Prostate International 7 (2019) 25–29

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Original Article

Hematologic toxicity of radium-223 in elderly patients with metastatic Castration Resistant Prostate Cancer: a real-life experience

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ARTICLE INFO

Article history:
Received 2 February 2018
Received in revised form
21 August 2018
Accepted 27 August 2018
Available online 10 September 2018

Keywords:
Cancer
Older
Prostate
Ra-223
Toxicity

ABSTRACT

Background: Treatment with radium-223 has been shown to increase survival and to delay skeletal events related to bone metastases of patients with metastatic Castration Resistant Prostate Cancer (mCRPC). This treatment has also proved to be well tolerated, and hematological toxicity, in particular anemia, represents the most represented adverse event.

Materials and methods: We evaluated the hematologic toxicity of Ra-223 treatment in a real-life experience of 38 patients from two Italian cancer centers, with bone metastases from mCRPC. The main endpoint of the study was the evaluation of the efficacy and tolerability of treatment with radium-223, with greater reference to hematological toxicity (especially anemia) as the cause of interruption of treatment, specifically in the elderly patient.

Results: From August 2016 to October 2017, a total of 38 consecutive nonselected patients, 20 of them aged >75 years, with mCRPC symptomatic bone metastases, were enrolled for radium-223 at standard doses. Hematologic adverse events were recorded more frequently (72.4% with AE), and 36.8% had anemia. The most frequent cause of treatment discontinuation due to AEs was anemia [8/10 patients (80%)], followed by thrombocytopenia (2 patients) and neutropenia (1 patient). Hematologic AEs were more represented in elderly patients with greater disease burden and previously treated with docetaxel.

Conclusions: Anemia is the most represented AE related to radium-223 treatment in elderly patients with greater disease burden and previously treated with docetaxel, besides representing the main reason for interruption of treatment. Correct patient selection, appropriate timing, and adequate supportive care are elements that could facilitate successful treatment with radium-223, preventing premature interruption of the same. The results of this experience support the opportunity to propose treatment with radium-223 mostly in patients in the earliest stages.

1. Introduction

Prostate cancer is the most common cancer among adult men in Western countries.[1] Patients with hormone-refractory prostate cancer frequently develop skeletal metastases. The mechanisms of bone metastases in prostate cancer patients include factors released by tumor cells that stimulate both osteoclast and osteoblast activity.[2,3] Bone metastases are clinically characterized by pain, spinal cord compression, pathological fracture, and pancytopenia, which represent the most skeletal-related events (SREs) that are capable of modifying patient survival.[4] Bisphosphonates,[5] denosumab,[6] and radioisotope[7] treatments are used for pain relief and the delay of skeletal events. Radium-223 dichloride (radium-223) is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 μm).[8,9] The mechanism of action of this radiopharmaceutical consists in selectively binding to areas of increased bone turnover in and around metastases and emitting energy. The high-energy alpha-particle radiation induces predominantly nonreparable DNA double-strand breaks that cause cytotoxic

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https://doi.org/10.1016/j.prnil.2018.08.001

effect in the target metastases.[9,10] The cytotoxic effect on bone marrow is reduced because of the short range (from 40 to 100 ìm) of energy emitted.[11]

In Phase 2 and Phase 3 studies, radium-223 showed a favorable safety profile with low myelotoxicity.[11,12]

Radium-223 is approved in the USA[13] and Europe[14] for men with mCRPC with symptomatic bone metastases and no visceral metastatic disease.

In Phase 3, randomized, double blind, placebo-controlled ALSYMPCA trial,[15] radium-223 has shown an advantage in median survival versus placebo (14.9 months vs. 11.3 months). The treatment also prolonged the time to the first symptomatic skeletal event (median, 15.6 months vs. 9.8 months). In ALSYMPCA trial, radium-223 was well tolerated.[15] Hematologic AEs were the most common, and in particular, all-grade anemia was recorded in 31% and Grade 3–5 in 13% of patients.

Data from 3-year safety follow-up analysis from ALSYMPCA trial showed that radium-223 continued to be well tolerated, with a low incidence of myelosuppression, long-term preservation of hematopoietic function, and no new safety signals.[16]

The efficacy and tolerability data of a real-life experience of patients treated with radium-223 will be illustrated in the following.

