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Treatment outcome of radium-223 treatment for castration-resistant prostate cancer and bone metastases at a single university hospital

T. Takayama*, T. Sugihara, T. Kameda, M. Yamazaki, M. Komatsubara, J. Kamei, A. Fujisaki, S. Ando, T. Fujimura

Department of Urology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

► ***Original article***

Corresponding author:
Tatsuya Takayama, M.D, Ph.D.,
E-mail: *ttakayam@jichi.ac.jp*

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ABSTRACT

Background: We investigated therapeutic outcomes of Radium-223 (Ra-223) treatment in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases. ***Materials and Methods:*** Outcomes were retrospectively examined in 20 patients starting Ra-223 treatment at a single university hospital from January 2017 to January 2020. ***Results:*** Median patient age was 70 years. Median values included prostate specific antigen (PSA) 10.73 ng/ml, PSA doubling time (PSADT) 3.7 months, alkaline phosphatase (ALP) 315 IU/L, lactate dehydrogenase (LDH) 186 IU/L, neutrophil-to-lymphocyte ratio (NLR) 2.22, and Gleason score 9. Extent of disease (EOD) was 3 or more in 55%, and Eastern Cooperative Oncology Group performance status was 0 in 80%. 16 patients (80%) completed Ra-223 treatment. Ra-223 was administered in 11 (55%) with ≤ 3 lines of treatment and 9 (45%) with ≥ 4. Concomitant drug was enzalutamide and abiraterone in 6 and 7 patients, respectively. Bone modifier agents (BMA) were used in 11 patients. Symptomatic skeletal events (SSE) occurred in 5 patients and were associated with abiraterone combination. BMA during Ra-223 treatment did not affect SSE. Median overall survival from initiation of Ra-223 treatment was 32.7 months. Prognosis was significantly better with PSADT ≤ 3 months, EOD ≤ 2, no SSE, no opioid use, and completion of Ra-223 treatment. PSA, LDH, NLR, PSADT, and Ra-223 treatment line after mCRPC were associated with Ra-223 completion. Anemia of Grade 3 occurred in 1 patient. ***Conclusion:*** Ra-223 treatment is safe, with good prognosis if completed. Combination treatment with abiraterone during Ra-223 treatment may cause SSE.

INTRODUCTION

Bone is the most common distant site of metastasis in prostate cancer, and up to 90% of patients with advanced disease develop bone metastases [1]. Existing bone metastases may in turn become a hotbed for new metastases [2]. Androgen deprivation therapy (ADT), the mainstay treatment for metastatic prostate cancer, leads to bone fragility, and consequent skeletal-related events result in substantial morbidity, increased pain, reduced quality of life and poor survival [3]. This adverse scenario highlights the importance of treatment for bone metastases, including bone health management, in patients with metastatic castration-resistant prostate cancer (mCRPC).

Radium-223 (Ra-223), also called Xofigo, is a novel targeted radioisotope that, as a bone-seeking calcium mimetic, selectively binds mineral hydroxyapatite of newly formed bone stroma in areas of increased metabolic activity, such as bone metastases [4]. It emits high-energy alpha-particle radiation of short range (<100 mm; <10 cell diameters) that induces double-stranded DNA breaks with cytotoxic effects in target areas, with limited damage to surrounding normal tissue, particularly the bone marrow [5]. Ra-223 has improved overall survival (OS) and reduced Symptomatic skeletal events (SSE) in patients with mCRPC and symptomatic bone metastases (ALSYMPCA trial) [6]. An international early access phase 3b trial extended to asymptomatic patients with mCRPC demonstrated that Ra-223 can be safely combined with abiraterone (Abi) or enzalutamide (Enz), which are now both part of the standard of care for patients with mCRPC [7]. In addition, subsequent post hoc analysis showed that using Ra-223 earlier in the disease course may improve treatment outcomes in asymptomatic and minimally symptomatic patients compared to symptomatic patients [8]. However, a randomised double-blind placebo-controlled phase 3 study (ERA223) conducted in light of these results found that addition of Ra-223 to Abi or prednisolone did not improve SSE-free survival in patients with asymptomatic or mildly symptomatic CRPC and bone metastases, but was associated with an increased

