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Radium-223 in Heavily Pretreated Metastatic Castrate-Resistant Prostate Cancer

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Abstract

An increasing prostate-specific antigen (PSA) level during radium therapy for metastatic castrate-resistant prostate cancer (mCRPC) is not an uncommon phenomenon, especially in heavily pretreated patients; however, an increasing PSA level does not always indicate progressive disease. Bone scan, chest and abdomen imaging should be performed to determine the cause of PSA increase, which could be true disease progression in the form of new visceral metastasis or flare reaction.

Background: Radium-223 is a bone-targeting radiopharmaceutical that extends survival in mCRPC. Postapproval data are limited, and the value of biochemical and radiologic monitoring during radium therapy is unknown.

Patients and Methods: We conducted a retrospective study of 29 patients with mCRPC who received radium-223 at 1 of 3 participating institutions between August 2013 and December 2014. Trend of PSA, radiographic changes, and association of biochemical and clinical variables with PSA trend were measured.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental table and figures accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clgc.2016.03.002>.

Results: The median age of patients was 70 years, 79% of patients (N = 23) were European Americans, and 17% of patients (N = 5) were African Americans. Twenty patients (69%) had received at least 3 lines of prior therapies. Some 38% of patients (N = 11) received all 6 cycles of radium-223. Twenty patients (69%) had an increase in PSA during radium therapy, and 4 patients (14%) had a decline in PSA levels. Five patients had visceral metastases on computed tomography imaging performed during the course of radium-223.

Conclusions: Radium therapy in mCRPC was associated with an increase in PSA in the majority of these heavily pretreated patients. The development of visceral disease was not uncommon, suggesting a need for follow-up computed tomography monitoring during radium-223 therapy. The significance of early increases in PSA and pain with radium-223 is still uncertain. Although pain and PSA flare have been reported in patients who subsequently have a dramatic response to therapy, we observed that a PSA increase or pain flare correlates to an improvement in bone scans only in a minority of patients.

Keywords

Alpha-emitter; Bone scan; Bone-targeting radiopharmaceutical; Pain flare-up; Prostate-specific antigen

Introduction

Prostate cancer is the second most common cancer in men worldwide. Among men in the United States, it is the most commonly diagnosed cancer and the second leading cause of cancer death.¹ Bone is the predominant site of metastasis in prostate cancer, affecting more than 90% of patients with metastatic disease. In addition to the lethal outcome associated with metastatic disease, bone complications (typically pain, fracture, and spinal cord compression) are a leading cause of morbidity in this population.²⁻⁴

Radium-223 dichloride is an alpha-emitter that selectively targets bone metastases. It is the first calcium-mimetic radioisotope that has been shown to improve overall survival in metastatic castrate-resistant prostate cancer (mCRPC). A phase III randomized placebo-controlled trial (ALSYMPCA) evaluating the efficacy of radium-223 in mCRPC with bone metastases showed 3.6 months improvement in median overall survival in the radium arm.⁵ The time to the first symptomatic skeletal event was delayed in the radium arm (15.6 vs. 9.8 months with placebo). Some 47% patients in the radium-223 group demonstrated a 25% reduction in total alkaline phosphatase from baseline, and 16% patients had at least a 25% reduction in prostate-specific antigen (PSA). On the basis of the results of this trial, radium-223 was approved by the Food and Drug Administration for use in patients with mCRPC with symptomatic bone metastases and no known visceral disease.

Given its mechanism of action, the development of visceral disease is a clear indication of radium-223 treatment failure. Although PSA and pain outcomes have been reported, the development of visceral metastatic disease while undergoing radium-223 treatment has not been well described. We conducted a retrospective study of patients who received radium-223 for castration-resistant prostate cancer to assess biochemical and radiographic changes during the treatment and their correlation with clinical outcomes. In addition to

describing our postapproval experience with radium-223, we considered the development of visceral metastatic disease to be of particular clinical interest.

