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ORIGINAL ARTICLE

A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary

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Abstract Radium-223 dichloride is an alpha-emitting radiopharmaceutical which significantly prolongs overall survival in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. This was a retrospective analysis of the efficacy and safety of Radium-223 in the first 41 patients treated at a single center in Hungary. Radium-223 was given at a dose of 50 kBq/kg intravenously every 4 weeks for up to 6 cycles. Between 23rd July 2014 and 23rd February 2016, 41 patients were treated. Patient demographics, laboratory values, treatment outcomes and adverse events were collected from medical records. The mean age was 72.2 years (SD: 7.1). 24 patients received Radium-223 as first-line treatment (58%), 7 patients as second (17%), 3 as third (7.3%), 6 as (14.6%), and 1 as fifth-line therapy (2.4%). The mean number of cycles administered was 5.5 (SD: 1.1). The most common side effects were anemia (32% grade 1–3), nausea (28%, grade 1), diarrhea (4%, grade 2), thrombocytopenia (4%, grade 3). The mean baseline PSA level was 307.2 ng/ml (SD: 525.7), which increased to a mean value of 728.5 ng/ml (SD: 1277) by the end of treatment. The baseline mean ALP of 521.1 U/L (SD: 728) decreased to 245.1 U/L (SD: 283.5). The majority of patients experienced a decrease (37%) or complete cessation (43%) of bone pain intensity. In our symptomatic prostate cancer patient population, Radium-223 proved to be efficient in terms of pain relief, with moderate side effects. No PSA response was detected, while alkaline phosphatase levels significantly decreased.

Keywords Bone pain · Metastatic castration-resistant prostate cancer (mCRPC) · Radium-223

Introduction

Castration-resistant prostate cancer (CRPC) is defined by disease progression despite androgen depletion therapy (ADT), and may manifest as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases [1]. CRPC represents a spectrum of disease ranging from patients without metastases or symptoms with rising PSA levels despite ADT, to patients with metastases and significant debilitation due to cancer symptoms [2]. Metastatic castration-resistant prostate cancer (mCRPC) frequently metastasizes to the bone, often resulting in painful skeletal events, reduced quality of life, and shorter survival [3, 4]. Previous studies have shown that as prostate cancer transitions from castration sensitive to castration resistant, the incidence of bone metastasis increases, and eventually more than 90% of patients with metastatic castration-resistant prostate cancer (mCRPC) develop bone metastases [5].

Patients with mCRPC and bone metastases often experience skeletal-related events (SREs) such as pathologic fractures and spinal cord compression, which are major causes of morbidity and can lead to other comorbidities [6]. Skeletal complications due to bone metastases are strong determinants of quality of life and survival in these patients [7]. A previous post-hoc analysis of clinical trial data found that patients with

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no SREs had significantly longer survival, better health-related quality of life, and significantly lower pain intensity, than patients with at least one SRE [4]. These findings underline the importance of bone pain management in this patient population.

Traditionally, the treatment strategies of bone metastases in patients with mCRPC were aimed at managing pain and reducing skeletal complications [8]. However, ongoing research led to the development of targeted therapeutics, such as the radiopharmaceutical Radium-223 dichloride (Radium-223, Xofigo®). Radium-223 is a calcium-mimetic alpha-emitting radiopharmaceutical, which selectively targets bone, specifically the areas of bone metastases, while sparing normal tissue [9, 10]. Alpha particles travel much shorter distances than beta particles, and are therefore less damaging to normal tissue, which explains the fewer side-effects observed with Radium-223 therapy compared to beta-emitting radiopharmaceuticals [11–18]. Unlike previous radiopharmaceuticals, Radium-223 was found to prolong survival in patients with mCRPC in the pivotal phase III ALSYMPCA trial [19]. Based on the results of this study, Radium-223 was approved by the U.S. Food and Drug Administration in May 2013 for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease, which was followed by the granting of marketing authorization in Europe by the European Commission in November, 2013. The approved dosing of Radium-223 is 50 kBq/kg given intravenously over 1 min every 28 days for 6 doses [20].

Radium-223 has been reimbursed in Hungary since July 2014 on an individual basis. The National Healthcare System covers the medicine for patients with progressive mCRPC and bone pain, at least two bone metastases detected on skeletal scintigraphy, lymph nodes with a maximum size of 3 cm in the case of lymph node metastases, and no known visceral metastasis. Eligibility for the initiation of Radium-223 treatment is judged by a scientific committee in accordance with the approved indication. Currently, six Hungarian treatment centers are licensed to administer Radium-223, out of which our institute has the largest patient cohort. In this article, we report our first experience with Radium-223 treatment in patients with mCRPC, bone metastases and bone pain in a real-world setting. Our specific aim was to investigate the efficacy and safety of Radium-223, and to assess the changes in pain intensity as a result of Radium-223 therapy.

