Original Study

Radium-223 Use in Clinical Practice and Variables Associated With Completion of Therapy

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Abstract

Radium-223 has shown improvements in overall survival in men with metastatic castration-resistant prostate cancer (mCRPC). In this study, we investigated clinical variables associated with radium-223 therapy completion in mCRPC. We show the previous and concurrent mCRPC therapies and laboratory data that are associated with the number of radium-223 doses received. These data are hypothesis-generating and warrant prospective testing.

Background: Radium-223 has shown clinical efficacy in metastatic castration-resistant prostate cancer. Despite improvement in quality of life and survival, practice patterns and utility of this agent outside the context of clinical trials have not been fully characterized. The primary objective in this study was to evaluate variables associated with completion of 5 to 6 radium-223 doses. **Patients and Methods:** We conducted retrospective analyses of patients who received radium-223 (n = 135). Patients were classified into 3 cohorts: 1 to 2, 3 to 4, or 5 to 6 radium-223 doses. We evaluated the association of clinical and laboratory variables with the number of cycles administered (5-6 vs. 1-4 doses). **Results:** Twenty-five patients (18.5%) received 1 to 2 radium-223 doses, 27 (20.0%) received 3 to 4, and 83 (61.5%) received 5 to 6. The most common reasons for treatment discontinuation included disease progression (61.5%, n = 40), patient preference (15.4%, n = 10), and toxicity (10.8%, n = 7). Factors associated with therapy completion in univariate analysis included previous sipuleucel-T treatment ($P = .068$), no previous abiraterone or enzalutamide treatment ($P = .007$), hemoglobin ≥ lower limit of normal (LLN; $P = .006$), white blood cell count ≥ LLN ($P = .045$), absolute neutrophil count (ANC) ≥ LLN ($P = .049$), lower alkaline phosphatase ($P = .029$), and lower lactate dehydrogenase levels ($P = .014$). Factors associated with therapy completion in multivariable analysis included previous sipuleucel-T treatment ($P = .009$), hemoglobin ≥ LLN ($P = .037$), and ANC ≥ LLN ($P = .029$). **Conclusion:** Several clinical parameters are associated with radium-223 therapy completion. In general, these parameters reflect earlier disease stage. These data are hypothesis-generating and prospective testing of the optimal number of radium-223 doses is warranted.

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Introduction

The skeleton is the most frequent site of metastasis in metastatic castration-resistant prostate cancer (mCRPC).[1] Patients with bone metastases are vulnerable to skeletal morbidity leading to worsening quality of life. Skeletal-related events, including pathologic fracture, radiation or surgery to the bone, and cord compression, occur in 20% to 50% of mCRPC patients.[1]

Radium-223 is a radioisotope with natural bone-seeking proclivity.[2] In contrast to β-particles, α-particles provide ionizing radiation in a more narrow range resulting in low myelotoxicity and they induce DNA double-strand breaks leading to cancer cell death at all stages of the cell cycle.[2] The efficacy of radium-223 in mCRPC was demonstrated in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial.[3] This phase III, double-blinded trial randomized 922 men with mCRPC with bone metastases who had received previous docetaxel treatment or were

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unfit for docetaxel 2:1 to radium-223 (50 kBq/kg at 4-week intervals for 6 cycles) or placebo with best supportive care. The phase II study tested 4 injections of radium-223 (50 kBq/kg).[4] Because of limited toxicity and benefit related to treatment duration, the number of doses was extended to 6 in the ALSYMPCA trial. Updated analysis of 921 patients confirmed that radium-223 significantly improved overall survival (OS) (14.9 vs. 11.3 months; $P < .001$) and prolonged time to first symptomatic skeletal event (SSE; 15.6 vs. 9.8 months; $P = .0037$).[5] Data from the ALSYMPCA trial provide evidence that the administration of radium-223 (50 kBq/kg) at 4-week intervals for 6 doses improves survival, however, does not provide rationale for the dosing schedule. No study to date has compared the benefit of 4 versus 6 doses of radium-223 and thus the incremental effect of more or less radium-223 on OS is unknown. Prospective studies are warranted to fully evaluate the minimum number of radium-223 doses needed to confer a survival benefit and maximum number at which further dosing is no longer beneficial.

Despite the positive effect of radium-223 on OS in men with mCRPC, the limited clinical experience with this agent warrants investigations of clinical practice patterns outside the context of trials. Because most patients in the ALSYMPCA trial received 6 radium-223 injections, in this study, we aimed to identify variables associated with therapy completion. We anticipate our results, if validated prospectively, will inform the general oncology community about optimal patient selection and radium-223 dosing.

