



Factors Influencing Outcome Post-Radium-223 Dichloride in Castrate Resistant Prostate Cancer: A Review of Some Real-World Challenges

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Abstract

Aim Radium-223 has been the first-approved targeted Alpha therapy agent. We retrospectively assessed different factors influencing the overall survival (OS) and patient management.

Setting and Design Thirty-two metastatic castration-resistant prostate cancer (mCRPC) patients' hematological parameters, number of cycles, performance status, and toxicities were evaluated for OS. Radium 223 dichloride (Radium-223) was administered every 4 weeks for a maximum of six cycles. Primary and secondary end points were OS, progression free survival (PFS), therapy toxicities, change in performance status, biochemical response, and skeletal-related events (SREs).

Materials and Methods Patients' median age was 77 years (range: 57–90 years) and median follow-up was 399 days (range: 5–1,761 days). A total of 163 cycles were administered in 32 patients, with 4 or less cycles in 8 patients (25%) and 5 or more cycles in 24 patients (75%). Among eight patients with 4 or less cycles, three patients died, of which two patients died due to neutropenic sepsis.

Statistical Analysis Mann–Whitney test was used to compare the cycle groups; Spearman's correlation coefficient was used to see the relation of different variables with OS. Log rank test was used for group comparison while Kaplan–Meier survivorship was used for OS.

Results Statistical correlation was seen between the number of cycles ($p = 0.037$) and hemoglobin ($p = 0.028$). Kaplan–Meier OS ($p = 0.038$) was correlated with the number of cycles (≤ 4 cycles and ≥ 5 cycles). OS was 173 days in patients with one to four cycles, 226 days in five cycles, and 493 days in six cycles. Myelosuppression leading to stopping of full six cycles was seen in 7 of 32 patients (22%) and significantly correlated to inferior OS ($p = 0.048$).

Conclusion Higher number of Radium-223 cycles was seen to be associated with better OS. Prior myelosuppression was associated with poor OS. Patients with better hematological profile were more likely to complete the maximum number of the cycles with a better OS.

Keywords

- ▶ Radium-223
- ▶ overall survival
- ▶ myelosuppression
- ▶ toxicity
- ▶ health economics

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Key Message

Better patient selection with good hematological profile can lead to maximum chances of completion of most cycles with a better OS. Radium-223 may be considered at an earlier state in patient management.

Introduction

Prostate cancer is one of the most common male cancers and a leading cause of cancer related mortality.^{1,2} A total of 10 to 20% of the patients may progress to castration-resistant prostate cancer (CRPC) with poor prognosis. Of these, 85% patients may have proven evidence of metastases^{3,4} bone being the dominant metastatic site in more than 90% of men, impacting the quality of life (QoL), morbidity, and mortality.^{5,6} With little cure for metastatic CRPC (mCRPC), prolongation of life and improving QoL are the goals of treatment.⁷

Newer therapeutic agents aimed at improving survival and QoL in mCRPC has been considered. Treatment recommendations are dependent on tumor load, patient symptomatology, prior therapy, presence of visceral or bone metastases, and the Eastern Cooperative Oncology Group (ECOG) performance status. Various approved therapies, for example, newer agent ADTs (abiraterone and enzalutamide), taxel-based chemotherapy agents (docetaxel and carbazixel), and radionuclide therapeutic agents, such as Radium-223 dichloride (Radium-223), have demonstrated survival benefit with or without supportive therapies.⁸ Several bone seeking β -emitting radiotracers have been used to treat pain secondary to bone metastases, such as samarium 153-EDTA, strontium 89-dichloride, and lutetium 177-EDTMP. Despite symptomatic pain relief and delay in skeletal-related events (SREs), these agents offered no significant survival benefit.⁸⁻¹¹ Radium-223 is the only commercially released Food and Drug Administration (FDA) approved α -emitter used for treatment of mCRPC that targets osteoblastic bone metastases affecting patient survival.¹²

Radium-223 selectively targets osteoblastic bone metastasis, producing nonrepairable double-stranded DNA breaks and cytotoxicity.¹³⁻¹⁵ Shorter range of α particles (100 μ m) provides a wider utility and better hematological toxicity profiles. Optimal sequencing and combination of Radium-223 with other agents remains undetermined making patient selection one of the practically essential criteria for better results.^{8,16} Given the high cost of Radium-223, the objective of our study was to gain understanding of the patient selection and subgrouping insight for patient characteristics for better outcome in real-world clinical scenario.

