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One-Year Postapproval Clinical Experience with Radium-223 Dichloride in Patients with Metastatic Castrate-Resistant Prostate Cancer

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Abstract

Objectives: We report our 1-year postapproval clinical experience with Radium-223 dichloride for treatment of castrate-resistant prostate cancer with bone metastases.
Methods: The clinical courses of the first 25 patients treated were reviewed retrospectively. Incidence of hematologic, gastrointestinal, and other adverse events were identified, including those events that led to cessation or delay in treatment. Alterations in bone pain and serum alkaline phosphatase and prostate-specific antigen (PSA) levels were evaluated.
Results: Six patients received all 6 scheduled doses of Radium-223 dichloride, 2 completed 5 doses, 6 received 4 doses, 2 completed 3 doses, 6 patients had 2 doses, and 3 patients received one dose, for a total of 91 doses administered. Nine patients discontinued treatment after receiving at least one dose due to progressive disease, 5 required blood transfusions, 5 developed gastrointestinal symptoms, 4 reported worsening bone pain, and 1 developed dermatitis. Downward trends in serum alkaline phosphatase and PSA were seen in 11 and 5 patients, respectively.
Conclusions: About one-quarter of cohort completed the entire six-dose treatment. Advancing soft tissue disease was the primary reason for cessation of therapy. The adverse events were mild and manageable. A decline in serum alkaline phosphatase was more common than a decline in PSA.

Key words: bone, cancer, castrate, metastasis, prostate, radium

Introduction

Bone metastases develop in the majority of patients with castration-resistant prostate cancer.[1] The skeletal-related events (SREs) from the bone metastases continue to be a major cause of disability, diminished quality of life, increased cost for treatment of complications (e.g., spinal cord compression and pathological fractures), and even death.[2] There have been great recent strides for the treatment of metastatic castration-resistant prostate cancer in view of improved understanding of the complex biology of prostate cancer. These recent therapies include novel taxanes such as cabazitaxel, cellular immunotherapy sipuleucel-T, androgen biosynthesis inhibitors such as abiraterone acetate, the androgen receptor antagonist, enzalutamide, and targeted radiotherapy of bone metastases with Radium-223 dichloride.[3]

Radium-223 dichloride is a calcium mimetic, and it targets the hydroxyapatite matrix in the bone, thereby accumulating in areas of active bone remodeling and formation, such as sites of osteoblastic bone metastases.[4] Radium-223 is the first α emitter that has undergone formal testing for clinical use. It has a physical half-life of 11.43 days, a short range of less than 10 μm, and has an emitted energy distribution of 93.5% α particle (average energy of 5.78 MeV), less than 3.6% β

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particle, and less than 1.1% γ radiation (154 keV) with 28 MeV combined energy for the complete decay.

The United States Food and Drug Administration (FDA) approved the clinical use of Radium-223 dichloride (Xofigo; Algeta-Bayer Healthcare Pharmaceuticals, Wayne, NJ) for targeted therapy of bone metastases in men with castration-resistant prostate cancer on May 15, 2013, and this treatment was later incorporated into the National Comprehensive Cancer Network guidelines.[5–7] The FDA approval was based on the results of the randomized, double-blinded, multinational clinical trial titled ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer). ALSYMPCA compared Radium-223 dichloride (50 KBq/kg intravenously every 4 weeks for six doses) with placebo (saline intravenously every 4 weeks for six doses) in men with castration-resistant prostate cancer with symptomatic bone metastases and no visceral metastases (although lymph nodes up to 3 cm in short axis were acceptable) and who had adequate bone marrow reserve (www.clinicaltrials.gov, identifier: NCT00699751). Parker et al. reported the final results of the phase III clinical trial incorporating 307 patients in the placebo arm and 614 patients in the treatment arm.[8,9] The clinical trial demonstrated a 3.6-month overall survival benefit with Radium-223 dichloride in comparison with placebo (median, 14.9 months vs. 11.3 months; hazards ratio, 0.70; 95% confidence interval, 0.58–0.83; $p < 0.001$). The overall survival benefit was present regardless of previous docetaxel treatment (3.1-month survival benefit with previous docetaxel use and 4.6-month survival benefit without previous docetaxel use). There was also benefit with regard to longer median time to first symptomatic SREs (median, 15.6 months vs. 9.8 months; hazards ratio, 0.66; 95% confidence interval, 0.52–0.83; $p < 0.001$).

