DOI: *10.4081/aiua.2020.3.196*

CASE REPORT

Bone pain palliation outcomes and possibility of Radium-223 re-treatment in mCRPC

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Summary *Objective. Bone secondary localizations from metastatic castration-resistant prostate cancer are associated with an increase in mortality and a reduction in the patient's quality of life. Radium-223 is a targeted alpha-therapy approved for the treatment of mCRPC (metastatic castration resistant prostate cancer) patients with symptomatic bone metastases. To our knowledge, no previous study has been performed assessing the bone pain palliation outcomes following Radium-223 therapy.*
Materials and Methods. A mCRPC patient with symptomatic bone localizations and relevant bone pain symptoms has been subjected to Radium-223 treatment. Pain was assessed over time from the first administration of Radium-223 to follow-up.
Results. After Radium-223 treatment, patient showed a significant BPI (Brief Pain Inventory) decline from 7 to 4 and a concomitant partial regression of multiple bone hot spots in the bone scan exam. Three months after the last infusion of Radium-223, further BPI decline (from 4 to 2) with bone scan depicting stable disease was observed. However, after 6 months from Radium-223 treatment end, BPI increased from 2 to 10.
Conclusions. Taking into account the effectiveness on bone pain relief and the low toxicity profile showed by Radium-223 treatment, we encourage further analysis on large cohort to investigate the clinical outcome after Radium-223 treatment, in terms of bone pain palliation, together with the possibility of Radium-223 re-treatment in selected patients..

KEY WORDS: *Radium-223 dichloride; Bone pain; Palliative treatment; mCRPC.*

Submitted 28 January 2020; Accepted 18 February 2020

INTRODUCTION

Prostate cancer (PCa) in men worldwide is the second most common cancer (1, 2). Most subjects with metastatic PCa, following a median of 18-24 months of endocrine therapy, no longer respond to traditional androgen deprivation therapy (ADT) (3, 4) and are categorized as *castration-resistant prostate cancer* (CRPC), leading to disease progression (5, 6). CRPC disease progression is characterized by the presence of pain-inducing bone metastases (90% of patients), with the increase in *total alkaline phosphatase* (tALP) and *prostate-specific antigen* (PSA) levels (7, 8). The development of bone metastases is associated with an increase in mortality and a reduction in the patient's health-related *quality of life* (QoL) (9-11). Treatment options for *metastatic CRPC* (mCRPC) have recently and include cytotoxic therapy (e.g., docetaxel, cabazitaxel), immunotherapy, oral hormonal therapies targeting the androgen receptor axis (e.g., enzalutamide and abiraterone), bone health agents (e.g., denosumab and zoledronic acid) and targeted alpha-therapy (*Radium-223* dichloride) (12-14). *Radium-223* has been approved for the treatment of patients with mCRPC with symptomatic bone metastases and no known visceral metastatic disease (15). This radiopharmaceutical have a dual mechanism of action, destroying bone-metastatic cancer cells and affecting tumor-induced pathological bone activity (16). Currently, *Radium-223* is approved as monotherapy or in combination with a *Luteinizing Hormone-Releasing Hormone* (LHRH) analogue for the treatment of adult patients with mCRPC who are in progression after at least two prior lines of systemic therapy (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment (17). *Pharmacovigilance Risk Assessment Committee* (PRAC) of *European Medicines Agency* (EMA) carried out a review on *Radium-223* after data from a clinical study suggested that patients treated with *Radium-223* in combination with abiraterone and prednisone/prednisolone could be at risk of dying earlier and had more fractures than patients given placebo with abiraterone and prednisone/prednisolone (18). The above recommendations are based on the assessment of data resulting from a randomized, double-blind, placebo-controlled phase III trial (ERA-223), which showed an increased incidence of *skeletal-related events* (SRE) (28.6% *vs* 11.4%), a possible reduction in median *overall survival* (OS) (30.7 months vs 33.3 months, HR 1.195, p = 0.13) and an increased risk of radiological non-bone progression (HR 1.376, p = 0.07) among patients receiving *Radium-223* in combination with abiraterone acetate plus prednisone/prednisolone (n = 401) compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone (n = 405) (19). Despite several clinical trials and prospective studies have been carried out aiming to investigate the outcomes of *Radium-223* therapy in terms of OS, *progression-free survival* (PFS), SRE and multiple QoL parameters (20), to our knowledge, in the literature there are no studies assessing specifically the bone pain palliation outcomes, as an independent factor, following the end of *Radium-223* treatment. The following study

No conflict of interest declared.

describes a mCRPC patient, presenting a significant reduction of bone pain during the therapy, followed by further bone pain palliation after the first 3 months following the end of *Radium-223* therapy without modification of pain-relieving medications.