Materials and Methods

Patients

We conducted a retrospective study of men with mCRPC who received radium-223 after failing standard chemotherapy, hormone therapy, or immunotherapy and who were being treated at one of three participant centers: Karmanos Cancer Institute, Henry Ford Health Center, and McLaren Health Care. This study was approved by the institutional review boards at each of the centers.

Electronic medical records were reviewed to identify all patients who received radium-223 from August 2013 to December 2014. Patients were eligible for analysis if they were aged (at start of radium therapy) more than 18 years, had histologically or cytologically confirmed adenocarcinoma of the prostate, and had evidence of bone metastasis by bone scan/plain radiograph. Radium-223 was given according to standard prescribing practices (intravenously every 4 weeks, with a dose of 50 kBq/kg for a maximum of 6 cycles). In addition, all patients continued to receive androgen deprivation therapy (the majority with luteinizing hormone-releasing hormone agonists).

We evaluated the trend of PSA during treatment, the association of clinical and biochemical variables with PSA trend, and the correlation of PSA trend with clinical outcomes and changes in bone scans. The demographic, clinical, and biochemical variables collected before the start of therapy, before each cycle, and at the end of radium-223 therapy were age, race, PSA, alkaline phosphatase, lactate dehydrogenase (LDH), complete blood count, pain score by visual analog scale, and pain flare-up during radium-223 treatment. Pain flare-up was defined as worsening of pain immediately after radium treatment, requirement for escalation of pain medications, or pain associated with reduced functional capacity.

Bone scans findings were reviewed at baseline and at the end of the third and sixth cycles of radium-223. The bone scan responses during radium-223 were classified into worsening, stable, and improving. The worsening bone scan was defined as increased number of metastatic lesions during radium-223 therapy. Bone scan was considered to be improving if the number of lesions or the uptake within the preexisting lesions was less than previous bone scan. A stable bone scan was defined as one with no significant changes from prior bone scan. Computed tomography scan imaging findings also were assessed at the end of the third and sixth cycles, and grouped into improved and worse scans.

Statistical Analysis

Descriptive statistics was used to summarize demographic and baseline characteristics among study populations. Continuous variables were summarized with median and range, whereas counts and percentages were used to summarize categorical variables. Baseline characteristics were compared between subgroups with the use of the Kruskal—Wallis test for continuous variables and the chi-square test or Fisher exact test for categorical variables. For the primary analysis of radium-223 therapy, the associations between changes in PSA

levels and various biochemical/clinical variables were evaluated with the use of the Kruskal—Wallis test.

The changes in PSA levels were calculated by PSA levels at baseline and at the end of radium-223 therapy as follows:

$$\%(\text{PSA rise}) = 100 \times \frac{\text{PSA}_{\text{last}} - \text{PSA}_{\text{baseline}}}{\text{PSA}_{\text{baseline}}},$$

where $\text{PSA}_{\text{baseline}}$ and PSA_{last} represent PSA levels at baseline and at the end of radium-223 therapy, respectively. Therefore, the positive and negative values indicate an increase and a decline in PSA levels, respectively. Likewise, the changes in PSA level between consecutive cycles and biochemical variables (serum alkaline phosphatase, LDH, hemoglobin, white blood cell (WBC) counts, and platelet counts) were calculated using this equation. Pearson's correlation coefficient was obtained between pre- and post-therapy PSA levels after log-transformation along with Spearman's rank correlation coefficient without transformation. Statistical tests were 2-sided, with a *P* value of .05 or less considered to indicate statistical significance. However, the study was not powered to reach conclusions, so the results of these analyses should be regarded only as descriptive findings. Statistical analysis was performed with the use of R software, version 3.2.2 (www.r-project.org).