We adopted this novel treatment at the Keck School of Medicine of the University of Southern California, in Los Angeles, California, soon after the FDA approval. In this article, we report our early clinical experience with this agent in the context of ALSYMPCA clinical trial findings and briefly comment on the administrative logistics in providing this treatment to our patients.

Methods

Patient referral and preparation

We followed the clinical course of the first 25 patients who were treated with Radium-223 dichloride. Patients were referred by medical oncology (21 patients) and urology (4 patients). The nuclear medicine physicians treated all patients in the nuclear medicine clinic. Before scheduling a treatment session, all the pertinent clinical, radiographic, and laboratory information was collected by the nuclear medicine technologist and presented to the nuclear medicine physician for review. A signed approval for treatment by the nuclear medicine physician prompted the nuclear medicine technologist to call the patient for scheduling an appointment for treatment in the nuclear medicine clinic. In many cases, the patient visited the oncology clinic first for establishing a reliable intravenous access before the scheduled time in the nuclear medicine clinic.

Treatment procedure

The treatment room included a chair without arms and a table that was completely covered with blue chux. Underneath the table and the chair there were additional blue chux covering the floor. Two saline flushes and a double-bagged red biohazard bag were available. The patient's intravenous access tubing was connected to a 3-way stopcock. The intravenous access was checked by pushing some saline. The nuclear medicine physician checked the order, including appropriateness of the treatment, the calculated weight-based dose, and the name, birthdate, and medical identification number of the patient. The procedure was described to the patient, and the patient's caregiver if present, and all questions were answered. A signed informed consent was obtained.

We receive the patient-specific dose (50 KBq/kg or 1.35 μCi/kg) that is then measured in a dose calibrator before administration. The nuclear medicine physician with gloved hands removes the radioactive material from the container and checks the name and dosage written on the container. The dose syringe is then connected to the three-way stopcock. The dose is administered over approximately 1 minute followed by two 10 mL saline flushes after changing the stopcock position appropriately. The dose syringe is placed back in the carrying container and removed by the nuclear medicine technologist. The nuclear medicine technologist also surveys the hands and feet of the physician and the treatment area. All flushes, gloves, contaminated gauze, and intravenous tubing are placed in the biohazard bag and taped shut. The patient is observed for 15 minutes for any signs of immediate complications. If no immediate complications or complaints are evident, the patient is discharged from the clinic and reminded about the next dosing schedule in 4 weeks as appropriate. A list of instructions is discussed with and given to the patient to be followed after the treatment procedure.

Clinical, radiological, and laboratory follow-up

The electronic records of the patients were reviewed for incidence of hematologic, gastrointestinal, and other adverse events. Circumstances that resulted in cessation or delay in treatment were documented. Alterations in bone pain and serum alkaline phosphatase and prostate-specific antigen (PSA) levels were also evaluated.

Results

Patient characteristics

Table 1 summarizes the patient characteristics. During the period, May 2013 to May 2014, 25 patients (median age 70 years, age range 56–88 years) were referred to our nuclear medicine clinic for Radium-223 dichloride therapy. The initial definitive treatment included radical prostatectomy in 10 patients, external bean radiation therapy (EBRT) in 5 patients, and missing primary treatment history in 5 patients. Androgen deprivation therapy was instituted in all patients who had undergone EBRT and in 4 patients who had also undergone previous chemotherapy. The primary tumor Gleason score ranged between 6 and 10 in 15 patients; in 10 patients, the data on Gleason score were missing. The range of interval between initial diagnosis and referral to Radium-223 dichloride therapy was 2–23 years.