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frequency of bone fractures compared with placebo. Accordingly, this combination was not recommended [9]. While the PEACE III trial comparing Enz and Ra223 versus Enz alone in patients with conditions similar to those for ERA223 is ongoing, an interim analysis found that the addition of Ra-223 to Enz significantly increased the risk of bone fractures, but that continued compulsory bone modifier agents (BMA) administration eliminated most of this risk. The authors emphasized the importance of treatment of patients with mCRPC by BMA.

Apalutamide [11] and Enz [12] with ADT have recently been approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC). Docetaxel (DTX) [13,14] and Abi [15,16] with ADT have already been approved for mCSPC patients with high volume tumors. Moreover, a new diagnosis and treatment modality using prostate-specific membrane antigen (PSMA) has appeared: in patients previously diagnosed with non-metastatic CRPC, PSMA-ligand positron emission tomography (PSMA-PET) detected any disease in nearly all patients and M1 disease in 55%, including subgroups with a prostate specific antigen doubling time (PSADT) of ≤ 10 months and Gleason score of ≥ 8 [17].

These substantial developments in diagnosis and treatment choices for mCRPC warrant ongoing evaluation and assessment to ensure that treatment is optimized. Here, we evaluated outcomes of Ra-223 treatment against real-world mCRPC at our university hospital, both to validate current protocols and for future reference use. We report that Ra-223 treatment is safe, with good prognosis if 6 regular treatment is completed, and that combination treatment with abiraterone during Ra-223 treatment may cause SSE.

MATERIALS AND METHODS

This study was a retrospective analysis of our clinical experience with a cohort of patients with mCRPC and bone metastases treated with Ra-223 at the urology department of Jichi Medical University Hospital from January 2017 to January 2020. CRPC was defined as a serum testosterone level of < 50 ng/dl following surgical or pharmaceutical castration. All patients had bone metastases detected by bone scan and/or computed tomography scan and no known visceral metastases, except for malignant lymphadenopathy of less than 3 cm in short-axis diameter, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-1 and adequate hematological, liver and renal function. Patients with a blood pressure > 140/90 mmHg and those receiving antihypertensive agents were regarded as positive for hypertension, while patients receiving hypoglycemic agents and/or insulin injection were regarded as positive for diabetes mellitus.

Patients underwent comprehensive medical evaluation at each visit. Blood tests were performed monthly and images were evaluated at the discretion of the attending physician. Ra-223 was administrated intravenously at a dose of 55 kBq/kg body weight. A total of six injections were given at intervals of 4 weeks, resulting in a total of 24 weeks of therapy. All patients were followed up every month after Ra-223 treatment. All adverse events that occurred during the treatment period were graded according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0). The protocols were approved by the Institutional Research Review Board of Jichi Medical University with an opt-out system (No. A-18-210).

Statistical validation

Numeric variables are described as median, minimum and maximum. Categorical variables are expressed as frequencies and percentages, and differences were compared using the chi-square test and Mann–Whitney U test. PSADT was calculated using 3-4 consecutive measurements taken at intervals of 2 weeks or longer before the start of Ra-223 treatment. SSE were counted as defined in the ERA-223 study [9]. The number of treatment sequences from the time a patient was classified with CRPC to the start of Ra-223 therapy was counted without including antiandrogen withdrawal syndrome or oral steroid monotherapy. OS was calculated from the date of the start of Ra-223 treatment to the date of death from any cause or the date of last follow-up, whichever occurred first. Survival curves were plotted according to the Kaplan–Meier method and differences between groups were analyzed using the two-tailed log-rank test. All *P* values presented are two-sided. Statistical significance was calculated using StatView ver. 5 (Abacus Concepts, CA, USA), with *P* values of <0.05 considered to indicate statistical significance.

