

Review

Radiopharmaceutical Ra-223 Prostate Cancer Treatment: Where we are and where we are going

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Received: July 10, 2018; Accepted: July 24, 2018; Published: July 30, 2018

Abstract

Prostate cancer is one of the most common cancers in men, and in the last decade several therapeutic agents have been approved. However, one of the major challenges is related to metastatic castration-resistant prostate cancer (mCRPC), since there are no curative treatments for this stage but rather palliative treatments in which the main objective is to relieve pain and complications associated with bone metastases. The Ra-223 is the first α -particle emitting radiopharmaceutical to be approved in 2013 for the treatment of patients with symptomatic mCRPC and no known visceral metastases. Upon completion of the ALSYMPCA study Ra-223 became the first mCRPC therapy, which showed significantly improved overall survival compared to placebo. This study also demonstrated the beneficial effects of radio-223 on symptomatic skeletal events related to disease, pain and quality of life. This radiopharmaceutical is a calcium mimetic, the main target being bone, forming complexes with the mineral bone hydroxyapatite, preferentially targeting new bone growth around the bone metastases while emitting α -particles within the tumor microenvironment. However, it is essential to perform a treatment for Ra-223 therapy, it is essential to check the selection of treatment, to confirm if there are no bone metastases and to evaluate the results of the laboratory tests. At the end of the procedure, the health professional should discuss with the patient and his / her caregiver what Ra-223 therapy consists of, justify the selection, inform what the patient can expect during the treatment and what care to take. The Ra-223 therefore is a relatively new treatment option with great potential, however further study is needed to see if Ra-223 can be administered concomitantly with other standard agents or even in patients with other types of cancer.

Keywords: α -particle, prostate cancer, Ra-223, radiopharmaceutical.

Introduction

Prostate cancer (PCa) is the second most common cancer in men, the fourth most common malignancy in the world as well as the fifth leading cause of death by cancer in men. In 2012, there were 1,1 million new cases of prostate cancer and 307.000 of deaths due to this neoplasm Worldwide, representing, respectively, 15% of all cancers diagnosed in men and 6,6% of the total cancer mortality in men [1].

All men may develop a PCa, however, there are several factors associated with a higher risk of developing this disease, such as, family history, genetic changes, ethnicity and age (the most significant risk factor) [2].

Despite the slow progress and the late manifestation of symptoms, PCa can be diagnosed early, through specific medical examinations, especially with the quantification of the prostate-specific antigen (PSA) in the blood

serum, associated or not to a digital rectal exam and even through prostate transrectal ultrasound. However, if the result of these test are not conclusive a prostate biopsy may be needed to confirm the result [3]. When PCa is confirmed, it is important to consider the staging of cancer, in order to choose the best therapeutic option. It is also necessary to know if it is localized, in an advanced phase or even metastasized [4].

However, the greatest challenge is the treatment of metastatic castration-resistant prostate cancer (mCRPC) because there are no curative treatments available for this stadium but only palliative treatments. This may involve a radiopharmaceutical that relieves symptoms caused by bone metastases, standing out radium-223 (Ra-223), being the first to also provide an overall survival (OS) advantage [5].

Ra-223 mimics calcium and binds selectively, after intravenous administration, to bone metastases. The high-linear energy-transfer by α -particle emitters induce double strand breaks on DNA after capture by the bone tissue, inducing the death of tumor cells. Therefore, due to the low power of penetration of the α -particles, this radiopharmaceutical has the advantage of causing minimal damage in the surrounding normal tissues [5]. Therefore, the aim of this review will be to provide an update of the literature, observing the therapeutic efficacy of Ra-223 from the ALSYMPCA study, the treatment with this radiopharmaceutical and its mechanism of action, making a small approach to what should be explained to the patient and their caregiver at the start of Ra-223 therapy.

Materials and Methods

The literature used in this review is available on the indexed search engine "PubMed". The selected keywords were " α -particle", "Mechanism", "Oncology", "Prostate cancer", "Ra-223" and "Radiotherapy". The papers were previously identified, analysed and selected according to the inclusion and exclusion criteria established. Inclusion criteria include Scientific Article (SA), systematic reviews (SR) and clinical trials (CT), written in English and with a publication date equal to or less than 5 years. Regarding the exclusion criteria, this consist in cover articles that did not have availability of free full text and those where the title and abstract were not relevant.

The research strategies used are provided in detail in figure 1, and all the sources that provided theoretical support were duly referenced (Figure 1).