Subject and Methods

Study Design

Patients with mCRPC treated with Radium-223 over a 6-year period till June 2020 were retrospectively evaluated. Patients who received minimum of one Radium-223 injection were retrospectively reviewed with regard to indications, labora-

tory evaluation, previous treatments, comorbidity, histology, SREs, and overall survival (OS).

Radium-223 Therapy Standard of Care

Institutional criteria for initiation of Radium-223 therapy included CRPC patients with bone metastases, no or small (< 3 cm in short-axis diameter) lymph node metastases and no visceral metastases and no evidence of cord compression. The dose regimen of Radium-223 is 55 kBq per kg body weight, given at 4-week intervals for six injections, as advocated by National Institute of Health and Care Excellence (NICE) guidelines.^{16,17} Laboratory requirements before the first dose administered were baseline absolute neutrophil count greater than $1.5 \times 10^9/L$, platelet count greater than $100 \times 10^9/L$, and Hb (Hb) 10 g/dL or higher. Imaging with Tc99m MDP bone scintigraphy or ¹⁸F-fluoride positron emission tomography (PET)/computed tomography (CT) was performed within 3 months prior to start of Radium-223 therapy.

Prior to every Radium-223 injection, hematobiochemical profile consisting of Hb, white blood cell (WBC), platelet counts, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and prostate-specific antigen (PSA) levels; along with ECOG, performance status and pain score were recorded and evaluated. The work was reviewed and performed as per the institute's clinical treatment guidelines and compiled with the Declaration of Helsinki. All patients gave their written informed consent prior to treatment. No additional institutional ethics approval was therefore required.

Biochemical and Radiological Response Evaluation

Changes in hematological parameters were calculated from baseline to week 24 (after three injections) from baseline to end of therapy as a maximal percentage change at any time from baseline. Patients who had no baseline level or no follow-up measurements were excluded from biochemical response evaluation. More than 25% decline or increase from baseline of PSA, ALP, and LDH was considered to be clinically significant as per the Prostate Cancer Working Group 3 criteria. Clinically meaningful pain at baseline (e.g., < 4 on a 10-point pain intensity scale) and a response defined as clinically meaningful score improvement at a subsequent time point (two-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an opiate use) was considered as an adequate pain response. The primary end point was OS while secondary end points were evaluation of hematological parameters, SREs, response, biomarkers, and imaging assessment and pain score.

Statistical Analysis

The continuous data were given as mean \pm standard deviation (SD) and range or median. Mann-Whitney test was applied to compare the patient groups receiving 4 cycles or less and 5 cycles or more. Spearman's correlation coefficient was calculated to see relation of different variables with OS. The OS was measured as the time interval from the date of first Radium-223 injection to the date of death and was assessed with the Kaplan-Meier survivorship function,

while group comparisons were made with the log-rank test. All statistical tests were two-sided and performed at a significance level of $\alpha \leq 0.05$. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

Results

Patient Characteristics

A total of 32 patients were treated with Radium-223 during the study. Of the 32 patients, two patients had incomplete blood investigation, hence were excluded from the final analysis with regard to the biochemical evaluation for OS. The numbers of cycles related to OS were examined in all 32 patients. The median age of the patients treated was 77 years (range: 57–90 years) and median follow-up was of 399 days (range: 5–1,761 days). The patient characteristics and cycles are described in **Table 1**.

Of the eight patients with 4 or less cycles, three patients were died of which one patient died of unknown cause after the first cycle, while another two patients were admitted with neutropenic sepsis and died. Adverse effect in the form of myelosuppression leading to cessation of therapy before completion of six cycles of treatment was seen in 7 of 32 patients (25%). Of these seven patients, low Hb was seen in five patients, while death due to neutropenic sepsis was seen in two patients. Also, 13 of the total 32 patients had grade 1 or 2 thrombocytopenia, while none experienced grade 3 or 4 thrombocytopenia requiring any cycle delay or stopping of therapy cycle. Myelosuppression significantly correlated to inferior OS with a *p*-value less than 0.048.

There was a statistically significant difference in the OS in patients who received 4 or less cycles and 5 or more cycles on the Kaplan–Meier cycles OS ($p = 0.038$; **Fig. 1**). Similar difference in OS was noted on subgroup analysis less than 4 cycles, 5 cycles, and 6 cycles ($p = 0.019$) with the median OS in patient with 4 or less cycles was 173 days, 226 days in patients who received 5 cycles, and 493 days in patients who received all 6 cycles of Radium-223.