RESULTS

Patient characteristics before Ra-223 treatment and treatment information before, during, and after Ra-223 treatment are shown in tables 1 and 2, respectively. We included 20 patients with a median age of 70 years (range 53–85), median PSA 10.73 ng/ml (range 0.05-279.4), median PSADT 3.7 months (range -9.4-25.1), median alkaline phosphatase (ALP) 315 IU/L (range 139-1997), median lactate dehydrogenase (LDH) 186 IU/L (range 97-339), median neutrophil-to-lymphocyte ratio (NLR) 2.22 (range 0.83-5.44), median Gleason score 9 (range 7-9), extent of disease (EOD) 3 or more in 55%, and ECOG-PS 0 in 80%. Fifteen patients (75%) had a history of smoking.

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One patient (5%) underwent radical prostatectomy, and two (10%) underwent radiation therapy. All patients received ADT in combination with first-generation antiandrogens such as bicalutamide and flutamide. Second-generation antiandrogens such as Enz and Abi were administered to 14 (70%) (Enz 12 (60%) vs. Abi 5 (25%)), 13 (60%) (Enz 6 (30%) vs. Abi 7 (35%), and 17 (75%) (Enz 12 (60%) vs. Abi 11 (55%)) patients before, during, and after Ra-223 treatment, respectively. DTX was administered to 5 (25%) and 6 (30%) patients before and after Ra-223 treatment, respectively. Cabazitaxel (CBZ) was administered to 3 (15%) and 4 (20%) patients before and after Ra-223 treatment, respectively. BMA such as zoledronic acid (ZA) and denosumab (DMAB) was administered to 11 (55%) (ZA 6 (30%) vs. DMAB 6 (30%)), 11 (55%) (ZA 5 (25%) vs. DMAB 6 (30%), and 10 (50%) (ZA 4 (20%) vs. DMAB 6 (30%)) patients before, during, and after Ra-223 treatment, respectively.

Ra-223 was administered in different lines of treatment for mCRPC: median treatment line of Ra-223 after mCRPC was 3 (range 1-7), with 5 patients (25%) receiving Ra-223 as first-line treatment and 9 (45%) as fourth or later line treatment (table 1). 16 patients (80%) received the standard number of six cycles of Ra-223 treatment. All 11 patients (55%) with up to three sequential therapies completed six cycles of Ra-223 (table 4).

Median follow-up duration from the start of Ra-223 treatment for prostate cancer was 20.0 months with a range of 4.4–33.4 months. Median OS was 32.7 months (figure 1a). Table 3 shows univariate analysis for OS. Prognosis was significantly better in patients with PSADT ≤ 3 months (p=0.0176), EOD ≤ 2 (p=0.0397), completion of Ra-223 treatment (p<0.0001, figure 1b), and no SSE (p=0.0397), as well as those who were opioid-naive (p=0.0112). Univariate and multivariate analyses using Cox's proportional hazards model could not in principle be performed because, regarding the completion of Ra-223 treatment, one of the groups had no death until the other group had been totally censored, as shown in figure 1b.

Significant factors before Ra-223 treatment which were associated with the completion of Ra-223 treatment were PSA, LDH, NLR, PSADT, and treatment line of Ra-223 after mCRPC (table 4). Regarding the relationship between SSE during and after Ra-223 treatment and specific variables (table 5), Abi combination during Ra-223 treatment appeared to be associated with SSE. BMA use during Ra-223 treatment did not affect SSE.

The most frequent adverse event observed was anemia, at Grade 1 in 13 (65%) patients, Grade 2 in 2 (10%), and Grade 3 in 1 (5%). The patient with Grade 3 anemia was at an advanced stage with disseminated carcinomatosis of the bone marrow and received only 2 cycles of Ra-223, and his Grade 3 anemia might not have been due to Ra-223 treatment. Sensory disturbance of Grade 3 was seen in one (5%) patient, presumably due to DTX (table 6).

Table 1. Patient characteristics before Radium-223 treatment.