Results

Bone metastases are a clinically significant cause of morbidity and mortality, often leading to pain and skeletal-related events (SREs), including pathologic fractures, spinal cord compression, and bone marrow failure, which can result in functional disability, reduced quality of life or

even other complications [6,7]. At this stage of the disease, the treatment is directed towards improving the survival and comfort of the patient [8,9].

Recently years there has been a significant advance in the development of specific treatments for bone metastases, in which the main objective is to relieve the pain and complications associated with these metastases [9].

The formation of bone metastases associated with PCa involves detachment of the primary tumor cells and migration into the blood or lymph vessels, extravasation into the bone marrow and initiation of interaction with cells within the microenvironment, as well as with osteoblasts within the bone matrix [10]. Within the bone environment, osteoblasts promote the growth of prostate cancer cells and the activity and proliferation of osteoblasts is increased. This results in the formation of abnormal and fragile osteoblastic (bone-forming) metastases (braided bone), these metastases being the target of Ra-223, a recently approved, α -particle emitting radiopharmaceutical - Xofigo® [5,6,11].

However, before its approval, this radiopharmaceutical underwent a clinical trial - ALPharadin no SYMptomatic Prostate CANcer (ALSYMPCA) - with the objective of establishing its safety and efficacy in the treatment of mCRPC [5,6].

Therapeutic efficacy -ALPharadin no SYMptomatic Prostate Cancer

The ALSYMPCA was a multi-center, randomized, double-blind, phase III international study comparing the efficacy of Ra-223 versus placebo in 921 patients [6,11,12]. The main inclusion criteria were men with mCRPC symptomatic with disease progression after or during treatment with docetaxel (the only agent available at the time of the study that showed some benefit in mCRPC) [9,10,13]. In this study, symptomatic disease was defined as regular use of opioid or non-opioid analgesic medication or treatment with external beam radiation therapy (EBRT) in the last 12 weeks for cancer-related bone pain [5,8].

The main exclusion criteria were patients with visceral metastases or malignant lymphadenopathy > 3cm, chemotherapy in the last 4 weeks, previous radiotherapy with an external hemibody beam, therapy with previous systemic radioisotopes at 24 weeks, previous blood transfusion or erythropoietin in 4 weeks and compression of the spinal cord [11,13]. In the study, patients were randomized in a ratio of 2:1 (614 for the trial of Ra-223 and 307 for placebo) to receive 6 intravenous (IV) injections of Ra-223 or placebo (solution infusion saline) administered every 4 weeks (50 kBq / kg body weight) (10,12). In addition to injections, all patients received the best standard of care, defined as the routine treatment offered at each centre, which included ketoconazole,

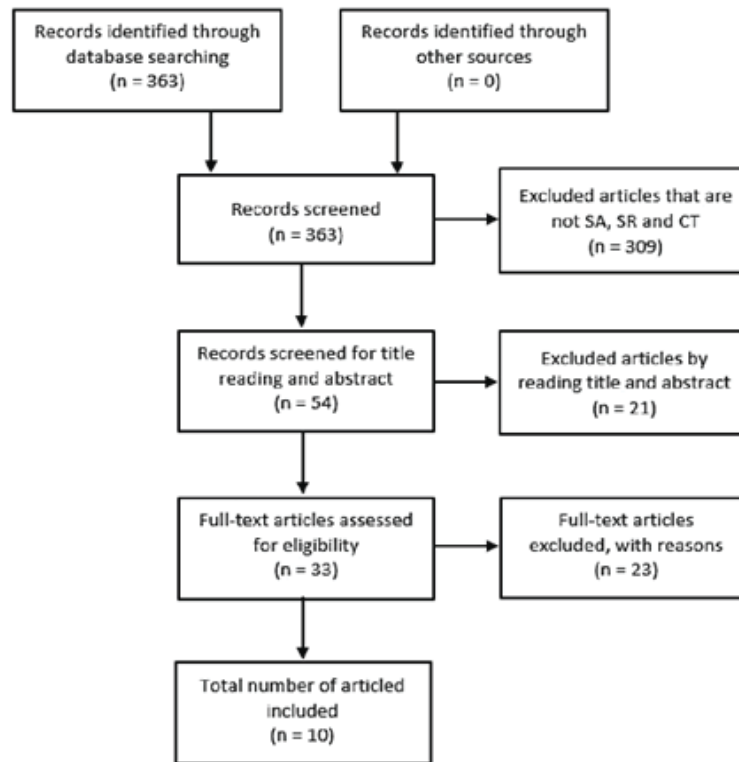


Figure 1. PRISMA flow diagram of study selection process.