Hematotoxicity was the reason for premature stopping of Radium-223 treatment in 7 of the 10 patients. In the remaining three patients, Radium-223 treatment was stopped in one patient due to change of treatment plan and regulatory recommendation (concomitant use of Abiraterone), while two patients were lost to follow-up. All 32 patients had prior therapy with the Radium-223 chosen as an alternative after failure of previous line(s) of therapy. Bisphosphonate therapy with Zoledronate was administered in 19 patients who were considered as high risk of SRE. Cord decompression due to SREs was done in one patient. (**Table 1**). ECOG performance status and pain score were evaluated prior to every cycle (**Table 2**).

Hematobiochemical analysis was performed in 30 patients with decrease in Hb levels noted in 17 patients (57%), no significant change in eight patients (27%), increased levels in 1 patient (3%), and nontraceable in 4 patients (13%). Statistical correlation was seen between OS with Hb ($p = 0.028$) and number of cycles ($p = 0.037$).

Mixed response was seen with regard to biochemical parameters as PSA, ALP, albumin, WBC, neutrophils, lymphocytes,

Table 1 Patient characteristics and cycles

Characteristic	Total patients (n = 32)
Age (y)	77 (57–90)
Follow-up period (d)	399 (5–1,761)
Death	22 (69%)
Within 12 months	13
12–18 months	5
18–24 months	2
> 24 months	2
Gleason's score	
≥ 8	28 (87.5)
≤ 7	4 (12.5)
Indication	
Rising PSA	24 (75)
Progressive bone metastases	15 (16)
Rising PSA and progressive bone metastases	2 (6)
Not responsive to other treatment/not fit for chemo	1 (3)
Total no of cycles	163
5 cycles	15 (n = 3)
4 cycles	16 (n = 4)
3 cycles	3 (n = 1)
2 cycles	0
1 cycles	3 (n = 3)
6 cycles	126 (n = 21)
Reason for early cessation of cycles	
Fall in Hemoglobin	5 (16)
Died after first dose due to neutropenia sepsis	2 (6)
As per protocol with concurrent abiraterone and Radium-223	1 (3)
Lost to follow-up	1 (3)

Abbreviation: PSA, prostate-specific antigen.

Note: Data are presented as median (range) or *n* (%).

and neutrophil-to-lymphocyte (N/L) ratio, with no significant fall in the blood levels or any relation to the OS. Grade-1 or -2 thrombocytopenia was noted in 13 patients.

No statistically significant correlation was seen between the different comorbidities, prior therapies, or concurrent bisphosphonate therapy on OS.

Discussion

The FDA approval for Radium-223 for clinical use in patients with CRPC and symptomatic skeletal metastases was based on an improvement in OS; however, not all patients have the same level of benefit.^{12,13,16}

On retrospective evaluation of our patients, we found that Radium-223 had benefits in treatment of mCRPC with a

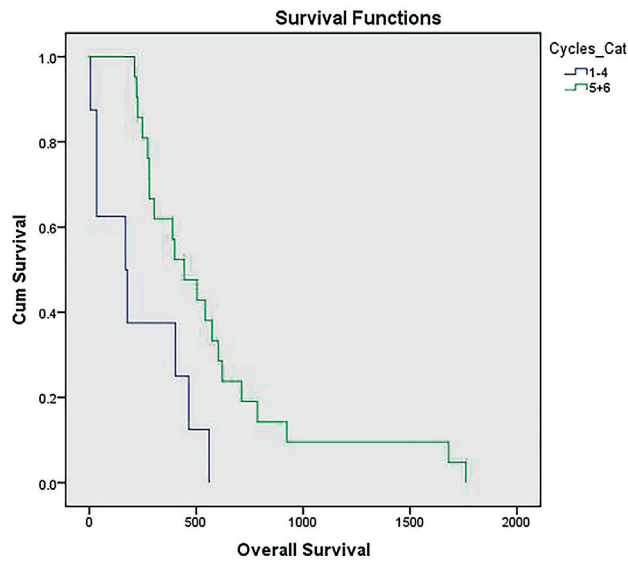


Fig. 1 Kaplan–Meier cycles of overall survival.

positive correlation between the number of cycles and OS. The patients who had 4 or more cycles had a better statistically significant OS than patients who received 4 or less cycles. The median OS of patients who completed all cycles was 17.6 months (493 days), slightly longer than OS in the ALSYMPCA trial which had an OS of 14.9 months, and quite similar to OS of 17.5 months seen in some studies.^{13,16} In contrast, patients who had 5 cycles had an OS of 8.1 months (226 days) and for patients with 4 or less cycles, it was 6.2 months (173 days). The study results were in line with other studies confirming higher survival in patient who completed the course of therapy where OS significantly increased with the number of the Radium-223 cycles received.^{11,13}