Results

Patient Characteristics

Baseline characteristics and outcomes are summarized in Table 1. A total of 29 patients with mCRPC were reviewed. The median age of the patient population was 70 years. Five patients (17%) were African Americans, and 23 patients (79%) were Caucasian (European Americans). Sixty-nine percent (*N* = 20) of the patients received at least 3 prior therapies, whereas 10% (*N* = 3) did not receive any prior therapy. Androgen deprivation therapy was administered concomitantly with radium-223. Two patients received concomitant abiraterone. Concomitant chemotherapy was not given. Previous therapies included docetaxel in 83% of patients (*N* = 24), cabazitaxel in 21% of patients (*N* = 6), enzalutamide in 72% of patients (*N* = 21), abiraterone in 69% of patients (*N* = 20), itraconazole in 17% of patients (*N* = 5), sipuleucel-T in 3% of patients (*N* = 1), mitoxantrone in 10% of patients (*N* = 3), bevacizumab in 10% of patients (*N* = 3), and ketoconazole in 3% of patients (*N* = 1). The majority of our patients had already received abiraterone or enzalutamide (16 patients received both, 5 patients received prior enzalutamide, and 4 patients received prior abiraterone). The median number of radium-223 cycles received was 4 (range, 1 to 6). Thirty-eight percent of patients (*N* = 11) received all 6 cycles of radium-223, 6% of patients (*N* = 2) received 5 cycles, 10% of patients (*N* = 3) received 4 cycles, 6% of patients (*N* = 2) received 3 cycles, 24% of patients (*N* = 7) received 2 cycles, and 13% of patients (*N* = 4) received only 1 cycle. Twenty-three patients (79%) had received bisphosphonates/denosumab during radium-223, including 3 patients receiving bisphosphonates, 18 patients receiving denosumab, and no records available for 2 patients.

Prostate-Specific Antigen Trends With Radium-223 Treatment

A waterfall plot for PSA response is presented in Figure 1. Twenty patients (69%) had an increase in PSA during radium-223 treatment, whereas 4 patients (14%) had a decline in PSA. Data were unavailable for 5 patients. Three of 4 patients with PSA decline demonstrated at least 30% PSA reduction. Fifty-two percent of the patients (N = 15) had > 50% increase in PSA. PSA trends for individual patients are shown in Supplemental Figure S1, in the online version. Median pretherapy PSA was 92.7, and post-therapy PSA was 366.15 (Table 2; Supplemental Figure S1, in the online version). Patients demonstrated 0% to 18% increase in PSA between consecutive cycles (Figure 2). Of the 4 patients whose PSA ultimately declined at the end of radium therapy, 3 had at least 1 PSA increase above baseline during therapy (% PSA increase of 4%, 117%, and 411%). In these 3 patients, the PSA was first noted to decline after cycles 2, 4, and 3, respectively. None of the patients with a decline in PSA developed visceral metastatic disease. Bone scan was reported as improved in 2 of these patients. Two of these 4 patients reported a pain flare during therapy, which ultimately resolved (pain score of zero after radium treatment). Pain flare was noted at cycles 2 and 3.

Characteristics of patients with a PSA increase or decline are presented in Table 3. Patients with a decline in PSA were less likely to have high disease burden ($P = .02$). Other trends did not meet statistical significance, including comparisons based on the number of the prior therapies, pain flare, bone scan changes, and survival status. Statistical comparisons were limited by the small sample size. Boxplots of % PSA increase depending on bisphosphonate use, bone scan changes, and pain flare are presented in Figure 3.

Trends in Other Biochemical Variables

Trends for serum alkaline phosphatase, LDH, hemoglobin, platelet count, WBC count, and albumin are presented in Supplemental Table S1 and Supplemental Figure S1, in the online version. The median % change of serum alkaline phosphatase from baseline to the end of radium-223 therapy was a 6% decline (range, -71% to 326%). Sixteen patients (55%) experienced at least some decline in alkaline phosphatase. Although the majority of patients developed mild myelosuppression, bone marrow toxicity requiring radium-223 discontinuation was reported in 17% of patients (N = 5). Overall, patients were found to have a 15% median increase in LDH (range, -25% to 258%), an 11% median decline in hemoglobin (range, -73% to 20%), a 32% decline in WBC (range, -68% to 19%), and a 23% decline in platelet count (range, -73% to 20%) at the end of radium-223 treatment. Infections were documented in 2 patients, bleeding was reported in 1 patient, and the need for transfusions was reported in 2 patients. WBC counts did not recover in 3 patients, whereas prolonged recovery (14 weeks) was documented in 1 additional patient.