Characteristic	Value
Median age, years (range)	70 (53-85)
Hypertension, n (%)	7 (35)
Hyperlipidemia, n (%)	2 (10)
Diabetes mellitus, n (%)	3 (15)
Urinary protein, n (%)	1 (5)
Smoking history, n (%)	15 (75)
Median Hb, g/dL (range)	12.5 (10.5-14.7)
Median PSA, ng/mL (range)	10.73 (0.05-279.4)
Median PSA doubling time, months (range)	3.7 (-9.4-25.1)
Median ALP, IU/L (range)	315 (139-1997)
Median LDH, IU/L (range)	186 (97-339)
Median neutrophil-to-lymphocyte ratio (range)*	2.22 (0.83-5.44)
Gleason score at diagnosis	
Median (range)	9 (7-9)
≤ 7, n (%)	1(5)
8, n (%)	6 (30)
9, n (%)	11 (55)
unknown**	2 (10)
Number of bone metastases (extent of disease)	
< 6, n (%)	1(5)
6-20, n (%)	6(30)
≥ 20, n (%)	9(45)
Super scan, n (%)	2(10)
Lymph node metastasis at diagnosis***	
Yes, n (%)	7(35)
No, n (%)	13(65)
ECOG performance status	
0, n (%)	16(80)
1, n (%)	4 (20)
Radium-223 treatment after mCRPC	
Median (range)	3(1-7)
First-line, n (%)	5 (25)
Second-line, n (%)	3 (15)
Third-line, n (%)	3 (15)
Fourth-line, n (%)	4 (20)
Fifth-line, n (%)	3 (15)
Sixth-line, n (%)	1 (5)
Seventh-line, n (%)	1 (5)

*, 3 missing data; **, 1 missing data, 1 specific pathology; ***, At starting Radium-223 treatment, all lymph nodes were less than 1.5 cm in short-axis diameter. Abbreviations: Hb, hemoglobin; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase, ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer.

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Table 2. Drugs and modality before, during, and after Radium-223 treatment

	Before		During		After	
	n	%	n	%	n	%
Radical prostatectomy	1	5	0	0	0	0
Radiation as radical treatment	2	10	0	0	0	0
Hormone therapy with androgen deprivation*	20	100	20	100	20	100
Antiandrogens	20	100	14	40	19	80
first-generation	20	100	1	5	2	10
second-generation	14	70	13	65	17	85
enzalutamide	12	60	6	30	12	60
abiraterone	5	25	7	35	11	55
Others estramustine	8	40	3	15	4	20
Chemotherapy						
docetaxel	5	25	0	0	6	30
cabazitaxel	3	15	0	0	4	20
carboplatin	1	5	0	0	0	0
Palliative therapy						
Radiation	1	5	0	0	0	0
Bone modification agents	11	55	11	55	10	50
zoledronic acid	6	30	5	25	4	20
denosumab	6	30	6	30	6	30
Opioid	4	20	4	20	7	35
Non-steroidal anti-inflammatory drugs	4	20	4	20	5	25

Each drug use before, during, and after Radium-223 treatment is counted as a single use. *, All patients received androgen deprivation therapy, of whom 18 underwent pharmacological castration and 2 underwent surgical castration.

Table 3. Univariate analysis for overall survival from the start of Radium-223 treatment.

Variable	n	*P* value
Decreased PSA at 3 months after Radium-223 treatment*		
Yes/No	10/9	0.1950
PSA doubling time is 3 months or less		
Yes/No	4/16	0.0176
Decreased ALP at 3 months after Radium-223 treatment*		
Yes/No	13/6	0.2345
Docetaxel use before Radium-223 treatment		
Yes/No	6 /14	0.3338
Combined with enzalutamide or abiraterone during Radium-223 treatment		
Yes/No	13/7	0.7307
Number of sequential therapies after mCRPC		
≤3/≥4	11/9	0.0940
Extent of disease before Radium-223 treatment		
1-2/3-4	9/11	0.0397
Bone modification agents use		
Yes/No	11/9	0.9563
Symptomatic skeletal events during and after Radium-223 treatment**		
Yes/No	5/15	0.0247
Opioid use before Radium-223 treatment		
Yes/No	4/16	0.0112
6 cycles of Radium-223 treatment		
Yes/No	16/4	< 0.0001