2. Subjects, materials, and methods

2.1. Patients

We reported the cases of 38 consecutive nonselected patients with mCRPC symptomatic bone metastases treated in two Italian cancer centers from August 2016 to October 2017. All patients had the same characteristics as patients enrolled in the ALSYMPCA study,[15] i.e., patients symptomatic, progressive, and bone-predominant mCRPC with >2 bone metastases on imaging with no lung, liver, or brain metastases. Lymph node metastases were allowed. Symptomatic was defined as regular use of any analgesic medication for cancer-related bone pain (≥level 1; World Health Organization ladder for cancer pain). All treated patients were symptomatic for bone pain, and 15.8% of them were highly symptomatic. Progressive was defined as the appearance of new bone lesions or two subsequent increases in serum prostate-specific antigen (PSA) above the previous reference value.

The mean age of the patients in the study was 74 years; 20 of these were old patients aged ≥75 years. All patients had histologically confirmed, progressive castration-resistant prostate cancer with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases, and 57.8% of patients had >20 metastatic lesions. Castration-resistant disease was defined as a serum testosterone level of 50 ng/dL or lower in progression after androgen deprivation therapy (ADT) treatment. More than half of the patients (57.8%) had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and 42.2% of them had performance status ≥ 2.

Twenty-two patients (57.9%) had cardiovascular comorbidities (hypertension, dilated cardiomyopathy, and arrhythmias), and almost all (97.3%) had good renal and hepatic function.

Of all patients who began treatment with radium-223, 24 (63.2%) had previously been treated with docetaxel (11 also with abiraterone or enzalutamide and 12 also with cabazitaxel), and 14 patients had not previously been treated with docetaxel (6 had received only abiraterone or enzalutamide and 8 only ADT). Eight patients had undergone previous external-beam radiation therapy, four patients on the prostatic loggia, and six patients also received radiotherapy on the bone. Eight patients treated with radium-223 also underwent concomitant treatment with bisphosphonates, and three patients with denosumab (Table 1). No other treatment, with the exception of bisphosphonates or denosumab, had been tried by all patients.

2.2. Study design and treatment

We performed a retrospective observational study in real life of 38 patients treated with radium-223 in two Italian cancer centers.

All treated patients were able to perform radium-223 treatment according to the indications of the drug, and they performed the standard dose of 50 kBq per kg of body weight, administered at 4-week intervals for six injections.

The treatment period was the time from the first radium-223 dose to 30 days after the last dose. Visits were made for each cycle (i.e., every 4 weeks 67 days) for treatment and evaluation of ECOG performance status, clinical laboratory tests, SSEs, and AEs.

The clinical data of each patient were identified, in particular the blood values (Hb, PLT, and granulocyte counts), PSA, and alkaline phosphatase values in baseline and the detection of pain in baseline and the possible response antalgic, the various treatment-related toxicities in different degrees of expression in subsequent evaluations.

2.3. Outcomes

Primary outcomes of our study were acute and long-term safety of radium-223, with greater reference to hematological toxicity (especially anemia) as the cause of interruption of treatment, specifically in the elderly patient. The efficacy of treatment was also

Table 1
Baseline clinical characteristics of patients treated with radium-223.

Characteristic	Patients (38)
Age	
Median (range), yr	74.02 (56–86)
<75 yr, no. (%)	18 (47.3)
≥75 yr, no. (%)	20 (52.6)
ECOG performance status score, no. (%)	
0	4 (10.5)
1	18 (47.3)
≥2	16 (42.2)
Extent of disease, no. (%)	
<6 metastases	9 (23.6)
6–20 metastases	7 (25)
>20 metastases	22 (57.8)
Median basal biochemical values (range)	
Hemoglobin, g/dL	12.6 (10.3–15.2)
Total alkaline phosphatase, U/liter	125.1 (58–255)
PSA, ng/dL	46.9 (0.17–419)
Pain at baseline, n (%)	
Mild	8 (21.1)
Moderate	24 (63.1)
Severe	6 (15.8)
Any previous use of docetaxel, no. (%)	
Yes	24 (63.2)
Also Abi/Enza no. (% of yes)	11 (45.8)
Also cabazitaxel no. (% of yes)	12 (50)
No	14 (36.8)
Only ADT (% of not)	8 (57.2)
ADT + Abi/Enza (% of not)	6 (42.8)
Previous external-beam radiation therapy, no. (%)	
Yes	8 (21.05)
Prostate	4 (10.5)
Bone	6 (15.7)
Current use of bisphosphonates, no. (%)	
Yes	8 (21.05)
Current use of denosumab, no. (%)	
Yes	3 (7.8)

PSA, prostate-specific antigen.

evaluated which included survival status, radiographic response rate, and the response to the total alkaline phosphatase and PSA level.