Pain Flare.—Fifty-two percent of patients (N = 18) experienced pain flare-up during radium therapy (Table 1). Initial pain flare was noticed after cycle 1 in 9 patients (31%), after cycle 2 in 5 patients (17%), and after cycle 3 in 3 patients. There was no statistically significant relationship found between PSA changes and pain measures. The correlation between % PSA increase and pain score was 0.07 using the Spearman's rank correlation coefficient ($P = .77$) and -0.05 using the Pearson's correlation coefficient ($P = .83$)

(Supplemental Figure S2, in the online version). Median % PSA increase was not appreciably different in patients with pain flare-up (130 [range, 8 to 544]) compared with patients without flare-up (83 [range, -36 to 272]) (Figure 3B). There was no significant difference between pain scores for patients depending on whether they had or < 50% PSA increase (Supplemental Figure S3, in the online version). As described earlier, the percent of patients with pain flare did not differ significantly depending on decline in PSA (Table 3).

Radiographic Changes.—Seventeen patients (59%) had more than 20 sites of bone metastases. Fourteen percent (N = 4) of patients had improvement in bone scans, 21% (N = 6) of patients had worsening of bone scan, and 38% (N = 8) of patients had stable bone scan (Table 1; Figure 4). PSA increase was more significant among patients with worse and stable bone scans, that is, 104% (range, 29 to 544) and 214% (range, 16 to 544), respectively, compared with improved bone scans who had 35% (range, -36 to 248) PSA increase (Figure 3C). Furthermore, PSA decline was usually associated with improved bone scan.

Of 10 patients who had computed tomography imaging by 3 cycles of therapy, 5 patients had stable scans and 5 patients (15%) had worsening imaging findings. Computed tomography imaging at the end of radium therapy documented progression in 10 patients (34%) and stable findings in 7 patients (24%). Progression was documented in the following anatomic sites: lymph node (N = 5), liver (N = 4), lung (N = 1), and central nervous system (N = 3). Overall, 8 patients developed visceral (non-bone; non-lymph node) metastatic disease. Discontinuation for radiographic progression occurred after cycle 2 in 4 patients, after cycle 3 for 2 patients, and after cycle 4 for 1 patient.

Discussion

Although radium-223 is the first bone-targeting agent that has shown a survival advantage in mCRPC with bone metastasis, the optimal monitoring strategy during treatment is unknown. One barrier to monitoring treatment efficacy is the difficulty in interpreting PSA changes. A PSA flare phenomenon is known to occur with radium-223 treatment, whereby an initial increase in PSA with radium was later associated with PSA decline and dramatic clinical and radiographic improvement.⁶ Most patients in our cohort had at least 1 PSA above baseline while undergoing radium-223 therapy (the only exception was 1 patient who had continuous decline in PSA through radium-therapy). Even in our small cohort of patients, we identified 3 patients who experienced an ultimate decline in PSA with radium-223 after an initial early PSA increase. In 2 of these cases, the increase in PSA was dramatic (2- and 5-fold above baseline PSA values). We also observed improvement in pain or bone scans with declines in PSA. Taken with the case report described by McNamara et al,⁶ early increase in PSA should not be the reason to abandon therapy with radium-223.