*, 1 missing data; **, Two patients developed jaw osteonecrosis after Radium-223 treatment. Abbreviations: PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer

Table 4. Factors before Radium-223 treatment associated with completion of 6 cycles of Radium-223 treatment

Factor	6 cycles of Radium-223 treatment (Median, IQR*)		*P* value
	Yes (n=16)	No (n=4)	
Median PSA (ng/mL)	2.78 (45.7)	116.2 (120.5)	0.0233
Median LDH (IU/L)	179 (42)	277 (80)	0.0123
Median ALP (IU/L)	275 (205)	548 (836)	0.0588
Median neutrophil-to-lymphocyte ratio	1.987 (0.924)	3.088 (0.471)	0.0315
Median Hb (g/dL)	12.9 (2.1)	11.2 (2.8)	0.2501
Median Plt (10^4/μL)	21.1 (6.6)	26.9 (20)	0.0890
Median Alb (g/dL)	4.5 (0.5)	3.9 (0.7)	0.1306
PSA doubling time (months), >=3/< 3	15/1	1/3	0.0021
ECOG PS, 0/1	14/2	2/2	0.0935
Extent of disease, 1-2/3-4	8/8	1/3	0.3687
Number of treatment lines before starting Radium-223 treatment after mCRPC, ≤3/≥4	11/5	0/4	0.0134
Docetaxel use before Radium-223 treatment, Yes/No	3/13	3/1	0.0281

*IQR, interquartile range. Abbreviations: PSA, prostate-specific antigen; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; Hb, hemoglobin; Plt, platelet; Alb, albumin; ECOG, Eastern Cooperative Oncology Group; PS, performance status; mCRPC, metastatic castration-resistant prostate cancer.

Figure 1A

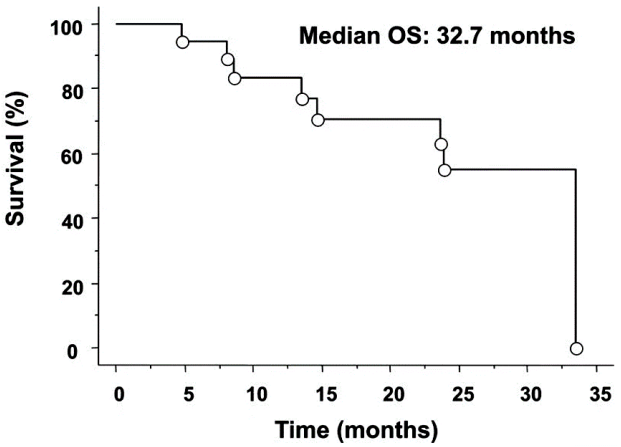


Figure 1B

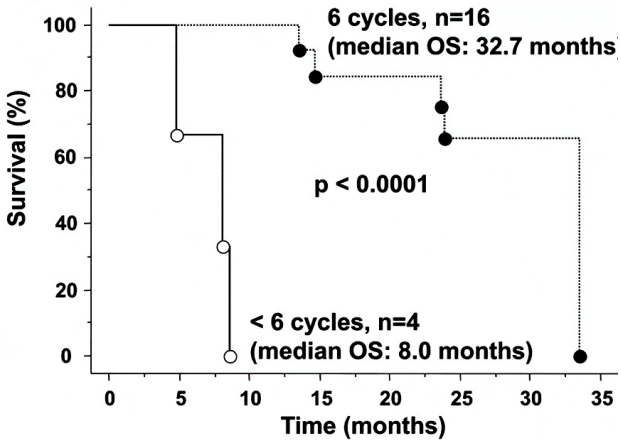


Figure 1. Kaplan-Meier estimates (a) OS and (b) OS stratified by number of radium-223 cycles (6 cycles vs < 6 cycles). OS: overall survival.