Radiographic response rate was evaluated with the use of either computed tomography or ^{11}C-Choline positron emission tomography/computed tomography (PET/CT) and with the use of bone scanning. Imaging was performed at the time of screening and at the end of the treatment. Radiologists at a central location who were unaware of the study group assignments determined whether there was progressive disease on the basis of Response Evaluation Criteria in Solid Tumors, version 1.1, for soft tissue or on the basis of criteria adapted from the Prostate Cancer Clinical Trials Working Group 2[17] for osseous disease.

Safety was assessed on the basis of AEs, hematologic values, clinical laboratory variables, and findings on electrocardiography and physical examination. All AEs that occurred after the start of treatment and within 12 weeks after the last injection of radium-223 were reported and evaluated.

AEs were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.[18]

3. Results

Overall, 20 of 38 patients (52.6%) had received all six injections of the treatment radium-223. The median number of injections was 4.1 in patients aged ≥75 years and 4.6 in patients aged <75 years.

3.1. Safety

The number of patients with AEs related to treatment with radium-223 was quite remarkable: 29 of 38 patients (76.3%) had AE of any grade, 28.9% (11 pts) had Grade 3 or 4 AE, and 10 patients (26.3%) stopped the treatment because of AEs. Eight patients did not complete treatment for other causes (3 for visceral progression during treatment and 5 died).

Hematologic and nonhematologic AEs that occurred are shown in Table 2.

Hematologic AEs were recorded more frequently [21 of 29 patients (72.4%) with AE]: 14 of all patients (36.8%) had anemia, 8 of which were severe anemia (21.05%), neutropenia was reported in 3 patients (7.8%), Grade 3 febrile neutropenia in one patient (<3%), and thrombocytopenia in four patients (10.5%). The most common nonhematological AEs were fatigue (15.7%) and diarrhea (18.4%), two of Grade > 2, none of which resulted in discontinuation of treatment.

The most frequent cause of treatment discontinuation due to AEs was anemia [8/10 patients (80%)], followed by thrombocytopenia (2 patients) and neutropenia (1 patient).

3.2. Exploratory efficacy

At the interim analysis, at 16 months from the beginning of the study, of the 38 patients enrolled, 33 of them (86.8%) are still alive, and five are dead from causes related to the tumor.

The responses obtained in the 20 patients who completed the treatment (carried out six injections) were verified: 11 of 20 (55%) patients had a metabolic (evaluated with ^{11}C-Choline PET/CT) and clinical (pain response) partial response, 2 patients (10%) had a disease stability with objective response rate 65%, and 7 of 20 (35%) patients had an iconographic disease progression. Responses to alkaline phosphatase and PSA levels were also assessed: 15 of 38 patients (39.4%) had a reduction > 30% in the levels of alkaline phosphatase during treatment, 11 of whom had taken 6 injections of Ra-223; 29 patients had PSA levels increased during treatment, and only 9 patients (23.6%) had a PSA response > 30%, 6 of whom had completed treatment.

4. Discussion

Radium-23 treatment is an excellent alternative for patients with mCRPC and bone metastases, as described by numerous literature data and the increasing experience in real life. In addition to an effective treatment that is able to offer a survival advantage and a reduction of skeletal events related to bone metastases,[15] radium-223 is also a well-tolerated treatment, and related toxicities are far from those recorded with antiblastic treatments.

In the ALSYMPCA study, the number of patients who had AEs was consistently lower in the radium-223 group than in the placebo group for all AEs [558 of 600 patients (93%) vs. 290 of 301 patients (96%)], Grade 3 or 4 AEs [339 patients (56%) vs. 188 patients (62%)], serious AEs [281 patients (47%) vs. 181 patients (60%)], and study drug discontinuation because of AEs [99 patients (16%) vs. 62 patients (21%)].[15] The most frequent nonhematological AEs in the radium-223 patient group were nausea (36%), fatigue (26%), diarrhea (25%), and constipation (18%), although with frequency overlapping that of the control group, with the exception of diarrhea (25% vs. 15%). The rates of myelosuppression recorded in the

Table 2
Adverse events recorded and broken down by age (>or < 75 years) and in relation to previous treatment with docetaxel (yes or not).