Although an increasing PSA may precede PSA decline in a small number of patients, the majority of patients with an initial increasing PSA continued to experience a PSA increase. Patients with a PSA increase showed a mixture of improved, stable, or worse bone scans, which indirectly suggests that there is no significant association between PSA increase/decline and bone scan changes. In some of these patients, the increase in PSA was associated with clear disease progression in the form of visceral metastatic disease. Visceral

disease (non-osseous and non-nodal metastases) developed during radium-223 treatment in 8 of our 29 patients (28%). The development of visceral metastatic disease during radium-223 therapy was not reported in the ALSYMPCA trial or preceding phase II studies.^{5,7-10}

A previous case series in the postapproval setting reported that 9 of 25 patients (36%) did not complete radium-223 because of disease progression, although it was not specified how many of these patients had non-osseous/non-nodal disease.¹¹ In contrast, only 2 withdrawals for disease progression were reported in a phase II study of 33 patients treated with a 16-week course of radium-223.⁷ In the ALSYMPCA trial, 37% of patients discontinued therapy, but the reasons for withdrawal were not disclosed.⁵ Given the significant numbers of patients who developed visceral metastatic disease (liver, lung, central nervous system) during radium-223 therapy, routine cross-sectional imaging, along with a careful history and physical, seems prudent, especially in patients with increasing PSA.

As mentioned earlier, 37% of patients in the ALSYMPCA trial discontinued therapy, whereas the remaining 63% were able to complete all 6 cycles of radium-223. In our study cohort, patients tolerated a median of 4 radium cycles, and only one third (38%) of the patients completed all 6 cycles. One possible explanation for this could be underlying severe and refractory disease that made them less suitable for radium-223 treatment. The majority of our patients had disease refractory to 3 or more therapies. The extent of prior therapy was not reported in the ALSYMPCA trial, although 57% of patients had prior docetaxel. More refractory disease may be reflected in somewhat lower PSA response rates.

In our cohort of 29 patients, 3 (10%) had at least a 30% PSA decline in contrast to the 16% of patients with at least a 30% PSA decline in the ALSYMPCA trial.⁵ Our observations are in line with those reported by Nome et al,¹² where 11 of 14 patients had significant increases in PSA and 3 patients had stable PSA. Other reports of PSA response are difficult to compare because of differences in treatment dose, schedule, and concomitant therapies.^{7,10} We note that the majority of our patients receiving radium already received secondary hormonal therapies and thus did not receive them concomitantly. Although limited by sample size, our data suggest a significant correlation between PSA increase and a greater number of bone metastases ($P = .02$). In addition to disease progression, heavier pretreatment and a higher disease burden may predispose patients to greater hematologic toxicity, which can also lead to treatment discontinuation. The majority of patients developed mild myelosuppression. However, 5 patients (17%) developed myelosuppression requiring discontinuation of therapy. Prior docetaxel has been reported to influence the development of myelosuppression with radium-223.¹³

The palliative benefit of radium-223 for cancer-related pain in prostate cancer is unclear. Pain response rates of more than 50% have been reported.^{8,9,14} In our experience, pain levels generally increased during radium treatment. Approximately 52% of patients experienced pain flare-up during radium-223 therapy. Although all patients with pain flare had an initial increase in PSA, 2 of these patients ultimately experienced PSA declines. Furthermore, a greater increase in PSA was associated with higher pain levels. Increases in pain responded to up-titration of pain medications.

Study Limitations

The major limitation of our study is limited sample size. Because of the small sample size, most of the associations described did not reach statistical significance; thus, at this point, most of our conclusions remain descriptive. Nevertheless, the frequent development of visceral metastatic disease and, conversely, the confirmation of a PSA, pain, and radiographic response in a small number of patients with PSA flare call attention to the need for further studies to identify clinical and biochemical predictors of treatment benefit for radium-223.