Treatment schedule

By inclusion criteria, all patients had osseous metastases in either Tc-99m-based bone scintigraphy or 18F-NaF

Table 1. Summary of Patient Characteristics

Pt.	*Age (yrs)*	*GS*	*Initial Rx*	*Years from Dx to Ra-223 Rx*	*Range of Ra-223 administered activity (μCi)*	*No. of Ra-223 doses received*
1	66	9	RP + RT + AD	18	168–175	3
2	58	n/a	RP	10	119–122	2
3	65	9	RT + RT + AD	10	112	2
4	82	n/a	RP + RT + AD	23	82–84	4
5	67	n/a	n/a	n/a	108–116	4
6	72	8	RP + AD	20	103–106	6
7	66	n/a	n/a	n/a	122–133	4
8	76	7	AD	7	92	5
9	71	9	RP	9	100–106	4
10	68	n/a	RT + RT	14	132–136	6
11	78	7	RT + AD	n/a	87–91	5
12	67	10	AD	2	77	1
13	81	6	RT + AD	15	100	1
14	64	9	RT + AD	7	96–98	6
15	64	n/a	AD	9	117	2
16	57	6	RT	5	108–113	4
17	56	n/a	RP + RT + AD	5	106–113	6
18	81	n/a	n/a	6	97–100	6
19	75	n/a	AD	11	82–86	6
20	86	6	AD	9	113	1
21	88	8	RP	15	93–105	3
22	85	7	RP	11	124–125	4
23	65	n/a	n/a	n/a	140–145	2
24	70	9	AD	5	128–130	2
25	72	n/a	n/a	n/a	103–107	2

GS, primary tumor Gleason sum score; RP, radical prostatectomy; RT, radiation therapy; AD, androgen deprivation therapy; Dx, diagnosis; Rx, therapy; n/a, not available.

positron emission tomography/computed tomography (PET/CT). All patients also had adequate bone marrow reserve with absolute neutrophil count >1500/mL, hemoglobin >10 g/dL, and platelet count $>100{,}000$/mL. Six patients (24% of total) received all 6 scheduled doses of Radium-223 dichloride (full treatment), 2 completed 5 doses, 6 received 4 doses, 2 completed 3 doses, 6 patients had 2 doses, and 3 patients received one dose, for a total of 91 doses administered over a period of 12 months. The administered activity was based on patient's weight, as outlined earlier, and it ranged between 77 and 175 μCi. The syringe and tubing residual activity after radionuclide administration was 2.7 ± 2.0 μCi (mean $\pm$ SD).

Complications and adverse events

Nine patients (36% of total) discontinued the treatment schedule after receiving at least one dose due to a variety of complications related to progressive disease, including increasing soft tissue metastases (hepatic, nodal), development of dural metastases and intracerebral hemorrhage, intractable nausea and vomiting, and death. Five patients (20% of total) required blood transfusions for anemia during the course of treatment. Five patients (20% of total) developed mild to moderate gastrointestinal symptoms (diarrhea, loss of appetite, constipation). Four patients (16% of total) reported worsening bone pain during treatment although in one of these patients, the bone pain resolved completely after the second dose of the treatment. One patient developed biopsy proven dermatitis that was not clearly due to other potential causes.

Serum alkaline phosphatase and PSA trends

The serum alkaline phosphatase was available in 18 patients. A slow downward trend in serum alkaline phosphatase was noted in 11 patients (44% of total), and an upward trend was noted after a transient downward trend in 7 patients (28% of total). Serum PSA was available in 20 patients. Serum PSA showed an upward trend in 15 patients (60% of total), and a slow downward trend was observed in 5 patients (20% of total).