Discontinuation of any treatment in mCRPC patients, in general, follows two out of the three criteria: PSA progression, imaging progression, and clinical progression. The discontinuation rates in the literature with Radium-223 range from 16 to 21%.^{12,18,19} In ALSYMPCA study, only 58% patient had complete six cycles, quite comparable to 66% patient in our group who had full six cycles.¹⁶

Radium-223 therapy poses fewer marrow toxicities due to the physical characteristics of α radiation compared with chemotherapy drugs. However, poor hematological profile, especially of Hb and platelets may often cause interruption of cycles, contributing to treatment resistance and disease progression.^{20,21} The safety profile of Radium-223 in our group was favorable with only 7 of the 32 patients suffered from hematological toxicities, leading to discontinuation of treatment with an inferior OS ($p = 0.048$). Decreased in Hb was seen in five patients, neutropenia in two patients, who died due to neutropenic sepsis. Hematotoxicity noted in our patient group was drastically lower compared with the patients in ALSYMPCA study where hematotoxicity was noted in up to 62% of patients.^{16,18}

Our study was similar to some of the multivariate analyses where patients with good hematological parameters, as Hb, WBC, and thrombocytopenia before Radium-223 therapy, are important risk factors for completion of Radium-223 therapy and improved OS.^{13,22,23}

Although thrombocytopenia is more common in Radium-223 treated patients compared with placebo (12 vs. 6%), we saw grade-1 or -2 thrombocytopenia in 41% of patients ($n = 13$) but none of these patients required hospitalization or change in cycles. Most of our patients had grade-1 thrombocytopenia, contrary to other studies where almost 92% of patients developed grade-3 or -4 thrombocytopenia.^{12,24} In particular, as anemia seems to play a crucial role in all these patients, acute monitoring may be required with acceptance for performing blood transfusions, occasional delaying, or discontinuation of the cycles.^{25–27} Interrupted Radium-223 treatment due to hematotoxicity more often results in therapy resistance and reduced therapeutic efficacy. Elderly patients with advanced disease and bone marrow involvement are usually submitted to multiple prior therapies further impairing hematopoiesis, leading to poor prognosis, morbidity, and mortality. In these patients, treatment with Radium-223 may be less beneficial in terms of OS and QoL. Thus proper patient selection in terms of good hematological profile offers better results ensuring the best chance of completion of all six cycles and maximizing effectiveness of Radium-223.

It is also noted that the most frequently observed adverse reactions in patients treated with Radium-223, occurring in

Table 2 ECOG performance status and pain score

ECOG performance status		
Baseline status	Posttherapy status	Change in status posttherapy
0 = 4 (12%)	0 = 7 (22%)	Improved = 7 (22%)
1 = 22 (69%)	1 = 21 (66%)	Unchanged = 23 (72%)
≥ 2 = 6 (19%)	≥ 2 = 4 (12%)	Worsened = 2 (6%)
Pain score		
1–4 = 21 (66%)	1–4 = 19 (59%)	Improved = 6 (19%)
5–10 = 11 (34%)	5–10 = 13 (41%)	Unchanged = 21 (65%)
		Worsened = 5 (16%)

Abbreviation: ECOG, the Eastern Cooperative Oncology Group.

approximately 10 to 36% of patients, were nausea, vomiting, and diarrhea. In our patients, Radium-223 was well tolerated, with none of these patients having interruption of cycle due to any of the nonhematological toxicity.^{16,18,27,28} Overall Radium-223 was associated with a low incidence of myelosuppression and low-cumulative incidence rates for hematological and nonhematological adverse events.

Given the multiple treatment options available for patients with mCRPC, biomarkers are needed to identify which patients are more likely to respond and derive benefit from Radium-223. No significant correlation between the other hematobiochemical markers such as PSA, ALP, platelets, and WBC with the OS was found in our study, quite similar to Boni et al,¹³ yet ALP could still be useful for treatment monitoring.

Bone metastases have a profound impact on patients' QoL being distressing as a result of bone pain and fatigue. Radionuclide therapies as Radium-223 have been seen to improve the QoL. The SREs occurring in mCRPC patients are pathologic fractures, spinal cord compression, and impending fracture. Radium-223 therapies have shown to increase the median time to SREs, with improvement in QoL of patients.²⁹ The symptomatic skeletal events (SSE) were observed in only one of our patients, much less than approximately 10 to 38% as reported in other studies.^{19,30–32} The results could have been confounded by early initiation of the Radium-223 therapy during the disease course or bisphosphonate associated with health-related QoL benefits compared with placebo.