Adverse events N (%)	Patients treated with radium-223 (N = 38)							
	Previous docetaxel use (N = 24)				No previous docetaxel use (N = 14)			
	Age > 75 yr (N = 12)		Age < 75 yr (N = 12)		Age > 75 yr (N = 8)		Age < 75 yr (N = 6)	
	All Grade	G3–5	All grade	G3–5	All grade	G3–5	All grade	G3–5
Hematological adverse events								
Anemia	8 (21.05%)	5 (13.1%)	4 (10.5%)	2 (5.2%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	0 (0%)
Neutropenia	2 (5.2%)	1 (2.6%)	0 (0%)	0 (0%)	1 (2.6%)	1 (2.6%)	0 (0%)	0 (0%)
Thrombocytopenia	3 (7.8%)	1 (2.6%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)
Nonhematological adverse events								
Constipation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	3 (7.8%)	1 (2.6%)	1 (2.6%)	0 (0%)	2 (5.2%)	1 (2.6%)	1 (2.6%)	0 (0%)
Nausea/Vomiting	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)
Fatigue	2 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	2 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)
Anorexia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weight decreased	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	2 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)
Peripheral edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)

ALSYMPCA study were relatively low: all grades of anemia, 31%; thrombocytopenia, 12%; and neutropenia, 5%.[15]

In a recent analysis of patients included in the ALSYMPCA study, the AEs that have occurred and persisted for a long time after the discontinuation of treatment, including acute myeloid leukemia, myelodysplastic syndrome, and second tumors were examined. Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 week after the last study drug injection to 3 years from the first injection. Myelosuppression incidence was low. Grade 3/4 hematologic AEs in radium-223 and placebo groups were anemia (13% vs. 13%), neutropenia (2% vs. 1%), and thrombocytopenia (7% vs. 2%). Long-term follow-up showed no acute myeloid leukemia, myelodysplastic syndrome, or new primary bone cancer; secondary non–treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 mo after the last injection.[16]

Our data, in reference to the hematological toxicity, are in line with what was recorded in the ALSYMPCA study (anemia 36% vs. 31%, thrombocytopenia 10.5% vs. 12%, neutropenia 7.8% vs. 5%), although these toxicities, when they are of a high degree, have more determined the suspension of treatment (10/38: 26.3%). In detail, the discontinuity due to hematological toxicity occurred in 2 of 18 patients (11.1%) in the group aged <75 years and in 8 of 20 (40%) in the group aged ≥ 75 years. Furthermore, between the patients aged ≥75 years, 3 deaths occurred during treatment, although no correlation with the treatment was demonstrated. In addition, the 8 patients aged ≥75 years who discontinued the treatment for hematological toxicity (6 for anemia) had marked bone compromise with >20 metastatic lesions, 7 of 8 patients (87,5%) had received previous chemotherapy treatments and one of these was 85 years old at the start of treatment. Older age, previous myelotoxic treatments, and a large extent of disease could therefore be predictors of bone marrow toxicity.

The hematological toxicity related to the treatment with radium-223 is comparable to that registered with the new hormonal treatments, abiraterone and enzalutamide[19–21] and significantly lower than that recorded with cytotoxic chemotherapies (docetaxel and cabazitaxel), in which myelosuppression represents the most frequent toxicity.[22,23] Moreover, radium-223 is distinguished from beta-emitting radiopharmaceuticals, which are associated with significant hematologic events (mainly leukopenia and thrombocytopenia).[24]

A phase II, open-label, single-arm, multicenter U.S. expanded access program (EAP),[25] recently published, enrolled 184 patients with the same characteristics of the patients of the ALSYMPCA study who received radium-223 at standard doses for up to 6 cycles. Additional analyses were done by prior or concomitant abiraterone or enzalutamide use. Concurrent abiraterone was administered to 25 of 184 (14%) patients, and concurrent enzalutamide to 15 of 184 (8%) patients. Radium-223 concurrently administered with abiraterone or enzalutamide was well tolerated. The most frequent Grade 3–4 adverse events were anemia (abiraterone 16%, enzalutamide 13%), thrombocytopenia (abiraterone 4%, enzalutamide 0%), and back pain (abiraterone 0%, enzalutamide 13%). The results of this study demonstrate that concomitant use of radium-223 and androgenic receptor (AR)-target agents does not change the toxicity profile of the treatment.

Despite this tolerability profile, our data showed a greater discontinuity in treatment, especially in elderly patients with greater disease burden and previously treated with myelotoxic drugs.

Few literature data concern patients aged >75 years, but other authors suggest that some factors such as extensive bone disease and previous treatment with docetaxel may be predictive of myelotoxicity.