Conclusions

An increasing PSA level during radium therapy for mCRPC is not an uncommon phenomenon, especially in heavily pretreated patients. An increase in PSA is strongly associated with greater pain flare-ups, but its predictive and prognostic value in this setting seems to be limited because of its poor correlation with radiographic changes and overall response to treatment. An initial increase in PSA does not always indicate progressive disease. Bone scan, chest and abdomen imaging should be performed to determine the cause of PSA increase, which could be true disease progression in the form of new visceral metastasis or flare reaction. Finally, 20% to 50% decrement in blood count is expected during radium-223 treatment. Heavily pretreated patients with greater disease burden usually do not tolerate all 6 cycles of therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65:5–29. [PubMed: 25559415]
2. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351:1502–12. [PubMed: 15470213]
3. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004; 350:1655–64. [PubMed: 15084698]
4. Lipton A. Implications of bone metastases and the benefits of bone-targeted therapy. *Semin Oncol* 2010; 37(Suppl 2):S15–29. [PubMed: 21111244]
5. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369:213–23. [PubMed: 23863050]
6. McNamara MA, George DJ. Pain, PSA flare, and bone scan response in a patient with metastatic castration-resistant prostate cancer treated with radium-223, a case report. *BMC Cancer* 2015; 15:371. [PubMed: 25948240]
7. Nilsson S, Franzen L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007; 8:587–94. [PubMed: 17544845]
8. Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. *Eur J Cancer* 2012; 48:678–86. [PubMed: 22341993]

9. Nilsson S, Franzen L, Parker C, et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. *Clin Genitourin Cancer* 2013; 11:20–6. [PubMed: 23021204]
10. Parker CC, Pascoe S, Chodacki A, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. *Eur Urol* 2013; 63:189–97. [PubMed: 23000088]
11. Jadvar H, Challa S, Quinn DI, Conti PS. One-year postapproval clinical experience with radium-223 dichloride in patients with metastatic castrate-resistant prostate cancer. *Cancer Biother Radiopharm* 2015; 30:195–9. [PubMed: 25746633]
12. Nome R, Hernes E, Bogsrud TV, Bjoro T, Fossa SD. Changes in prostate-specific antigen, markers of bone metabolism and bone scans after treatment with radium-223. *Scand J Urol* 2015; 49:211–7. [PubMed: 25515952]
13. Hoskin P, Sartor O, O’Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol* 2014; 15:1397–406. [PubMed: 25439694]
14. Nilsson S, Larsen RH, Fossa SD, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. *Clin Cancer Res* 2005; 11:4451–9. [PubMed: 15958630]

Clinical Practice Points

- Radium-223 is a bone-targeting radiopharmaceutical that improves survival in patients with mCRPC.
- In this retrospective analysis of heavily pretreated patients with mCRPC, PSA increase and pain flare occurred frequently during the course of radium-223.
- Although increases in PSA and pain may be followed by evidence of response, true disease progression also is common, including the development of visceral disease.
- Radiographic imaging can be considered during radium-223 to differentiate between flare phenomenon and true progression of malignancy.

Figure 1. Percentage of PSA Increase for 24 Patients From Pretherapy to End of Therapy. *Empty Bars* Represent Patients Who Developed Visceral Disease. Note That the *Dotted Lines* Represent 50% and -30% PSA Increase, Respectively. Data Are Not Available for 5 Patients
Abbreviation: PSA = prostate-specific antigen.

Figure 2.

Percentage of PSA Increase Between Each Consecutive Cycle. The Median Percentages of PSA Increase Are 17.95%, 16.56%, 15.37%, 9.88%, 9.37%, and 0.00%, Respectively, for Base and Cycle 1, Cycles 1 and 2, Cycles 2 and 3, Cycles 3 and 4, Cycles 4 and 5, and Cycles 5 and 6. The *Right* Boxplot Represents the Percentage of PSA Increase Between the Baseline and the Last Radium Therapy Where the Median Percentage of PSA Increase Is 95.68%. Note That the 50% and -30% PSA Increases Are Indicated by the *Dotted Lines* Abbreviation: PSA = prostate-specific antigen.

Figure 3.
Boxplots With % PSA Increase in Patient Subgroups
Abbreviation: PSA = prostate-specific antigen.