Patients and Methods

Patient Population

The study cohort was composed of mCRPC patients who received and discontinued or completed radium-223 treatment. Radium-223 was administered as standard clinical practice or through the expanded access program (EAP). Eligible patients received radium-223 before February 1, 2015 so potentially 6 doses could be completed by the data retrieval date (August 12, 2015). The total cohort (n = 135) was comprised of 81 Dana-Farber Cancer Institute (DFCI) and 54 Tulane Cancer Center patients. This study was approved by the Institutional Review Board at each institution.

Procedures

Clinical data were retrospectively manually collected from the medical record into a secure database. Patients were classified according to the number of radium-223 doses received for descriptive purposes as cohorts 1 to 2, 3 to 4, and 5 to 6 doses and for testing as cohorts 1 to 4 versus 5 to 6 doses. Baseline laboratory data were categorized according to institutional normal ranges and/or meaningful clinical cut points. Duration of previous and/or concurrent therapy was censored at date of last radium-223 dose. Percent change in laboratory data was calculated from first radium-223 dose to second dose and ever change during treatment.

Objectives

The primary objective was to evaluate the potential association of clinical and laboratory variables with receipt of 5 to 6 radium-223 doses compared with < 5 doses. Secondary objectives included assessment of toxicity, SSEs, and OS.

Statistical Analysis

Descriptive statistics were used to characterize patients according to therapy cohort. Associations were assessed with the Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. The Cochran–Armitage test was used to assess therapy completion proportions across levels of ordinal variables. Adjustments were not made for multiple testing. Logistic regression was used to estimate the odds ratio (OR) for therapy completion (cohort 5 to 6 vs. 1 to 4) in univariate and multivariable models. On the basis of the former analyses of association, variables with a P value of $\leq .10$ were further evaluated in logistic regression models. For the multivariable analysis, a stepwise selection procedure was performed using the criteria of 0.10 significance level to enter and stay in the model. Survival distributions were estimated in a landmark analysis from the date of last radium-223 dose using the Kaplan–Meier method and compared between therapy cohorts using the log rank test.

Results

Patient and Disease Characteristics

The analysis included 135 patients of whom 46 (34.1%) received radium-223 through the EAP and 25 (18.5%) received 1 to 2 doses of radium-223, 27 (20.0%) 3 to 4 doses, and 83 (61.5%) 5 to 6 doses. Patient and disease characteristics were similar between cohorts (Table 1). The median age was 70 (range, 47-97) years and most patients had metastases at diagnosis (59.8%, n = 70). The median time from diagnosis to radium-223 initiation was 6 (range, 0.4-32) years. Approximately half of the cohort had ≥ 1 previous SSE (49.6%, n = 67).

Radium-223 Discontinuation

Overall, 50.4% of patients (n = 68) discontinued radium-223 before completion of 6 doses: 11 (8.2%), 14 (10.4%), 14 (10.4%), 13 (9.6%), and 16 (11.8%) for patients who received 1 to 5 doses, respectively. Reason for treatment discontinuation was reported by 65 patients and included disease progression (n = 40; 61.5%), toxicity (n = 7; 10.8%), patient preference (n = 10; 15.4%), physician preference (n = 2; 3.1%), or other (n = 6; 9.2%). Adverse events resulting in treatment discontinuation included anemia (n = 1), thrombocytopenia (n = 3), or both (n = 3).

Effect of Previous and/or Concurrent Therapies on Radium-223 Completion

The number of previous mCRPC therapies did not affect radium-223 completion (Table 2). Approximately one-third of patients in cohorts 5 to 6 and 1 to 4 received > 2 previous mCRPC therapies. Previous sipuleucel-T treatment was associated with an increased likelihood of completing therapy with use in 34% (n = 28) of cohort 5 to 6 versus 15% (n = 8) in cohort 1 to 4 ($P = .027$). Previous abiraterone or enzalutamide was associated with a less likelihood of completing radium-223 ($P = .016$) and receipt of no, one, or both agents affected radium-223 completion ($P = .010$; Table 2). Of patients from cohort 5 to 6, 47% (n = 39) and 20% (n = 17) received previous abiraterone and enzalutamide, respectively, compared with 69% (n = 36) and 33% for cohort 1 to 4. Previous chemotherapy did not vary significantly between cohorts (52% [n = 43] vs. 60% [n = 31] of cohort 5 to 6 vs. 1 to 4, respectively).