A high rate of anemia has been reported in patients with CRPC and bone metastases,[26,27] and therefore, the burden of bone disease could in itself represent a predictor of hematological toxicity. In ALSYMPCA study, anemia was the most common hematologic toxicity: current prescribing information recommends that hemoglobin be ≥ 10 g/dL before the first radium-223 administration. Ongoing protocols allow hemoglobin ≥8 g/dL (with transfusions).

In a *post hoc* analysis of data from ALSYMPCA study,[28] the efficacy and toxicity data of patients previously undergoing treatment with docetaxel were compared with those of patients who had not undergone this treatment. Radium-223 prolonged median overall survival compared with placebo, irrespective of previous docetaxel use (previous docetaxel use, hazard ratio 0.70, 95% confidence interval 0.56–0.88; $P = 0.002$; no previous docetaxel use, hazard ratio 0.69, confidence interval 0.52–0.92; $P = 0.01$). The benefit of radium-223 compared with placebo was seen in both docetaxel subgroups for most main secondary efficacy endpoints; risk for time to symptomatic skeletal event was reduced with radium-223 versus placebo in patients with previous docetaxel use, but the difference was not meant in those with no previous docetaxel use. Patients who had previously been treated with docetaxel had a higher incidence of Grade 3–4 thrombocytopenia with radium-223 than with placebo (9% vs. 3%), whereas the incidence was similar between treatment groups among patients with no previous docetaxel use (3% vs. 1%). The incidences of Grade 3–4 anemia and neutropenia were similar between the radium-223 and placebo groups within both docetaxel subgroups.[28]

A multivariate analysis of data from ALSYMPCA patients[29] identified baseline factors that may increase hematologic toxicity risk with radium-223. Authors suggest that the extent of disease (6–20 vs. < 6 bone metastases; odds ratio = 2.76; $P = 0.022$) and degree of PSA elevation (odds ratio = 1.65; $P = 0.006$) were predictive of Grade 2-4 anemia; prior docetaxel treatment with associated decreased hemoglobin and platelets was predictive of Grade 2-4 thrombocytopenia. There were no significant associations between hematologic toxicities and number of radium-223 injections received.[29]

Considering these results and the data of our patients, whose hematological toxicity from radium-223 was more represented in elderly patients previously treated with Docetaxel, in the choice of treatment, it could be possible to select patients with earlier bone disease and who are chemo naïve.

In this regard, a subgroup analysis of the ALSYMPCA study tested the results in terms of efficacy and tolerability in patients who had not undergone previous chemotherapy [30] but who had subsequently undergone treatment with antiblastic treatment (70% with docetaxel, 16% with mitoxantrone). In radium-223 and placebo patients receiving subsequent chemotherapy, median hematologic values (hemoglobin, neutrophils, and platelets) remained nearly constant up to 18 months after the start of chemotherapy. A low percentage of patients in both groups had Grades 3–4 hematologic values (<10%). Median overall survivals from the start of chemotherapy were 16.0 and 15.8 months after radium-223 and placebo, respectively.[30]

The results of our study showed that patients treated with radium-223 and who had never undergone previous chemotherapy (36.8%) had a much lower hematological toxicity than those who had previously been treated with chemotherapy [4/14 (28.5%) vs. 16/24 (66.6%)], most of whom [3/4 (75%)] were elderly. It may therefore be appropriate to anticipate the treatment with radium-223, postponing chemotherapy, to guarantee the same results with a better toxicity profile. Finally, we must consider that hematologic AEs are also easily managed if treated early with prophylactic or curative use of granulocyte and erythrocyte growth factors and transfusions of red blood cells/platelets. Correct patient selection,

appropriate timing, and adequate supportive care are elements that could facilitate successful treatment, preventing premature interruption of the same.

5. Conclusion

Radium-223 represents an important advance in the treatment of m-CRPC. Radium-223 offers a substantial improvement in the overall survival with a highly favorable safety profile.

Hematological toxicity, especially anemia, is the most common AE in patients treated with radium-223.

The results of our experience in real life, although with small numbers, probably unrepresentative of the general population, have shown that anemia is the most represented AE in elderly patients with greater disease burden and previously treated with docetaxel, besides representing the main reason for interruption of treatment.

This experience supports the opportunity to propose treatment with radium-223 in patients with more indolent disease and in the earliest stages.

Conflict of interest

There is no conflict of interests.

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