Figure 4.
Bone Scan Images. Improving Bone Scan (A), Stable Bone Scan (B), and Worse Bone Scan (C)

Table 1

Baseline Characteristics

Characteristic	Radium-223 (N = 29)
Age—median (range) years	70 (49-80)
Race—No. (%) ^a	
African American	5 (17%)
European American	23 (79%)
No. of bone metastasis before radium 223—No. (%)	
0-5 sites	3 (10%)
6-10 sites	3 (10%)
11-15 sites	3 (10%)
16-20 sites	3 (10%)
>21 sites	17 (59%)
Concomitant bisphosphonate/denosumab use—No. (%)	
No	6 (21%)
Yes	23 (79%)
Concomitant therapy—No. (%)	
Abiraterone	2 (7%)
Prior therapy—No. (%)	
Docetaxel	24 (83%)
Enzalutamide	21 (72%)
Abiraterone	20 (69%)
Cabazitaxel	6 (21%)
Sipuleucel-T	1 (3%)
Itraconazole	5 (17%)
Mitoxantrone	3 (10%)
Bevacizumab	3 (10%)
Ketoconazole/nilandron	1 (3%)
No. of radium 223 cycles—median (range)	4 (1-6)
ECOG—median (range)	
ECOG before radium 223 ^b	1 (0-2)
ECOG at the end of radium 223 ^c	1 (0-3)
Pain score—median (range)	
Pain score before radium 223 ^d	2 (0-10)
Pain score at the end of radium 223 ^d	1 (0-10)
Pain flare up—No. (%) ^e	
No	10 (34%)

Characteristic	Radium-223 (N = 29)
Yes	15 (52%)
Bone scan changes—No (%) ^f	
Improved	4 (14%)
Stable	8 (38%)
Worse	6 (21%)
Reason for discontinuation—No. (%)	
Bone marrow toxicity	5 (17%)
Side effects including fracture	2 (7%)
Symptomatic progression	3 (10%)
Radiological progression	7 (26%)
Physician discretion	3 (10%)
Therapy completion	11 (38%)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

^aData are not available for 1 patient.

^bData are not available for 7 patients.

^cData are not available for 6 patients.

^dData are not available for 3 patients.

^eData are not available for 4 patients.

^fData are not available for 15 patients.

Table 2

Prostate-Specific Antigen Levels During Radium 223 Therapy

Cycle	PSA Median (Range)	N (%)
Before radium 223	92.7 (2.5-3822.6)	29 (100%)
1	107.5 (2.6-5135.8)	25 (86%) ^a
2	111.4 (1.7-6247)	18 (62%) ^b
3	86 (1.7-7158.4)	16 (55%) ^b
4	82.3 (0.8-309.1)	13 (45%)
5	82.0 (3.5-358.2)	11 (38%)
6	34.9 (0.1-591.3)	11 (38%) ^c
End of radium 223	366.15 (0.1-7176.6)	29 (100%) ^d

Abbreviation: PSA = prostate-specific antigen.

^aData are not available for 2 patients.^bData are not available for 1 patient.^cData are not available for 4 patients.^dData are not available for 5 patients.

Table 3

Change of Prostate-Specific Antigen From Baseline During Radium 223 Therapy

	PSA Change		<i>P</i> Value
	Decrease (N = 4)	Increase (N = 20)	
No. of bone metastasis before radium 223—No. (%)			.02
0-5 sites	2 (50%)	1 (5%)	
6-10 sites	1 (25%)	1 (5%)	
11-15 sites	1 (25%)	2 (10%)	
16-20 sites	0 (0%)	2 (10%)	
>21 sites	0 (0%)	14 (70%)	
No. of treatments before radium 223—median (range) ^a	3 (1-3)	4 (1-6)	.14
Pain flare up—No. (%) ^b			.13
No	2 (50%)	6 (30%)	
Yes	2 (50%)	13 (65%)	
Death—No. (%) ^c			.60
No	3 (75%)	10 (50%)	
Yes	1 (25%)	9 (45%)	
Bone scan changes—No. (%) ^d			.25
Improved	2 (50%)	2 (10%)	
Stable	0 (0%)	7 (35%)	
Worse	0 (0%)	5 (25%)	

Abbreviation: PSA = prostate-specific antigen.

^aData are not available for 1 (< 0%) and 1 (> 0%) patients.^bData are not available for 1 (> 0%) patients.^cData are not available for 1 (> 0%) patient.^dData are not available for 2 (< 0%) and 7 (> 0%) patients.