. Ideally,
Ra-223 preparation for injection should start once patient attendance is confirmed
to avoid wasting a Ra-223 dose. It is worthy to remember that the survival benefit
with Ra-223 in the ALSYMPCA study was observed with some flexibility in the dosing
schedule: the 4-weekly injections could be administered within a window of -3 days
to +7 days from scheduled treatment date. When last-minute cancellations occur and
patient postponement is not possible, it may be possible to switch orders to another
patient of similar weight to avoid wasting the radium-223 dose. On the day scheduled
for treatment, Ra-223 dosage is determined according to current patient’s weight.
The volume to be drawn from the vial is calculated knowing initial concentration (6.6
MBq/6 mL at reference date) and the date of calibration assessed through the decay
table provided with the radionuclide. The required volume is then drawn in a syringe
and the final dosage is verified in the dose calibrator.

During radiopharmaceutical manipulation, care must be taken to prevent spillage
from occurring. Stabin and Siegel evaluated the potential risk of exposure due to an
occasional contamination occurred during Ra-223 handling. They assessed that
there are no major radiation safety concerns regarding both external exposure (dose
to whole body and direct skin contamination were analyzed) and internal exposure
(mainly due to inhalation of daughter radionuclide Rn-219) [27]. Furthermore, a
study from Denmark suggests that spills do not lead to significant fractions of airborne
activity [28]. Due to the presence of a minimal Ra-223 gamma-emission component,
no additional alpha-radiation specific equipment is needed to assess an event of
contamination.

**Radium-223 administration**

As assessed by Italian regulation, Ra-223 can be delivered in an outpatient setting.
Radiopharmaceutical is prepared according to current patient’s weight as described
above. Owing to the nature of alpha-particles radiation, it is easily shielded compared
with other types of ionizing irradiation. As a result, no particular shielding is required
for the syringe containing Ra-223 dose. The administration is performed through an
intravenous (IV) line. The IV access is verified by a flush of isotonic saline and Ra-
223 dichloride is administered as a slow injection over 1-2 minutes. After infusion,
the intravenous access is flushed again with saline. After administration, the syringe is
re-measured in the dose calibrator to check the actual amount of injected radioactivity.
As can be noticed, no additional training is required for authorized personnel to safely
handle and administer Ra-223 dichloride.
Patients injected with Ra-223 are immediately releasable due to the minimal external dose rate emission. Indeed, external exposure to others derived from photon emission from the patient is very low due to attenuation in the patient’s body. As assessed by Dauer et al, the estimated dose to a member of the public is expected to be below 1 mSv and below 5 mSv to health care workers [29]. Regarding potential exposure of medical staff, exposure rate constants of Ra-223 is comparable to Tc-99m as assessed by Smith and Stabin, while exposure from patients to others is very low compared to that of Technetium, so that a patient treated with Ra-223 is immediately releasable as per applicable guidelines on patient dose rates [30]. Because of Ra-223 excretion is predominantly through feces, contamination and intake of activity by family members or caregivers is unlikely. Furthermore, only 5% of injected activity is excreted through kidneys, subsequently the patient should be recommended to use standard daily hygiene measures [21].

**Waste and disposal**

Ra-223 is disposed of in a suitable clinical radioactive waste stream after an appropriate amount of time. Since there are no long-lived radioactive waste products after decay, Ra-223 can be disposed of by decay-in-storage. The used vial must be stored inside its lead container in a secure facility. The disposable equipment used during administration must be treated as a short-lived radioactive waste and is disposed of in accordance to Nuclear Medicine Department procedures. The remains of radioactivity and contaminated material are disposed in accordance with local regulations and hospital radiation safety measures.

**Biomarkers**

As stated in ALSYMPCA trial, PSA is not an objective biomarker in assessing Ra-223 efficacy [5]. Furthermore, a PSA flare phenomenon has been described by various authors [31,32]. This condition can be misinterpreted as therapeutic failure. We recommend not to discontinue Ra-223 therapy on the occurrence of a PSA level rise, not supported by a radiological report of disease progression, to prevent a premature discontinuation of a potentially effective therapy. Several studies on prostate cancer patients assessed that total serum ALP is a more reliable parameter than PSA in evaluating bone disease [33,34]. A separated analysis of CRPC patients treated with Ra-223 in phase II studies demonstrated that a decline in serum t-ALP during treatment was associated with a significantly better Overall Survival [35], suggesting that total ALP may be a useful dynamic marker to monitor as an indication of disease status. Further exploratory analysis of ALSYMPCA data on t-ALP dynamics during Ra-223 treatment confirmed that t-ALP decline at 12 weeks correlated with longer OS, but this biomarker did not meet statistical requirements as surrogate marker for survival [36].

**Bone imaging**

In order to assess bone lesions dynamics during treatment, a Tc-99m diphosphonate bone scan is performed at baseline and repeated every two Ra-223 cycles. Follow-up bone scans are repeated 3, 6 and 12 months after sixth Ra-223 treatment. Bone scans are evaluated by two experienced nuclear physicians. The extent of bone disease is expressed according to Soloway classification [37]. In the majority of patients undergoing Ra-223 therapy, mid-term bone scans show a stability of bone lesions. In our clinical experience with Ra-223 dichloride, only in follow-up bone scans few cases of radiotracer uptake regression were observed.

Notably, bone scans during Ra-223 treatment may also demonstrate a bone flare phenomenon. Enhanced Tc-99m diphosphonate uptake can be observed because of an increased osseous metabolism surrounding bone metastases due to alpha particles irradiation. Physicians should be aware of this phenomenon to avoid discontinuation of treatment in the hypothesis of disease progression.
However, evaluation of Ra-223 therapeutic efficacy through bone imaging (Tc-99m diphosphonate bone scintigraphy versus F-18 fluoride PET) is still a matter of debate.