Methods

This was a single-center retrospective study carried out at the National Institute of Oncology, Budapest, Hungary. Consecutive mCRPC patients receiving Radium-223 for the treatment of bone metastases between 23rd July 2014 and 23rd February 2016 were included in the analysis.

Castration-resistant disease was defined as a serum testosterone level of 50 ng per deciliter or lower (≤1.7 nmol/L) after bilateral orchiectomy or during maintenance treatment consisting of androgen-ablation therapy with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist. Patients who had not undergone bilateral orchiectomy received LHRH analogues throughout the treatment.

Patients were informed in detail for the purpose and modalities of data communication, and gave consent to the use of their anonymous data for research purposes. Patients were administered intravenous Radium-223 at a dose of 50 kBq/kg over one minute every 28 days for up to 6 cycles.

Medical records were reviewed for patient demographics and baseline characteristics, laboratory PSA and alkaline phosphatase (ALP) values, treatment outcomes, treatment-emergent adverse events, and changes in pain intensity. The patients' level of functioning was assessed by the ECOG Scale of Performance Status before Radium-223 treatment at the initiation of therapy.

Treatment outcomes were assessed subjectively and objectively by examining changes in pain intensity and changes in serum PSA and ALP levels throughout the treatment. Serum PSA and ALP values were measured one week prior to and every 4 weeks after the initiation of treatment. Baseline values and values measured one week after the last dose of Radium-223 were included in the analysis.

During the 6 months of treatment, imaging tests were only performed if there was a suspicion of disease progression based on emerging symptoms (use of analgesics, clinical worsening). Otherwise routine control imaging tests were not performed.

Pain intensity was subjectively assessed at every visit by asking the patients to report any change they had experienced since the previous visit. After the last dose of Radium-223, changes in bone pain compared to baseline intensity were classified as 'increase', 'no change', 'decrease', or 'complete cessation', and these were included in the analysis

Statistical analysis of the data was carried out using SPSS version 22.0 for Windows. Descriptive statistics were performed and we present the frequencies and the mean with standard deviation for analyzed domain.

Results

Baseline Characteristics

Between 23rd July 2014 and 23rd February 2016, 41 patients received Radium-223 treatment at our institute. The mean age of the patients was 72.2 years (SD: 7.1, range: 63–85 years). At the beginning of therapy, 23 patients had an ECOG status of 0, and 18 of them had an ECOG status of 1. Ten patients had less than 6 bone metastases, of which only one patient was

diagnosed with lymph node metastasis. Of the 31 patients who had at least 6 bone metastases, lymph node metastases were detected in 4 patients (Fig. 1). The mean time from the diagnosis of castration resistant prostate cancer to the beginning of Radium-223 treatment was 20.9 months (SD: 16.3).

Prior Treatments and Number of Cycles

Patients who had not undergone bilateral orchiectomy received LHRH analogues throughout the treatment.

Abirateron and enzalutamide are reimbursed only in the post-chemotherapy setting with an individual reimbursement submission method in Hungary; chemotherapy-naïve patients can only receive this treatment if they participate in a clinical trial. Cabazitaxel is available from the hospital budget, while Radium-223 treatment is available in the form of individual reimbursement submission as well, independently from previous chemotherapy.

24 patients received Radium-223 as first-line treatment (58.5%), 7 patients as second-line treatment (17.1%), 3 as third-line therapy (7.3%), 6 as fourth-line treatment (14.6%), and one patient as fifth-line therapy (2.4%). Prior treatments included docetaxel (16 patients), abiraterone (10 patients), mitoxantrone (5 patients), cabazitaxel (3 patients), and enzalutamide (1 patient) (Table 1).

The median number of cycles administered was 5.5 (SD: 1.1). Altogether 32 patients received the pre-planned 6 cycles without delay. 9 patients received a reduced number of cycles due to sudden cardiac death (1 patient), stroke (1 patient), brain metastasis (3 patients), and progression (4 patients, 2 of which due to bone marrow failure). Fig. 2 shows the brain MRI of a patient with a large brain metastasis invading the frontal lobe who received Radium-223 as fifth-line therapy after docetaxel, abiraterone, mitoxantrone, and cabazitaxel treatment (Fig. 2). Radium-223 resulted in the complete cessation of bone pain, as a result of which the patient no longer required potent opioid analgesic treatment.

