Original Study

Factors Associated With Survival Following Radium-223 Treatment for Metastatic Castration-resistant Prostate Cancer

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Abstract

The outcomes of 64 patients with metastatic castration-resistant prostate cancer after treatment with radium-223 were analyzed. Four factors were identified to be associated with survival in multivariate analysis. Future studies to evaluate earlier use of this radiopharmaceutical in newly diagnosed metastatic prostate cancer when the disease is sensitive to androgen deprivation therapy would be warranted.

Background: Radium-223 (^{223}Ra) improves survival in patients with metastatic castration-resistant prostate cancer (mCRPC). This retrospective analysis was performed to better understand its efficacy in routine clinical practice and identify factors associated with survival. **Materials and Methods:** Sixty-four patients with mCRPC who received ^{223}Ra between 2013 and 2015 were the basis of this retrospective study. Clinical outcomes and patient characteristics were obtained. Potential prognostic factors for survival were evaluated by univariate analysis using the log-rank test and multivariate analysis using the Cox proportional hazard method. **Results:** The median survival was 12.9 months. Twenty-one patients (33%) developed a skeletal event, and the median time to the first skeletal event was 4.4 months. In univariate analysis, factors significantly associated with survival included: no prior chemotherapy, $\leq$ 5 bone metastases, baseline prostate-specific antigen (PSA) $\leq$ 36 ng/mL, baseline alkaline phosphatase (ALP) $<$ 115 U/L, baseline hemoglobin $>$ 12 g/dL, ALP response after ^{223}Ra treatment, PSA decrease during ^{223}Ra treatment, and absence of $>$ 25% PSA increase during ^{223}Ra treatment. In multivariate analysis, 4 factors remained significant: no prior chemotherapy, $\leq$ 5 bone metastases, baseline ALP $<$ 115 U/L, and ALP response after ^{223}Ra treatment. **Conclusion:** When ^{223}Ra is administered in routine clinical practice, clinical outcomes can be more variable than those reported in the randomized study owing to patient heterogeneity. Four factors were identified to be significantly associated with survival after ^{223}Ra treatment. These pretreatment factors may be used as stratification factors in future studies to investigate whether ^{223}Ra would be more effective for patients with newly diagnosed metastatic disease that is sensitive to androgen deprivation therapy.

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Introduction

Prostate cancer is the most common cancer in men in the United States. Although most patients with localized disease can be cured, metastatic prostate cancer remains an incurable disease. Since Huggins and Hodges first reported the efficacy of castration and estrogen in the management of metastatic prostate cancer in 1941, androgen deprivation therapy (ADT) has been the mainstay for the management of metastatic prostate cancer. Unfortunately, the disease invariably progresses in spite of ADT, resulting in significant morbidity and mortality. There was little progress in

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the development of systemic therapy for metastatic castration-resistant prostate cancer (mCRPC) until 2004, when 2 randomized studies demonstrated a survival benefit of docetaxel by 2.5 months for these patients.[1,2] Since 2010, 5 additional new agents have been approved by the United States Food and Drug Administration for the treatment of mCRPC, including radium-223 (^{223}Ra).

^{223}Ra is an α-emitter with a half-life of 11.4 days. It is a calcium mimetic and forms complexes with bone mineral hydroxyapatite in areas of active bone remodeling. The α-particles cause double-strand DNA break of cells. With a range of penetration of < 0.1 mm, ^{223}Ra is able to achieve localized killing of cancer cells with less collateral damage to the nearby bone marrow. In the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study, patients with mCRPC were randomized to ^{223}Ra or placebo.[3] There was a significant improvement in median survival of 3.6 months in patients receiving ^{223}Ra for mCRPC as compared with placebo.

Although ^{223}Ra has been approved for the treatment of mCRPC with bone metastasis in 2013, post-approval data remain scant. In clinical practice, patient selection may be different from that specified in the ALSYMPCA trial, and the drug is often used in patients who have been heavily pretreated with other agents. To better understand the result of ^{223}Ra in routine clinical practice, we have performed a retrospective analysis of the use of this radiopharmaceutical at Mayo Clinic to evaluate the outcomes and identify factors that are associated with survival.