Materials and methods

A 77 years-old man was diagnosed with PCa (*Gleason score 9, 4+5*) in February 2014. He began ADT with Triptorelin and Bicalutamide for 19 months. Furthermore, after 2 years from the diagnosis, he has been treated with external beam radiation therapy (EBRT) to secondary bone lesions on the right pelvis. He came to our attention in November 2016 with a PSA recurrence (PSA 168 ng/mL) despite ADT, his testosterone level was 0.34 ng/dL), therefore he was diagnosed with mCRPC. The patient presented positive 99mTc-HDP bone scan imaging with increased uptake in the cranium, in both scapulae, in the left humerus and radius, in multiple ribs and vertebrae, in the pelvis and in the left femur (Figure 1A). The CT scan was negative for visceral metastasis. He was defined as a poly-metastatic patient (6-20 metastatic foci). Therefore, we started *Radium-223* treatment. The *Brief Pain Inventory* by *Numeric Rating Scale* (BPI) value was 7 in spite of *nonsteroidal anti-inflammatory drug* (NSAID) (ketorolac) and acetaminophen treatment.

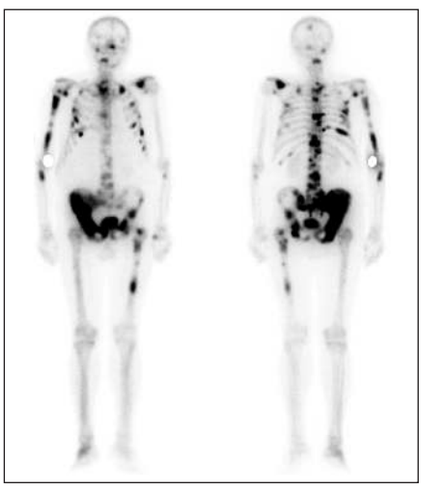


Figure 1A. *Baseline 99mTc-HDP bone scan imaging.*

Results

After 6 cycles of *Radium-223* treatment, BPI declined from 7 to 4 without modification of pain-relieving medications. The bone scan performed in April 2017 showed a partial regression of multiple bone hot spots (Figure 1B).
The patient reported further improvement with BPI that declined from 4 to 2 after 3 months from the last administration of *Radium-223* treatment with stable disease resulting in the bone scan. Nevertheless, at 6 months follow-up BPI increased from 2 to 10 without modification of pain-relieving medications. Pain score measurements during and after the *Radium-223* treatment are shown in Figure 2. The patient showed progression in the 99mTc-HDP bone scan performed in October 2017, after 6 months from the end of the *Radium-223* therapy (Figure 1C), with extension of the areas of pathological uptake previously reported. Unfortunately, after 13 months of follow-up, the patient died for multi-organ failure.

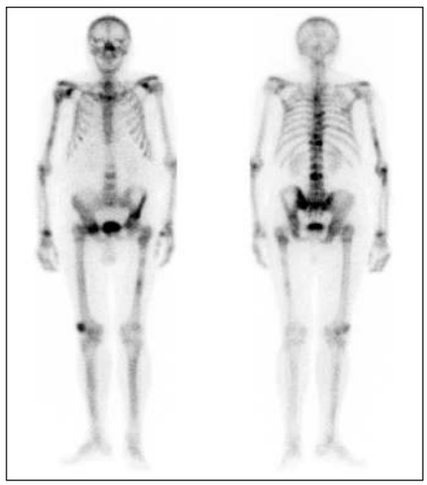


Figure 1B. *End-of treatment 99mTc-HDP bone scan imaging.*

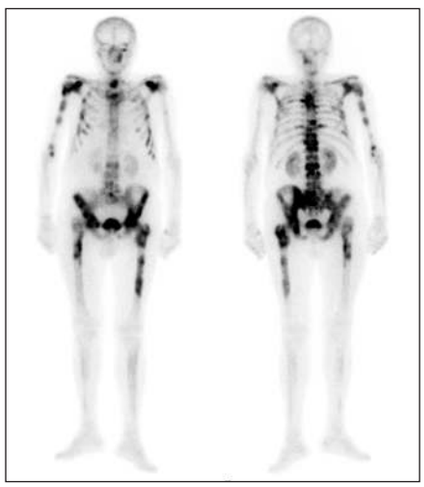
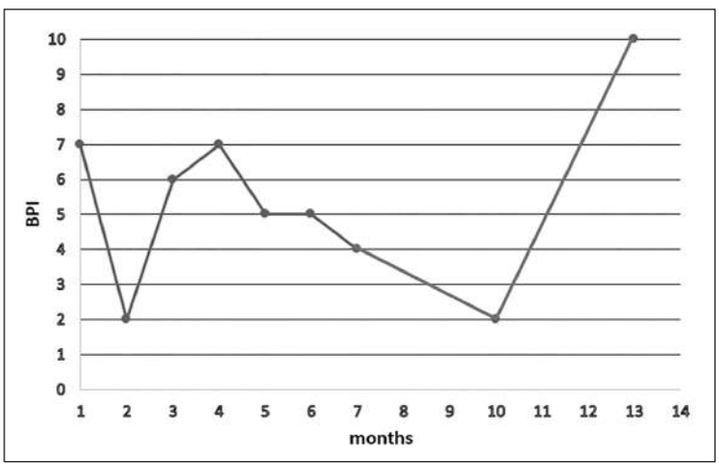