Discussion

New options for treatment of metastatic castrate resistant prostate cancer have become available spearheaded by advancements in understanding the biology of the disease and the other associated technical developments. All these FDA-approved novel treatments have been evaluated in phase III clinical trials against placebo, demonstrating overall survival benefit of about 4 months. Despite these strides, much needs to be learned about optimal solo (with the possibility of escalating dose amount and frequency), combination with other drugs, or sequencing of therapies in a patient-specific risk-adapted manner.[10–15] Given the remarkable inter-patient and intra-patient heterogeneity of bone metastases in prostate cancer, identification of a course of most encompassing and effective therapy regimen with the least and/or manageable adverse events remains both a challenge and an opportunity.

While use of bone-targeted radiopharmaceuticals in cancer management is not new, however, Radium-223 dichloride is a

first-in-class agent that incorporated an alpha particle and demonstrated an overall survival advantage compared with placebo with generally mild and manageable adverse events portfolio.[16–21] The overall survival benefit, manageable adverse events, safety, buy-in from the medical community, and the ease of administration have contributed to the early adoption of this therapy. We introduced the Radium-223 dichloride therapy in our clinic soon after its approval through the attentive combined efforts among leaders in oncology, nuclear medicine, radiology business administration, and the Cancer Center.

The goal of this report was to decipher our 1-year experience with this new therapeutic option in prostate cancer care. It is interesting to note that many patients in our community were aware of this potential therapeutic option and indeed were inquiring about its availability at our Center. Both the patient and referring physicians' interests in this therapeutic option were key in the streamlining of the efforts in providing the treatment at our Cancer Center soon after the announcement of the FDA approval.

While 25 patients were referred to our nuclear medicine clinic for treatment, only about 25% of them received the full 6-dose treatment schedule. The major reason for not receiving the entire 6-dose treatment schedule was progression of the underlying metastatic disease process. The adverse events were similar in nature and frequency to the ALSYMPCA trial that included transient anemia and thrombocytopenia. The most common adverse event in our cohort was gastrointestinal adverse events, which were manageable and may have been related to the physiologic localization of the agent in the gastrointestinal tract. However, in the ALSYMPCA trial, there were no statistically significant differences in the gastrointestinal symptoms between the cohort who received Radium-233 dichloride and those who received placebo.

The ALSYMPCA trial showed a statistically significant benefit of Radium-223 dichloride therapy compared with placebo with regard to a decline in time to total alkaline phosphatase progression, time to PSA progression, both 30% and 50% reductions in serum alkaline phosphatase level, and the total serum alkaline phosphatase normalization. In our cohort, there were more patients (by a factor of 2–3) with slow downward trends in both serum alkaline phosphatase and PSA levels than those who showed upward trends. Our results are therefore in line with the results of the ALSYMPCA trial, although no patient in our cohort had normalization of his serum alkaline phosphatase level. With regard to bone pain, only a minority of patients reported worsening bone pain. This is also in line with the ALSYMPCA trial finding of no statistically significant difference in the report of bone pain between the placebo and treatment patient cohorts.

Radium-223 dichloride will likely be the first of many novel targeted radionuclide therapy regimens that will be developed to positively impact patient outcome. In response to the growing interest in this type of therapy, there have been recent joint workshops by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the National Cancer Institute (NCI) in 2013 and 2014 that have provided forums to discuss the opportunities and challenges of targeted radionuclide therapy.[22] Such interdisciplinary stakeholder gatherings and discussions in combination with increasing clinical experience and educational outreach with approved agents and developments in cancer biology and radiochemistry will assure a significant role for targeted radionuclide therapy in the overall armamentarium of multistep cancer treatment.

Conclusion

Our 1-year clinical experience with Radium-223 dichloride therapy in bone metastases of castration-resistant prostate cancer demonstrated that the treatment was associated with good patient and physician acceptance, was logistically and technically easy to administer, and was generally well tolerated with manageable adverse events. Apart from its current approved clinical application, we have also recently initiated a clinical trial to determine the safety of retreatment in patients who have already completed the initial 6-dose treatment schedule of Radium-223 dichloride.

