Asian Journal of Andrology (2020) 22, 437–438
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LETTER TO THE EDITOR

Prostate Cancer

Single-center experience with radium-223 in patients with castration-resistant prostate cancer and bone metastases

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Asian Journal of Andrology (2020) **22**, 437–438; doi: 10.4103/aja.aja_66_19; published online: 13 September 2019

Dear Editor,

Approximately 90% of men with metastatic castration-resistant prostate cancer (mCRPC) have bone metastases that can cause excruciating pain, bone fractures, disability, and death.[1–3] Radium-223 is a radioactive isotope that mimics calcium and emits alpha particle radiation that selectively targets bone metastases.[4,5] The results from the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study, a phase 3 randomized controlled trial, showed that radium-223 improved overall survival (OS) and time to symptomatic skeletal-related events (SRE) in men with mCRPC and bone metastases compared to placebo.[6] Despite the FDA approval, radium-223 appears to be less utilized for the treatment of mCRPC compared to oral agents that target the androgen receptor pathway. We report our initial experience and outcomes of men with mCRPC and bone metastases treated with radium-223.

After obtaining the Institutional Review Board (IRB) approval at McMaster University (Hamilton, ON, USA), we performed a retrospective review of men with mCRPC and bone metastases only who were treated at McMaster University with at least one cycle of radium-223 (Xofigo®, Bayer Health, Whippany, NJ, USA) between January 2015 and July 2017. Written informed consent was waived due to its respective nature. mCRPC was defined by disease progression despite castrate levels of testosterone (<1.7 nmol l^{-1}). The definition of disease progression included a continuous rise in prostate-specific antigen (PSA), the progression of preexisting disease and/or the development of new metastasis on imaging. The presence of bone metastases was determined by conventional technetium-99m bone scintigraphy. Patients offered radium-223 were required to have cancer-related bone pain, evidence of progressively increasing PSA values (2 consecutive rises in PSA), and adequate hematologic, renal, and liver functions. Patients were clinically followed with laboratory investigations prior to radium-223 therapy, every 2 weeks while on therapy, and then monthly thereafter, as well as routine computed tomography (CT) scans and bone scans.

At our center, 60 men were treated with radium-223 with a median age of 73 (range: 53–87) years and median baseline PSA and alkaline phosphatase (ALP) of 99 (range: 10–2471) mg l^{-1} and 154 (range: 55–2152) U l^{-1}, respectively. The median Eastern Cooperative Oncology Group (ECOG) performance status was 1. Prior to radium-223, 18 patients had received 1 prior systemic therapy, 19 received 2 prior therapies, 20 received 3 prior therapies, and 3 patients received >3 prior therapies. Previous systemic therapies included docetaxel (61.7%), abiraterone (71.7%), enzalutamide (68.3%), mitoxantrone (6.6%), and cabazitaxel (5.0%).

The median OS was 8.2 months (**Figure 1a**), lower than the reported median OS of 14.9 months in the ALSYMPCA trial.[6] The observation of poorer outcomes seen in real-world studies compared to patients in trials have been previously described in the mCRPC setting.[7] Clinical trials typically enroll patients with stringent inclusion/exclusion criteria, and thus, patients are typically healthier compared to the real-world setting. Furthermore, the majority of men in our series were heavily pretreated prior to radium-223. However, analysis stratified by previous therapies including docetaxel (HR: 0.86, 95% CI: 0.66–1.14, $P = 0.30$), abiraterone (HR: 1.05, 95% CI: 0.79–1.40, $P = 0.75$), and enzalutamide (HR: 0.78, 95% CI: 0.44–1.40, $P = 0.41$) showed that there were no differences in OS regardless of previous therapy use, suggesting that radium-233 remains effective even in heavily pretreated patients.