Figure 1C. *99mTc-HDP bone scan imaging at 6 months follow-up.*

Figure 2.
BPI trend over time.



Discussion

In this study, we presented the case of an mCRPC patient treated with *Radium-223*, showing bone pain reduction during the therapy which continued with a further decline for the next 3 months after the end treatment. Nevertheless, after 6 months from *Radium-223* treatment, BPI suddenly increased from 2 to 10 with the radiological progression of disease described in several bone districts, revealed with bone scan.

The phase 3 trial ALSYMPCA showed a significant effect of *Radium-223* on OS and a delay in median time to the first SRE (21). In the meantime, several retrospective studies reported a difference in median OS between patients who received 1 to 4 versus 5 to 6 injections, demonstrating that a higher number of *Radium-223* injections was associated with prolonged OS (median OS of 6.2 months, versus 17.9 months) (22). ALSYMPCA show furthermore that *Radium-223* patients reduced the risk of need for EBRT for bone pain and notably delayed the time to first use of opioids (23). This is associated with significant palliation of bone pain by the radiopharmaceutical. However, ALSYMPCA was not planned to evaluate the effect of *Radium-223* on pain; any response to pain observed or lack of it was not considered a reason to stop treatment with *Radium-223*. The effect of treatment on pain was not systematically documented as it was not one of the objectives of the study. Currently, patients receive up to six intravenous injections of *Radium-223*, 55 kBq/kg in 4-week intervals. There have been recent studies of re-treatment with *Radium-223* (24). One of these is the open-label, phase 1/2 study (NCT01934790) (25).

This study, including 44 patients with no disease progression in bone during the first treatment and presence of later progression, that received *Radium-223* re-treatment, up to 6 additional *Radium-223* injections, showed that re-treatment with *Radium-223* was well tolerated with favorable effects on disease progression. Another ongoing phase II study (NCT02023697) evaluated standard dose (55 kBq/kg every 4 weeks up to 6 injections) versus high dose (88 kBq/kg every 4 weeks up to 6 injections) and versus extended standard dose (55 kBq/kg every 4 weeks up to 12 injections) (26, 27). In literature has been already showed how *Radium-223* could significantly extend OS, associated with a delay in median time to the first symptomatic SRE, meaningful improvement in QoL and bone pain palliation (23, 28). Several trials showed that *Radium-223* is well tolerated and has a favorable hematologic safety profile (29), with a low incidence of myelosuppression (30). Such safety is confirmed from long-term safety ALSYMPCA analysis up to 3 years from first injection, which indicated that *Radium-223* remained still well tolerated, with low myelosuppression incidence and no new safety concerns (31). It is possible to postulate that some patients after initial treatment may derive benefit from extended treatment with *Radium-223*.

The open-label, phase 1/2 NCT01934790 trial (25) showed that re-treatment with *Radium-223* sustained benefit on disease and progression was well tolerated. In particular, it showed a low incidence of clinical events such as symptomatic SRE or radiographic bone progression.

Furthermore, in this study tALP declined from baseline values after re-treatment, suggesting a continuation of the biologic effects of *Radium-223*; moreover, the median OS increased to 24.4 months at the end of the 2-year active follow-up period. A further study focused on these patients confirms its safety in a 2-year active follow-up analysis, especially with regards to the minimal hematologic toxicity and efficacy outcome from 2-year follow-up of the re-treatment with *Radium-223*. In view of these remarkable results and based on our wide experience, we could reasonably assume that this patient would have provided clinical benefits if he continued the *Radium-223* therapy.

Conclusions

Further analysis should be conducted on a large cohort to evaluate the clinical outcome in terms of bone pain palliation after *Radium-223* treatment and the possibility, considering the low toxicity profile, of re-treatment in selected patients.

Ethical approval

This study has been approved by the local ethical committee.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals

This article does not contain any studies with animals performed by any of the authors.

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