**Treatment discontinuation**

Burden of bone disease at baseline affects development of hematologic adverse events during Ra-223 treatment. A *post-hoc* analysis of ALSYMPCA patients demonstrated that a greater extent of bone disease on bone scan and total ALP >220 U/l at baseline are correlated to an increased risk of developing grade 2-4 anemia during Ra-223 treatment [38]. Patients developing grade 3-4 anemia or thrombocytopenia should be supported with blood or platelets transfusions in order to continue Ra-223 treatment. There is, in fact, a significant correlation between the number of completed Ra-223 cycles and patients’ outcome, as assessed in a recent retrospective analysis. The study, conducted on 110 patients treated with Ra-223 in the US Expanded Access Program, showed that patients who completed six Ra-223 cycles despite disease progression presented a longer median OS than patients who discontinued Ra-223 therapy due to progression [39].

If a sustained Bone Marrow Failure (BMF) is observed, a delay in Ra-223 therapy is accepted to recover of adverse events. As stated in ALSYMPCA trial, the delay should not exceed 28 days from the scheduled treatment date, that is to say 8 weeks from the last Ra-223 injection. After this period has passed, if recovery from BMF has not been reached, treatment with Ra-223 should be discontinued. It is, however, on behalf of medical oncologist and nuclear medicine physician to decide if the patient's clinical conditions allow to continue Ra-223 treatment. Confirming literature data, in our clinical experience most common reasons for discontinuing treatment are disease progression, grade 3-4 anemia and death [40]. To date, in our centre 588 ²²³Ra cycles were delivered to 125 pts (mean age 73y, mean Gleason Score 8, mean ECOG Performance Status 1.1). Discontinuation rate was 40% due to disease progression (46%), bone marrow failure (23%) and death (31%).

**Follow-up**

Patients who completed six Ra-223 cycles enter a follow-up program consisting in evaluation of complete blood counts, PSA, total ALP values and bone scan after 3, 6 and 12 months from the last Ra-223 administration. Patients who underwent a Choline PET/CT scan before Ra-223 treatment are asked to be repeated it a month after last Ra-223 cycle and then accordingly to oncologic indications.

**Current status and future perspectives**

Radiometabolic therapy with Ra-223 dichloride is a promising treatment for patients with CRPC and symptomatic bone metastases. This new therapy is a proper example of multidisciplinary management of oncologic patients. Medical oncologist, urologist, radiation oncologist, nuclear medicine physician and radiologist should cooperate in the management of CRPC patients to identify the best therapeutic options in the appropriate sequencing. Given the favorable toxicity profile of this radiopharmaceutical and the non-overlapping mechanism of action, a significant interest is growing around possible associations of Ra-223 with other antitumoral drugs, characterized by a complementary pharmacological pathway. Clinical trials are currently ongoing to evaluate safety and efficacy of Ra-223 treatment in combination or sequence with recently approved drugs such as abiraterone acetate, enzalutamide and sipuleucel-T [41-43]. Ra-223 therapy is currently not approved in Italy for use in association to chemotherapy, due to the concern for additive myelosuppression effect. However, it is likely that this limitation will be overcome after the findings of a completed phase I-IIa clinical trial that evaluated safety of Ra-223 plus docetaxel vs docetaxel alone [44]. Unlike systemic therapies with beta-emitting radionuclides, Ra-223 therapy does not raise significant concerns about external radiation exposure,
allowing drug administration in an outpatient setting. This practical aspect, in association with the proven efficacy and safety of this novel radiopharmaceutical, will probably result in an extensive use of Ra-223 dichloride in CRPC patients with symptomatic bone metastases.

In this new scenario, it is important to identify the most appropriate subgroup of CRPC patients eligible for Ra-223 dichloride treatment. Due to the significant benefit on Overall Survival, there is growing interest in introducing Ra-223 dichloride in an upfront therapeutic setting, involving asymptomatic or mildly symptomatic mCRPC patients who would receive a major benefit from Ra-223. It has been shown, in fact, that patients who have been extensively pre-treated or characterized by a baseline ECOG PS≥2 present a higher risk of grade 3-4 hematologic adverse events during Ra-223 treatment [45].

Given the favorable toxicity profile of this treatment, extended and higher-dose therapeutic regimens are currently under evaluation. Results of a recent prospective clinical trial reported that Ra-223 re-treatment is safe and provides control of bone disease progression, while the phase I dose-escalation protocol investigating Ra-223 tolerability found that there are no major concerns on hematologic toxicity in administration of activities up to 250 kBq/kg [46,47]. On this basis, a prospective trial is currently enrolling patients to evaluate safety and efficacy of 6 administrations of 80 kBq/kg of Ra-223 dichloride versus standard activity [48]. Recently, feasibility of bone lesion dosimetry in patients undergoing Ra-223 treatment has been confirmed [49].

In this evolving scenario, the possibility to evaluate Ra-223 Absorbed Dose to bone lesions could lead, in the future, to a dosimetry-based therapeutic approach with Ra-223 activities tailored on patients’ bone lesion biokinetics. In addition to that, beyond prostate cancer, potential use of Ra-223 dichloride is currently under evaluation in other bone-metastatic neoplasms such as breast, thyroid and renal cancer [50-52]. Results of these promising clinical trials may help clarifying the optimal sequencing of new therapeutic possibilities for metastatic Castration-Resistant Prostate Cancer and the appropriate eligibility criteria for Ra-223 treatment in oncologic patients.

References