Approximately 41.7% (25/60) of patients received all six cycles of radium-223, and the median number of cycles was 5 (range: 1–6). The most common reason for treatment cessation was disease progression (26.7%), followed by symptomatic progression (10.0%) and marrow suppression indicated by hematologic laboratory parameters (10.0%). Subgroup analysis showed that patients who

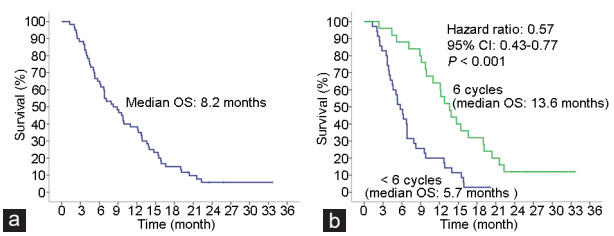

Figure 1: Kaplan–Meier estimates of (**a**) OS and (**b**) OS stratified by number of radium-223 cycles (6 cycles *vs* <6 cycles). OS: overall survival.

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Received: 22 October 2018; Accepted: 08 May 2019

received all six cycles of radium-223 (13.6 months) had a longer OS compared to those who received <6 cycles (5.7 months) (HR: 0.57, 95% CI: 0.43–0.77, $P < 0.001$) (**Figure 1b**). Patients who received six cycles of radium-223 were similarly pretreated to their counterparts who received <6 cycles (docetaxel 52.0% *vs* 68.6%, $P = 0.10$; abiraterone 68.0% *vs* 74.3%, $P = 0.30$; and enzalutamide 72.0% *vs* 65.7%, $P = 0.31$). Although this finding is likely biased as patients who were able to tolerate all six cycles were likely healthier with potentially lower burden disease, it encourages us to administer all six cycles to improve outcomes.

In terms of biochemical response, compared to only a 21.7% reduction in PSA (>25%), more patients (55.0%) had a reduction in ALP (>25%) following radium-223 therapy. Furthermore, time to >50% increase in ALP from nadir following treatment (5.5 months) was longer than time to PSA rise (2.1 months). However, analysis stratified by biochemical responses shows no difference in overall survival for either PSA (HR: 1.42, 95% CI: 0.74–2.76, $P = 0.29$) or ALP response (HR: 1.49, 95% CI: 0.87–2.56, $P = 0.15$).

During the study period, nine patients developed SRE (two patients during radium-223 therapy and seven posttherapy) and the median time to SRE was 3.7 (range: 1.8–9.0) months. Perhaps one of the most important characteristics of radium-223 is its favorable adverse event profile, particularly when compared to beta-emitting pharmaceuticals.[8] There was a 72% adverse event rate, 42% Grade 3–4 adverse event rate, and no Grade 5 events. The most common adverse events included fatigue (41.7%), followed by anemia (21.7%), nausea (28.3%), diarrhea (16.7%), and thrombocytopenia (15.0%).

Limitations of this study include the small sample size and retrospective design which would limit capture of events, particularly adverse events. The patients in our study were also heavily pretreated, perhaps more accurately representing real-world patients with mCRPC. The landscape of mCRPC continues to evolve and has undergone incredible positive changes since the introduction of docetaxel as several agents have been shown to improve survival including abiraterone, enzalutamide, docetaxel, cabazitaxel, and radium-223.[3] With the ongoing emergence of FDA-approved therapies for mCRPC, there is a growing challenge in determining the ideal sequencing of therapies for mCRPC and other prostate cancer disease states.[3,4] In the future, biomarkers may help identify men who will preferentially respond to select treatments.

Despite these limitations, this study characterized the utilization of radium-223 in a real-world setting, including aspects such as reason for treatment discontinuation and helping us refine the application of radium-223 in routine practice. Radium-223 remains effective in heavily pretreated patients and all six cycles should be encouraged to improve patient outcomes.

AUTHOR CONTRIBUTIONS

AK was responsible for the conception and design of this study. AK, NCW, and YDW contributed to the acquisition of data, and analysis and interpretation of data. AK, NCW, YDW, SM, SH, ID, and HL drafted the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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