Materials and Methods

Patients with mCRPC treated at the 3 Mayo Clinic campuses in Minnesota, Arizona, and Florida from September 2013 to May 2015 with ^{223}Ra for bone metastasis were included in this study. The study was approved by the institutional review board. Data were retrieved from the electronic medical records. All patients received the standard dose of ^{223}Ra, 50 kBq/kg every 4 weeks, up to a total of 6 doses. The use of ADT continued during ^{223}Ra treatment, usually with luteinizing hormone-releasing hormone agonists. Information on prior use and concurrent use of other systemic therapy, including chemotherapy and second-line ADT such as abiraterone and enzalutamide was collected. The use of zoledronate and denosumab was noted. Complete blood count was measured before each cycle of ^{223}Ra. Other laboratory studies, including prostate specific antigen (PSA) and alkaline phosphatase (ALP), were obtained during treatment and at follow-ups at the discretion of the treating physician. An ALP response after treatment was defined as $> 30\%$ decline in ALP level from baseline after completion of treatment. A skeletal event after ^{223}Ra treatment was defined as use of palliative external beam radiation therapy, new symptomatic pathologic fracture, spinal cord compression, or tumor-related orthopedic surgical procedure. Pain score was not consistently documented in patient records and was not included in this analysis.

Statistical analysis was performed using the *JMP* statistical program by SAS Institute. The overall survival of patients was calculated using the Kaplan-Meier method. Factors that might be associated with overall survival were evaluated by univariate analysis using the log-rank test and multivariate analysis using the Cox proportional hazard method.

Results

Sixty-four patients were included in the study. Table 1 summarizes the patient and clinical characteristics of this cohort. The median age was 74 years (range, 51-96 years). Forty-six patients initially presented with localized prostate cancer and then developed metastatic disease after a median time of 6.6 years. Eighteen patients presented with metastatic prostate cancer de novo. Forty-five patients (70%) had performance status (PS) of 0 to 1. Most of these patients had been heavily treated before receiving ^{223}Ra treatment. Thirty-nine patients (61%) had prior chemotherapy, including docetaxel (47%), cabazitaxel (5%), or both docetaxel and cabazitaxel (9%). Nine patients (14%) had prior treatment with sipuleucel-T. Twenty-nine patients (45%) had received abiraterone or enzalutamide prior to or during ^{223}Ra treatment. Most patients (86%) had more than 5 sites of bone metastasis on bone scan. The median PSA value at baseline was 35.8 ng/dL (range, 1.1-5000 ng/mL), and the median ALP level was 115 U/L (range, 48-499 U/L). Only 35 patients (55%) completed all 6 cycles of ^{223}Ra treatment. The reasons to discontinue treatment included: disease progression (26 patients), side effects (1 patient), and patient refusal (2 patients).

The median follow-up for survivors was 10.7 months. At last follow-up, 32 (50%) patients had died, with 29 of the deaths because

Table 1 Clinical and Patient Characteristics

Characteristics	N (%)
Total Patients	64
Median age, y (range)	74 (51-96)
ECOG performance status	
0-1	50 (77)
2-3	14 (23)
Prior chemotherapy	39 (61)
Docetaxel	30 (47)
Cabazitaxel	3 (5)
Both docetaxel and cabazitaxel	6 (9)
Prior or concurrent use of abiraterone or enzalutamide	29 (45)
Prior sipuleucel	9 (14)
Concurrent use of zoledronate or denozumab	29 (45)
Extent of bone metastasis	
1-5 sites	9 (14)
>5 sites	55 (86)
Median PSA before ^{223}Ra treatment, ng/mL	35.8 (1.1-5000)
Median alkaline phosphatase before ^{223}Ra treatment, U/L	115 (48-499)
Median hemoglobin before ^{223}Ra treatment, g/dL	12 (9.4-15.6)
Number of cycles of ^{223}Ra	
1	4 (6)
2	5 (8)
3	9 (14)
4	7 (11)
5	4 (6)
6	35 (55)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen; ^{223}Ra = radium-223.