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Table 5. Relationship between skeletal symptomatic events during and after Radium-223 treatment and specific variables.

Factor	Skeletal symptomatic event		*P* value
	Yes (n=5)	No (n=15)	
Combined with enzalutamide or abiraterone			
Yes/No	5/0	8/7	0.0581
Combined with abiraterone			
Yes/No	5/0	2/13	0.0004
Combined with enzalutamide			
Yes/No	0/5	6/9	0.0910
Bone modification agent use during Radium-223 treatment			
Yes/No	2/3	9/6	0.4363

Table 6. Adverse event profile during Radium-223 treatment.

Factor	Grade1, n (%)	Grade2, n (%)	Grade3, n (%)
Hematologic			
Anemia	13 (65)	2 (10)	1 (5)
Neutropenia	0 (0)	1 (5)	0 (0)
Nonhematologic			
Constipation	1 (5)	0 (0)	0 (0)
Diarrhea	2 (10)	0 (0)	0 (0)
Nausea	1 (5)	0 (0)	0 (0)
Fatigue	3 (15)	0 (0)	0 (0)
Peripheral edema	1 (5)	0 (0)	0 (0)
Pyrexia (common cold)	2 (10)	0 (0)	0 (0)
Anorexia	1 (5)	0 (0)	0 (0)
Decreased appetite	2 (10)	0 (0)	0 (0)
Stomach pain	0 (0)	1 (5)	0 (0)
Bone Pain	1 (5)	1 (5)	0 (0)
Back pain	3 (15)	0 (0)	0 (0)
General pain	1 (5)	0 (0)	0 (0)
Joint pain	1 (5)	0 (0)	0 (0)
Pathologic fracture	1 (5)	0 (0)	0 (0)
Progression of malignant neoplasm	0 (0)	4 (20)	0 (0)
Sensory neuropathy	0 (0)	0 (0)	1 (5)*

*, adverse event due to docetaxel

DISCUSSION

Our study is a retrospective analysis of mCRPC patients treated with Ra-223 in a clinical practice setting at a single university hospital. Ra-223 treatment was associated with a good prognosis when 6 standard cycles were completed, and efficacy appears better when started from an earlier disease stage. In addition, Ra-223 treatment was safe, although concomitant use with Abi was associated with a higher incidence of SSE; accordingly, this combination should not be used, as previously noted by the ERA223 study [9].

In summarizing five other recent retrospective reports [19-23] with fewer than 100 patients (range 32-64) undergoing Ra-223 treatment for mCRPC in five single centers similar to ours, median PSA level range was 36-500 ng/mL; frequency of receiving 6 cycles of Ra-223 and Ra-223 as first-line systemic therapy for mCRPC was 40-91% and 0-19% (data not shown in Reference 9), respectively; and median OS was 8-17 months. In our study, median PSA was 10.7 ng/mL (table 1); frequency of 6 cycles of Ra-223 and Ra-223 as first-line treatment was 80% and 25%, respectively; and median OS was 32.7 months (figure 1a). Thus, our median PSA level was lowest among these reports; the frequency of 6 cycles of Ra-223 and Ra-223 as first-line treatment were second highest and highest; and median OS was longest [3,4,6-9,18-23]. Consistent with these previous reports [3,4,6-9,18-23], univariate analysis demonstrated that PSADT ≥ 3 months, EOD ≤ 2, completion of Radium-223 treatment, no SSE, and opioid-naive were significant prognostic factors (table 3). As shown in table 4, factors associated with the completion of 6 standard cycles of Ra-223 were low median PSA and LDH, PSADT ≥ 3 months, DTX-naive, and treatment with Ra -223 early in the mCRPC treatment sequence. As reported by McKay and colleagues, these parameters reflect an earlier disease stage [24]. In addition, the median OS in patients with completion of 6 standard cycles of Ra-223 was also 32.7 months (figure 1b). Moreover, patients in the ALSYMCA study had symptomatic mCRPC with an OS of 14.9 months, 3.6 months longer than placebo, and an extended time to first SSE. In addition, median OS was further extended to 16 months in a single-arm Phase 3b trial of asymptomatic mCRPC, including patients treated with Abi and Enz. The completion rate of 6 standard cycles in the two trials was closely similar, at 63% and 58%. Thus, one reason for the long OS in our present study is that patients were treated in an earlier stage of mCRPC and had higher completion of 6 cycles of Ra-223 than these other reports [3,4,6-9,18-23], including the ALSYMCA study. Thus, our findings confirm the benefit of starting Ra-223 treatment earlier, in the asymptomatic stage, and completing the standard 6 cycles of Ra-223.