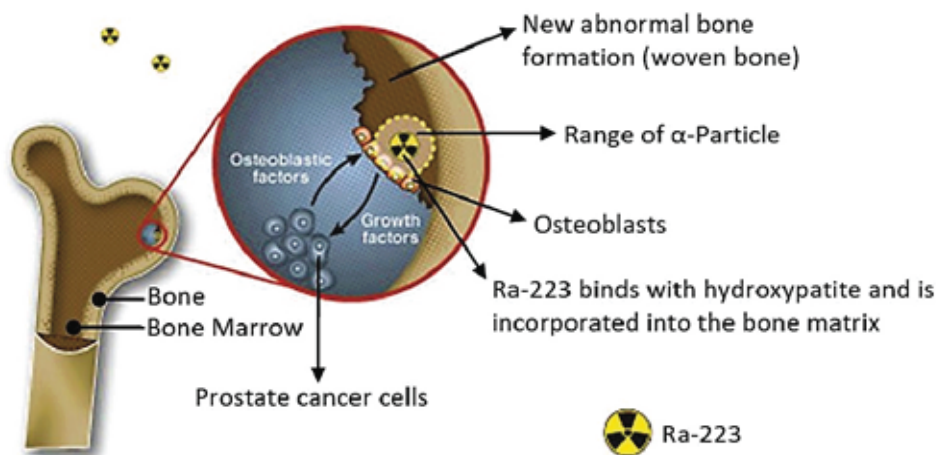


Figure 2. Mechanism of action of radium-223 (5).

glucocorticoids, antiandrogens, oestrogens, or local EBRT [5,7].

In contrast to other major radiopharmaceuticals trials, which primarily evaluated palliative pain treatment, the primary endpoint in ALSYMPCA was OS, defined as time from randomization to death from any cause [6,9,11]. Major secondary endpoints included time to the first symptomatic skeletal event (SSE), defined as the time to first use of EBRT to relieve skeletal symptoms, new fractures symptomatic pathological (vertebral or nonvertebral), spinal cord compression or tumour-related orthopaedic surgery, changes in PSA and alkaline phosphatase (ALP)

levels, and safety and quality of life assessment [5,6,9]. Effects on Overall Survival

The ALSYMPCA study found that Ra-223 significantly improved the median OS of patients with symptomatic mCRPC compared to placebo. Patients receiving Ra-223 had a median overall survival of 14,9 months, compared with a median survival of 11,3 months for patients receiving placebo (Hazard Ratio [HR] 0,70; Confidence Interval [CI] 95%, 0,58 -0,83; $p < 0,001$) [6,10,11].

This trial demonstrated that Ra-223 together with the best standard of care significantly improved OS resulting

in a 30% reduction in the risk of death compared to placebo concomitantly with the best standard of care [7,12].

Effects on Symptomatic Skeletal Events

Ra-223 was related to a considerable delay in the median time of the first SSE compared to placebo (15,6 vs. 9,8 months; HR 0,66; CI 95%, 0,52-0,83; $p < 0,001$) [6,10,11]. This radiopharmaceutical also significantly extended the time to the first event for two of the four components that define SSE: spinal cord compression and the use of EBRT to relieve skeletal symptoms, with 48% risk reductions (HR 0,52; CI 95%, 0,29-0,9; $p = 0,025$) and 33% (HR 0,67; CI 95%, 0,53-0,85; $p = 0,001$), respectively [6,9-11].

Effects on Prostate-Specific Antigen

Ra-223 was associated with a significant delay in time for an increase in PSA level compared to placebo (3,6 vs. 3,4 months; HR 0,64; CI 95%, 0,54-0,77; $p < 0,001$). In addition, a significantly higher percentage of patients in the Ra-223 group than in the placebo group had a PSA response at 12 weeks (16 vs. 6%; $p < 0,001$) [6,11].

Effects on Alkaline Phosphatase

RA-223 was also associated with a significant delay in time for an increase in total ALP compared to placebo (7,4 vs. 3,8 months; HR 0,17; CI 95%, 0,13-0,22; $p < 0,001$). In addition, a significant number of patients treated with Ra-223 had a 30% or greater reduction in the total ALP level compared to placebo (47 vs. 3%) [6,11].

Therefore, changes in PSA level were less marked in comparison to the level of ALP, making the latter the main biomarker for the response to treatment with Ra-223 (6). Quality of life during treatment was assessed with two self-report questionnaires (EuroQol-5D and FACT-P v4) showing a significant improvement in patients treated with RA-223 than in placebo [7,10]. Ra-223 was well tolerated. However, the most frequently observed adverse reactions ($\geq 10\%$) were diarrhea, nausea, vomiting and thrombocytopenia, with the most severe thrombocytopenia and neutropenia [9,13].