The ECOG performance score of 0 or 1 was reported in 81% of our patients and similar to the ALSYMPCA trial where 87% of people had an ECOG performance score of 0 or 1. Pain response has not been seen to be associated with OS, despite two-thirds of patients experiencing improvement in the pain compared with our 19% of our patient group who showed improvement in pain.³³

Despite improvement in pain the performance status remained the same in 23 patients, improved in 7 patients, and worsened in 2 patients. Discordance between the performance status and pain score was noted in 13 patients of which 5 patients had similar or better performance status despite worsening bone pain. The worsening bone pain could be related to nonmalignant processes such as degenerative disorders or osteoporotic fractures, while fatigue can be a side effect of treatment and not a sign of disease progression. Hence physician's pain assessment may be variable compared with the patient's reported outcomes. Although the pain response was not associated with the OS, and it has been seen in ALSYMPCA trial that Radium-223 improved the most secondary endpoints in patients with CRPC. Hence, use of focused questions with emphasis on the everyday activity, energy level, fatigue, pain, and sleep cycle while creating a dash board charting for gauging the response to these parameters with clinical disease evaluation should be encouraged.

In the real-world scenario, sustainability of these therapeutic radionuclide therapies in long term is dependent on reliable supply of radionuclides at affordable cost along with

comparison with other medical therapies in clinical trials. Health economic evaluations (HEEs) are increasingly adopted by different government structures to assess the treatment and is becoming an integral part of health technology assessment and decision-making in health care, almost 82% of NICE decisions being predicted by economic calculations.^{34,35} Although it has been seen with economic modeling that adding Radium-223 to health plan formulary, the per member per person (PMPM) cost minimally increased, about \$0.02,³⁶ caution needs to be maintained when interpreting economic evaluations of high-cost treatments of α therapies, given the complexities associated with comparisons across heterogeneous trials with confounding outcome.

Although there is no direct comparison or economic evidence of cost of Radium-223 or any other radionuclide therapy in the low- and middle-income countries due to wide variability in cost, cost description, and reimbursement procedures. However the economic burden associated with the SRE's related quality-adjusted life-year (QALY) is likely high to suggest potential for cost saving through preventive measured of SRE's events. Other β -emitter therapies such as Lutetium-177, as well as newer targeted α therapy (TAT), such as Actinium-225 or Bismuth-213 are being evaluated in the treatment of prostate cancer with the potential target being overexpression of prostate specific membrane antigen (PSMA). These can be delivered to PSMA expressing tumors regardless of the metastatic location. The PSMA based therapies can be considered for the nodal and skeletal metastases compared with Radium-223 which is reserved for patient with bony metastases.

After highly promising initial results and progressive clinical trials, rapid development of these agents is anticipated. These targeted α and β therapies may develop independently or in synergy with other treatment approaches as hormonal therapies, chemotherapies, radiosensitizers, DNA repair inhibitors, or modulators.³⁷ The present clinical trials are produced to evaluate the use of new therapy and extrapolate its utility in long terms. The future induction of these newer TAT many depend on the cost effectiveness as one of the major factor for reimbursement decision with the clinical studies increasing the scope of information available for effective intervention supporting the reimbursement decisions.

Conclusion

Our study showed that patient selection plays an important role in maximizing the effectiveness of Radium-223 therapy while ensuring appropriate utilization of resources. Ideally, full six-cycle Radium-223 therapy should be completed to obtain the maximum survival benefit. Despite patient selection with favorable safety profiling for therapy, low incidence of myelosuppression do occur with hematotoxicity being a significant limiting factor.

The Radium-223 therapy is well tolerated with low rate of hematological and nonhematological toxicities compared with the other available therapies such as chemotherapy

among the elderly age group. Presently, Radium-223 is being chosen far later in the treatment algorithm after the bone metastasis has become symptomatic when it may be less likely to benefit patients. Low myelotoxicity of Radium-223 could permit its association or/and combination with other myelotoxic treatments including radiochemotherapies in symptomatic patients.

The impact of intervention with Radium-223 at an earlier stage of bone disease needs to be established with preferred sequencing in patients with mCRPC. The challenge remains in the timing of its sequencing in the clinical scenario, preferably at an earlier stage of disease management with occasional needful utility for retreatment with Radium-223 and its impact in mCRPC treatment, among the various therapeutic regimes.

Additional randomized trials are needed to establish the optimal sequence and combination strategies for the use of Radium-223 in patients with mCRPC. As the border between beneficial therapy and causing relevant side effects is very narrow, robust patient selection for Radium-223 treatment is essential to guarantee the most effective therapeutic patient care in the patient population. Future clinical induction of newer radionuclide therapies shall depend on the cost efficacy and cost effectiveness, making them more efficient for wide-spread use.

Note

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form.

Conflict of Interest

None declared.

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