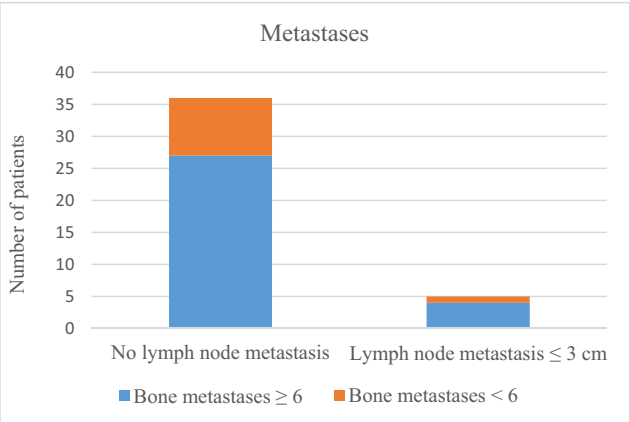

Fig. 1 Distribution of patients based on the presence and number of bone and lymph node metastases

Table 1 Distribution of patients based on the positioning of Radium-223 in the treatment sequence, and previous agents

Positioning of radium-223	Number of patients	Previous agents
First-line	24	-
Second-line	7	1 abiraterone
		6 docetaxel
Third-line	3	1 docetaxel, enzalutamide
		2 docetaxel, abiraterone
Fourth-line	6	2 docetaxel, abiraterone, cabazitaxel
		4 docetaxel, abiraterone, mitoxantrone
Fifth-line	1	1 docetaxel, abiraterone, mitoxantrone, cabazitaxel

PSA and ALP Levels

The mean PSA level at the beginning of treatment was 307.2 ng/ml (SD: 525.7), which increased to a mean value of 728.5 ng/ml (SD: 1277) by the end of treatment. The mean ALP level before treatment initiation was 521.1 U/L (SD: 728), while at the end of treatment the last measured mean ALP value was 245.1 U/L (SD: 283.5). 13 patients had elevated baseline ALP levels, of which a 30% decrease in ALP levels was detected in 3 patients, a 50% decrease in 6 patients, and altogether 9 patients showed a complete normalization of ALP levels.

Side Effects

The most common side effects of Radium-223 treatment were also examined, and the severity of each adverse event was rated on a scale from 1 to 4 (grade 1–4). The most common adverse event was anemia observed in 11 cases (26.8%), 3 of which were classified as grade 1, 2 as grade 2, and 6 as grade 3. Nausea occurred in 9 patients (21.9%), all cases were rated as grade 1. Four patients reported treatment-emergent diarrhea (9.8%), 3 of which were classified as grade 1, and one as grade 2 in severity. Thrombocytopenia developed in 2 patients (4.9%), the severity was grade 2 in both cases (Fig. 3).

Pain-Related Outcomes

Before the initiation of Radium-223 therapy, 40 patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief. Nearly two thirds of patients were only receiving one type of analgesics (63.4%), most of which were NSAIDS (97.6%). In addition to NSAID treatment, 3 patients

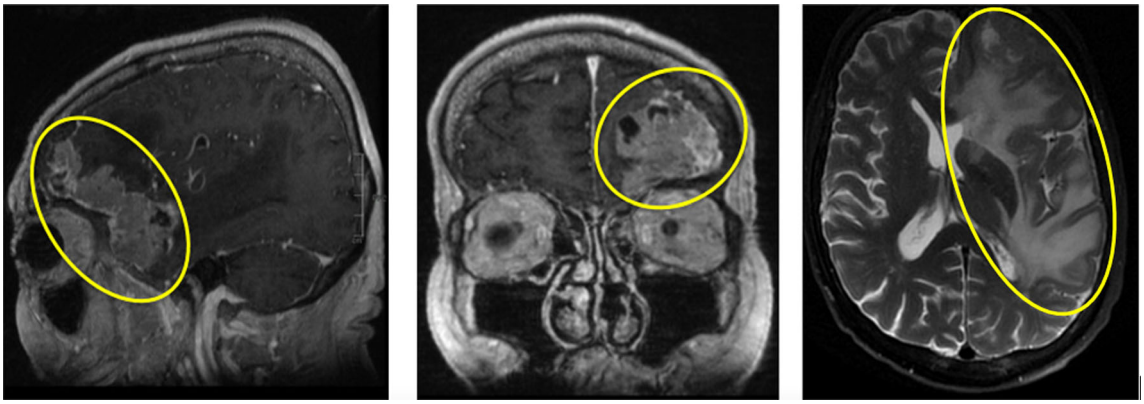

Fig. 2 Frontal lobe brain metastasis detected in a mCRPC patient showing behavioral changes

were managed with palliative radiotherapy, 5 patients were receiving NSAID + opioid, 2 patients were treated with NSAID + opioid + radiotherapy, 4 patients were treated with NSAID + major analgesics, one patient with NSAID + major analgesics + radiotherapy, and one patient was only receiving an opioid analgesic (Table 2).