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Disclosure Statement

Hossein Jadvar, Sudha Challa, and Peter S. Conti declare no relevant conflicts of interest. David I. Quinn is on the Scientific Advisory Board of Bayer Health Care Pharmaceuticals, Wayne, NJ.

References

1. Bubendorf L, Schopfer A, Wagner U, et al. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. Hum Pathol 2000;31:578Y583.
2. Yong C, Onukwugha E, Mullins CD. Clinical and economic burden of bone metastases and skeletal-related events in prostate cancer. Curr Opin Oncol 2014;26:274.
3. Ezzell EE, Chang KS, Geoerge BJ. New agents in the arsenal to fight castrate-resistant prostate cancer. Curr Oncol Rep 2013;15:239.
4. Jadvar H, Quinn DI. Targeted α-Particle therapy of bone metastases in prostate cancer. Clin Nucl Med 2013;38:966.
5. FDA Approves New Drug for Advanced Prostate Cancer. US Food and Drug Administration. Available at: (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352363.htm) Accessed May 15, 2013.
6. Kluetz PG, Pierce W, Maher VE, et al. Radium Ra 223 dichloride injection: US Food and Drug Administration drug approval summary. Clin Cancer Res 2014;20:9.
7. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 1.2014. J Natl Compr Canc Netw 2013;11:1471.
8. 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.
9. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: Results from a phase 3, double-blind, randomized trial. Lancet Oncol 2014;15:738.
10. Sartor O, Gillessen S. Treatment sequencing in metastatic castrate-resistant prostate cancer. Asian J Androl 2014;16:426.
11. Ryan CJ, Saylor PJ, Everly JJ, et al. Bone-targeting radiopharmaceuticals for the treatment of bone-metastatic

castration-resistant prostate cancer: Exploring the implications of new data. Oncologist 2014;19:1012.
12. Basch E, Loblaw DA, Oliver TK, et al. Systematic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol 2014;32:3436.
13. Dreicer R. How to approach sequencing therapy in patients with metastatic castration-resistant prostate cancer. Can J Urol 2014;21(2 supp1):93.
14. Sartor AO, Fitzpatrick JM. Urologists and oncologists: Adapting to a new treatment paradigm in castration-resistant prostate cancer (CRPC). BJU Int 2012;110:328.
15. Carrasquillo JA, O'Donoghue JA, Pandit-Taskar N, et al. Phase I pharmacokinetics and biodistribution study with escalating doses of 223Ra-dichloride in men with castration-resistant metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2013;40:1384.
16. Lewington VJ. Bone-seeking radionuclides for therapy. J Nucl Med 2005;46 (suppl1):38S.
17. Mulford DA, Scheinberg DA, Jurcic JG. The promise of targeted alpha-particle therapy. J Nucl Med 2005;(suppl1):199S.
18. Pandit-Taskar N, Larson SM, Carasquillo JA. Bone-seeking radiopharmaceuticals for treatment of osseous metastases, Part 1: Alpha therapy with 223Ra-dichloride. J Nucl Med 2014;55:268.
19. Wissing MD, van Leeuween FW, van der Pluijm G, et al. Radium-223 chloride: Extending life in prostate cancer by treating bone metastases. Clin Cancer Res 2013;19:5822.
20. Sridhar SS, Freeland SJ, Gleave ME, et al. Castration-resistant prostate cancer: From new pathophysiology to new treatment. Eur Urol 2014;65:289.
21. Turner PG, O'Sullivan J. Radium-223 dichloride for the treatment of metastatic prostate cancer. Exper Opin Pharmacother 2014;15:2105.
22. Fahey F, Zukotynski K, Capala J, et al. Targeted radionuclide therapy: Proceedings of a joint workshop hosted by the National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging. J Nucl Med 55:337.