Thus, within the design criteria of the ALSYMPCA clinical study, there was a clear benefit with the use of Ra-223 compared to placebo, namely OS, SSEs, pain and quality of life, not presenting a profile of toxicity. The encouraging result of this clinical trial resulted in Food and Drug Administration approval in May 2013 [9,11].

Treatment with Ra-223

Ra-223 is indicated for the treatment of adult men with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases [6,8,11,12]. The main goal of treatment with Ra-223 is to improve survival and not, fundamentally, to alleviate the symptoms.

Therefore, the severity of the symptoms should not be used as an indication for initiation of treatment with Ra-223 [12]. However, there are several indications for the use of this radiopharmaceutical relatively early during mCRPC when there is a clinical window of opportunity prior to the development of visceral metastases since the likelihood of developing these metastases increases over time [12].

The Ra-223 showed an improvement in OS both in minimally symptomatic patients and in more symptomatic patients with mCRPC, suggesting that there is no need to start treatment with this radiopharmaceutical if symptoms are not severe [12].

For posology, the recommended dose regimen of Ra-223 is 55 kilobecquerel (kBq) per kilogram (kg) body weight administered by slow IV injection over 1 minute at 4 week intervals for a total of 6 injections [10,12]. No dose adjustment is necessary in elderly patients, since no overall differences in safety or efficacy were observed in this age group (aged ≥ 65 years) and in patients with renal or hepatic impairment [6]. Ra-223 is usually given by radiation oncologists or certified nuclear medicine doctors to work with radioisotopes [7].

Monitoring Ra-223 safety

Before treatment with Ra-223 therapy, it is essential to check the eligibility for treatment, to confirm whether or not there are bone metastases through recent bone scintigraphy and to evaluate the results of the laboratory tests [9]. Since bone marrow suppression is the primary concern of Ra-223 therapy, haematological evaluation should be performed at the beginning and before each dose of radiopharmaceutical. Before the first dose, the absolute neutrophil count (ANC) should be $\geq 1,5 \times 10^9 /L$, the platelet count $\geq 100 \times 10^9 /L$ and the hemoglobin $\geq 10,0$ g/dL [5,6,12,13].

The decision to administer the next injection is based on clinical and biological parameters, measured before each subsequent administration of Ra-223, the ANC should be $\geq 1.0 \times 10^9 /L$ and the platelet count $\geq 50 \times 10^9 /L$. If the platelet or ANC count does not return to baseline values within six to eight weeks after the last administration of Ra-223, treatment with Ra-223 should be discontinued [5,6,12,13]. Other reasons for discontinuation of Ra-223 therapy prior to the completion of the 6 cycles of treatment include too rapid progression of the disease, preventing the achievement of a response to treatment and the presence of visceral metastases [6].

Mechanism of Action

Radio and Calcium, once belonging to the same group in the periodic table, confers to the Ra-223 mimetic properties of calcium. As a result, Ra-223 binds selectively to bone (since it has osteoblastic activity), forming complex-

complexes with the mineral bone hydroxyapatite, one of the main constituents of the bone matrix, preferentially targeting new bone growth around the bone metastases while emitting α - particles within the tumor microenvironment (Figure 2) [5,7].

The Ra-223, being a radioactive isotope, presents a decay chain, consisting of six stages, being: ^{223}Ra ($t_{1/2} = 11,4$ days, α decay) \rightarrow ^{219}Rn ($t_{1/2} = 3,96$ seconds ($t_{1/2} = 1,78$ milliseconds, decay α) \rightarrow ^{211}Pb ($t_{1/2} = 36,1$ minutes, β - decay) \rightarrow ^{211}Bi ($t_{1/2} = 2.15$ minutes, α) \rightarrow ^{207}Tl ($t_{1/2} = 4.77$ minutes, β - decay) \rightarrow ^{207}Pb (stable) [6,11,13].

Throughout this process, Ra-223 releasing two β -particles and four α -particles for each atom, the latter representing 95,3% of the total emitted radiation energy [5,11]. Considering that β -particles produce mainly single-stranded DNA breaks, which can be overcome by cellular repair mechanisms, α -particles have a high linear energy transfer rate (80 keV/ μm) with a higher capacity to induce lethal DNA breaks double-stranded cytotoxic effects, thereby causing greater cytotoxic effects on metastatic bone tumor. After the breakdown of the double strand of DNA, cell death can be initiated through various mechanisms or cell pathways [9,14].