Two patients reported an increase in pain intensity (4.8%), 6 patients reported no change (14.6%), 15 patients experienced decreased pain intensity (36.6%), and 18 patients reported a complete cessation of pain by the end of Radium-223 therapy (44%) (Fig. 4).

Discussion

This was a single-center retrospective study of patients with mCRPC receiving Radium-223 for the treatment of bone metastases at the National Institute of Oncology, Hungary. To the best of our knowledge, this is the first study in Hungary to analyze the experience with Radium-223 in a real-world setting since its introduction into clinical practice in 2014. In our cohort of patients with symptomatic mCRPC, Radium-223 proved to be effective in terms of pain relief, with moderate side effects. No PSA response was detected, while total ALP levels significantly decreased by the end of treatment. Our findings should be interpreted in view of the clinical evidence supporting the use of Radium-223 for the treatment of bone metastases in mCRPC patients.

The phase III, double-blind, randomized Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial investigated the efficacy and safety of Radium-223 compared to placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases [19]. Radium-223 significantly prolonged overall survival, the time to first symptomatic skeletal event, and reduced the risks of external beam radiation therapy for bone pain, and spinal cord compression [7]. The most common adverse reactions associated with Radium-223 treatment in the ALSYMPCA trial were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic laboratory abnormalities in the Radium-223 arm were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia [21].

Hungarian centers did not participate in the ALSYMPCA registration trial. Our clinical experience is in line with the results of the ALSYMPCA trial in terms of the efficacy and safety of Radium-223 treatment. The most common side effects observed in our patient cohort were anemia and nausea, other adverse events included thrombocytopenia and diarrhea. The reported adverse events were not severe, and none of

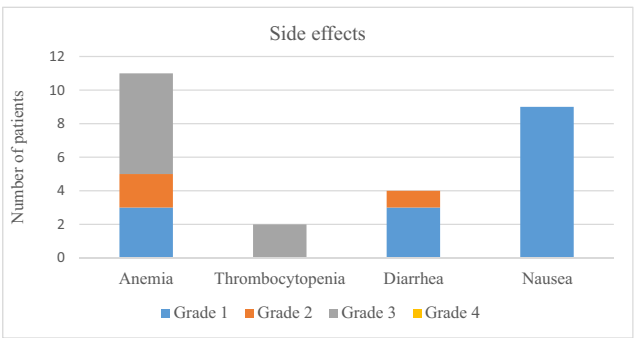

Fig. 3 Number and severity of treatment-emergent adverse events

Table 2 Number of patients according to the analgesic treatments received before Radium-223 therapy initiation

Pain management strategy	Number of patients
NSAID	40
•NSAID + palliative radiotherapy	3
•NSAID + opioid	5
•NSAID + opioid + radiotherapy	2
•NSAID + major analgesics	4
•NSAID + major analgesics + radiotherapy	1
Opioid	1

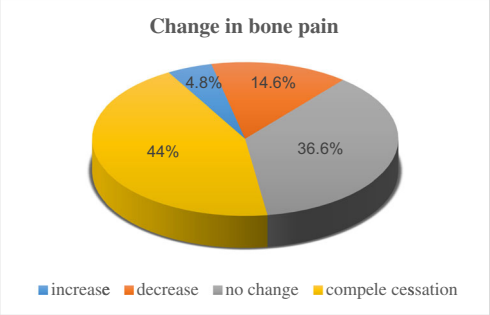

Fig. 4 Distribution of patients based on the change in bone pain intensity

them required the treatment discontinuation. The majority of patients receiving Radium-223 at our institute experienced a significant reduction of bone pain by the end of treatment.