In two large retrospective studies of real-world treatment patterns in 1855 and 2559 patients with mCRPC, Abi and Enz accounted for about 65% of first -line therapies and 54% or more of second-line therapies [25,26]. The medication distribution of Ra-223 in these studies by first-, second-, third-, or fourth-line use was 1.7% and 2%, 2.6% and 3%, 7.4% and 8%, and 13.1% and no data, respectively. Thus, Ra-223 is used infrequently in patients with mCRPC with bone metastases only, and tends to be delayed to later treatment lines. On the other hand, it was reported that PSMA-PET detected any disease in nearly all patients and M1 disease in 55% of patients previously diagnosed with non-metastatic CRPC. Taken together, these findings indicate that bone metastases will soon be more likely identified at an earlier disease stage. Accordingly, any increase in the number of new treatment options and combinations is likely to be accompanied by an increase in opportunities for the use of Ra-223.

Regarding safety (table 6), while attention should be focused on myelosuppression, given that Ra-223

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treatment is a kind of systemic radiation therapy, treatment is rarely limited [6-8], as also shown in our results. Dizdarevic and colleagues demonstrated that Ra-223 treatment can be safely used even after chemotherapy such as with DTX or CBZ [27]. As mentioned above, when available at an earlier stage in mCRPC, Ra-233 will be used more frequently before chemotherapy, thus reducing the risk of myelosuppression. Rather, the issue is the unfavorable effect on bone when Ra-223 is used in combination with Abi or Enz. All 5 patients with SSE in our study had combination treatment with Abi, indicating that this agent should not be used in combination with Ra-223, as also noted in the ERA223 study [9] and a subgroup analysis of Japanese patients in that study [28]. Our present study found no additional benefit on combination with BMA, but a retrospective study reported that incidence rates for SSE were reduced when BMA were used in concurrent or layered treatment with Ra-223 and Abi or Enz [29]. The results of the prospective PEACE III study on the effect of combined treatment with Ra-223 and Enz on bone is long-awaited.

Limitations of our study include the small number of patients, the heterogeneous patient population, the retrospective study design and the short observation period. Allowing for these limitations, this study characterized the utilization of Ra-223 in a real-world setting.

Current treatment for patients with mCSPC includes apalutamide [11] and Enz [12], while treatment for patients with high-volume disease includes DTX [13,14] and Abi [15,16]. In addition, a new modality, PSMA-PET, aims to detect mCRPC status before severe disease progression. It has been reported that approximately 60% of CRPC patients with metastases limited to bone only develop bone lesions but no other types of lesion during treatment with the initial second-generation anti-androgen drugs [30]. Use of Ra-223, which has a completely different mechanism of action, is expected to increase in the future, and the use of this modality in combination with these drugs therefore requires careful consideration.

In conclusion, we found that Ra-223 treatment was basically safe and offered a good prognosis if 6 standard cycles were completed. Careful selection of patients who are likely to complete the 6 standard cycles is therefore important. In addition, the combination of Abi during Ra-223 treatment was associated with a relatively high incidence of SSE, and should be deprecated.

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Author contribution: Provide

(T.T): conception and design; (T.S) and (T.T): administrative support; (T.T), (T.S), (T.K), (M.Y), (M.K), (J.K), (A.F) and (S.A): provision of study materials and patients and collection and assembly of data; (T.T), (T.S) and (T.F): manuscript writing; All authors: final approval of manuscript.

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