Although α -particles have high energies, their penetration into the biological tissue is very short (40 μm -100 μm), corresponding to two to ten cell diameters, leading to cytotoxic effects that are independent of oxygen concentration, being particularly interesting in bones (and bone metastases) because it is a very hypoxic organ. Thus, Ra-223 is a bone target with a relatively low impact on myeloproliferative tissue, thus minimizing the adverse events associated with myelosuppression [5,7,11].

Pharmacokinetic Properties

The Ra-223 radiopharmaceutical is administered by IV injection and, after being injected, is rapidly eliminated from the blood and is mainly incorporated into bone and bone metastases or is excreted through the intestine [6,8,11]. Fifteen minutes after the injection, about 20% of the radiopharmaceutical remains in the blood. After 4 hours, approximately 4% of the injected activity remains in the blood, decreasing to 1% 24 hours after the injection. 10 minutes after injection, activity is observed in bone and intestine, and the percentage of radioactive dose present in the bone 4 hours after administration is between 44 and 77% [6,8,11].

No significant radiation uptake is observed in other organs, such as the heart, kidneys, liver, bladder and / or spleen 4 hours after injection. Ra-223 is not metabolised by the body [6,8,11]. The excretion of the radiopharmaceutical occurs mainly through the fecal route, however, about 5% is excreted in the urine, and no evidence of hepatobiliary excretion is observed [6,8,11]. Seven days after the injection, about 76% of the administered activity was

excreted from the body [8].

The elimination rate of Ra-223 from the gastrointestinal tract is affected by the variability in the rates of bowel movement throughout the population, with the normal interval of bowel movement from once a day to once a week [8].

Discussions with the patient and their caregiver at the start of Ra-223 therapy. The health care provider has the responsibility to explain to the patient and his caregiver all the options available for the treatment of mCRPC, as well as justify his choice if selecting Ra-223, and what the patient can expect during treatment [7,12]. The most frequent adverse events associated with administration of Ra223 should therefore also be reported to the patient in order to prepare and not to alarm the patient than to wait for treatment [7,12].

The precautions required to ensure radiation safety are much less stringent for Ra-223 compared to other treatments with other radionuclides [7]. Concerning contact with other people immediately after the injections, there are no restrictions since the α -particles emitted by the radiopharmaceutical travel only a fraction of a millimeter inside the body [6,12,13]. However, by arrangement, the patient should avoid close and/or prolonged contact with pregnant women and young children during the first week after each injection [9].

At the end of each injection, the patient is monitored for a short time and then can return home [6,13]. In general, good hygiene practices should be followed during the administration of Ra-223, especially in the first week after the last injection. These measures minimize the risk of exposure to radiation that comes from body fluids particularly to domiciliary members and caregivers [12,13]. It is also useful to inform patients that Ra-223 is not targeting the androgen receptor and has a relatively modest effect on PSA levels. Consequently, patients should be aware that the lack of response of PSA to treatment with Ra-223 does not necessarily imply lack of efficacy [12,13]. That said, part of the discussion between doctor and patient should focus on the importance of patient adhering to treatment.

Conclusions

Treatment options for mCRPC patients have expanded in recent years, with Ra-223 being the first α -particle emitter and fifth to be approved for this phase of PCA. This radiopharmaceutical is indicated for the treatment of patients with mCRPC with symptomatic bone metastases [5]. The Ra-223 ALSYMPCA clinical trial clearly demonstrated that this radiopharmaceutical compared to placebo in men with symptomatic mCRPC increases OS, delays the time to first SSE, and is associated with a beneficial effect on pain and quality of life [5,6]. Coordination of care among multidisciplinary team members, patients

and caregivers is essential to optimize the safe and effective treatment of all CRPC therapies [6].

An only mode of action and a very good tolerability profile make the Ra-223 ideal for concomitant administration with other standard agents. However, the combination of Ra-223 and other agents are still under study in order to further improve the patient's prognosis in advanced disease. Ra-223 assays are also underway in patients with another type of cancer, such as breast cancer, thyroid cancer and metastatic kidney cancer to the bone [5,6]. In conclusion, Ra-223 heralds a new era in the treatment of osteoblastic bone metastases, a major source of morbidity and mortality for mCRPC patients, and as a result, the future has never looked brighter for this debilitating disease.

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To cite this article: Faria T, Mendes F, Cruz R. Radiopharmaceutical Ra-223 Prostate Cancer Treatment: Where we are and where we are going. *British Journal of Cancer Research*. 2018; 1:2. doi: 10.31488/bjcr.110

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