Radium-223, as compared with placebo, significantly prolonged the time to an increase in the total ALP levels, and the time to an increase in PSA levels in the ALSYMPCA trial [19]. In our cohort, Radium-223 treatment resulted in a significant reduction of baseline total ALP levels. The majority of patients (70%) having elevated ALP levels at baseline achieved a complete normalization by the end of treatment, and a decrease of at least 50% was observed in 46% of these patients. On the other hand, we found an increase in mean PSA levels by the end of treatment. However, it has to be noted that nearly half of our patients were not receiving Radium-223 as first-line therapy. In a recent retrospective study [22], Radium-223 treatment in mCRPC was associated with an increase in PSA in the majority of heavily pretreated patients, especially in patients who received Radium-223 as fourth- or fifth-line therapy, the significance of which is still uncertain. In our study, 4 patients had lymph node metastases with a size of <3 cm. The changes in serum PSA and ALP values were comparable in patients with and without lymph node metastases, however, the small sample size limits the applicability of statistical comparisons.

The primary purpose of Radium-223 therapy is to treat bone metastases and reduce bone pain, thus improving quality of life and prolonging survival. Therefore, changes in ALP levels should be preferred over PSA when it comes to monitoring the efficacy of Radium-223 therapy in terms of bone metastases and the reduction of bone pain.

One of the important remaining questions is the appropriate sequencing of agents for mCRPC in the larger context of response/survival benefit and risk/safety profile of various approved agents in the CRPC spectrum. In a pre-specified subgroup analysis of the ALSYMPCA trial [23], Radium-223 was effective and well-tolerated, irrespective of previous docetaxel use. In our cohort, more than half of the patients received Radium-223 as first-line therapy, but the most common previous agent used was docetaxel. The fact that in the majority of patients, bone pain intensity significantly improved by the end of treatment supports the positioning of Radium-223 as a first-line option for a large number of patients with symptomatic mCRPC and bone metastases. Another frequently discussed concern is optimal patient selection, i.e. the identification of patients who would benefit the most from Radium-223 therapy. Patients with mCRPC and bone metastases are often fragile with a poor general condition, therefore the development of treatment-emergent side effects, particularly bone marrow failure, might often require therapy discontinuation. In our cohort, the incidence of bone marrow failure was low, and none of the reported adverse events required the cessation of treatment, although a significant proportion of patients were heavily pretreated before the initiation of Radium-223 therapy.

Our observations regarding the baseline characteristics of patients with mCRPC and bone metastases highlights significant unmet needs in the field of pain management. Despite the commonly known World Health Organization cancer pain treatment step ladder and the generally poor health status of patients receiving Radium-223 as second-, third-, fourth-, or fifth-line therapy, a significant proportion of our patients were only receiving one type of analgesics at treatment initiation, most of which were NSAIDs. Furthermore, only a small proportion of patients were treated with major analgesics, and in many cases, combination analgesic therapy was not in line with current recommendations. These findings are in accordance with previous observations. A recent study examining the prevalence and severity of pain in unselected outpatients with mCRPC found that pain is commonly present, commonly undertreated, and often severe in these patients. Moreover, the study revealed an apparent underuse of analgesics, including narcotic analgesics, among patients with pain [24]. Suboptimal pain management in the mCRPC patient population might be due to the lack of clinical trials assessing pain palliation in a manner that could support a label for this purpose, and the resulting uncertainties of treating physicians. Our observations suggest that there is still room for improvement regarding pain management in patients with mCRPC, and highlight the importance of a comprehensive approach.

Interestingly, 3 of our patients were diagnosed with brain metastasis during Radium-223 treatment (7.3%), the suspicion of which was raised by epileptic seizures in all cases. Brain metastasis in men with mCRPC is not common, and appears to occur in less than 3% of all men with hormonally treated prostate cancer based on three large reviews on the incidence of brain metastasis from prostate cancer [25–27]. However, emerging evidence suggests that the incidence of brain metastasis may have been rising over recent years may be due to the fact that the range of effective treatment options has been increasing and patients live longer with metastatic disease [28]. Therefore, the improved survival associated with the introduction of new agents including Radium-223 is likely to ‘unmask’ brain metastases that would otherwise remain

clinically silent. Our experience supports this hypothesis, and suggests that physicians should suspect the possibility of brain metastasis in mCRPC patients developing central symptoms. Furthermore, in heavily pretreated patients, performing head CT before the initiation of Radium-223 therapy may be recommended to facilitate the early detection and management of asymptomatic brain metastasis, however, international guidelines do not provide recommendations for routine head CT examinations.

Conclusions

Our clinical experience suggests that Radium-223 is a safe and effective treatment option for mCRPC patients with bone metastases. In our study, Radium-223 therapy was associated with a remarkable reduction in bone pain intensity, which was accompanied by a decrease in total ALP levels. The majority of reported adverse events were mild or moderate. Further research is required to optimize patient selection and determine the positioning of Radium-223 in the treatment sequence of patients with symptomatic mCRPC and bone metastases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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