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CLINICAL CASE

Treatment with Radium 223 in a Patient with Castration-Resistant Metastatic Prostate Cancer: A Case Report

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Abstract **Introduction:** Prostate cancer is the second cause of cancer-related death. The treatment for metastatic disease with bone activity is multimodal and includes external beam radiation therapy and radiopharmaceuticals with bone affinity. The therapeutic decision is based on the presence or absence of symptoms, on prostate-specific antigen behavior, and on the distribution of metastatic disease, where the role of chemotherapy is well defined (presence or absence of visceral metastases or only bone disease). Radium-223 dichloride (223-Ra) is a calcium-mimetic radiopharmaceutical with activity in osteoblastic lesions that has demonstrated an increase in the time to first skeletal symptomatic event, a decrease in alkaline phosphatase and increased quality of life, with good tolerance. **Case presentation:** An 83-year old male diagnosed in 2011 with prostate adenocarcinoma with bone metastases, treated with hormone blockade for two years. In 2013, he developed hormone-refractory disease progression at the bone level, which was treated with abiraterone in 2014, with prostate-specific antigen elevation and bone pain due to bone progression without visceral disease. In January 2015, radium-223 was indicated every 28 days for four cycles, with important symptom improvement and adequate toxicity profile. **Conclusions:** Treatment with radium-223 provides adequate pain control with an important decrease of alkaline phosphatase and quality of life improvement, offering yet another alternative for patients with castration-resistant metastatic prostate cancer and symptomatic bone disease, with an acceptable toxicity profile. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

Prostate cancer is the most common non-cutaneous malignant tumor in men in the USA, it is the second cause of cancer-related death, and it is acknowledged as the most common malignancy in males older than 50 years. Average life expectancy for Mexican males in the year 2008 was 75 years, which increases the incidence and mortality of this malignancy.

In spite of these figures, most cases are diagnosed at early stages where the likelihood of cure is high, with only 5% of patients being estimated to present with advanced phases at diagnosis.

Up to 20-30% of patients diagnosed with local disease will have recurrence in the systemic form.

In patients with metastatic prostate cancer, the predominant site of disease is the bone. Bone metastases are a common event (65-85%), and have a notorious clinical impact by generating symptoms such as pain, weakness, or functional impairment.

Established treatment for advanced prostatic cancer initially includes androgen-blockage therapy. This approach shows high efficacy, which is estimated at 80%. However, benefit duration is limited in time, with a median of 18-24 months and with most patients progressing to a castration-resistance situation.

In this context, there are therapeutic options such as treatments that interfere with tumor-growth androgenic stimulus (abiraterone, enzalutamide), immunotherapy and chemotherapy with taxanes, among others. If patients show multifocal osteoblastic bone metastases, systemic treatments or external beam radiation therapy is administered and, if uncontrollable, therapeutic radiopharmaceuticals with bone affinity may offer significant palliative benefit.

Thus, the therapeutic decision is dependent on the presence or absence of symptoms, on prostate-specific antigen (PSA) doubling time, and on the distribution of metastatic disease (presence or absence of visceral metastases or only bone disease).

RADIUM-223 DICHLORIDE (223-RA)

Radium-223 dichloride (223-Ra) has been approved for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and without known visceral metastases.

Radium-223 dichloride (223-Ra) is a radiopharmaceutical for alpha particle-emission treatment that mimics calcium and selectively binds to the bone, specifically to areas of bone metastasis where it forms complexes with bone hydroxyapatite. Alpha particles' linear transference elevated energy (80 keV/micrometer) causes double-stranded DNA breaks in adjacent tumor cells rather frequently, which result in a potent cytotoxic effect.

It also elicits additional effects in the tumor microenvironment, including osteoblasts and osteoclasts; radium (223-Ra) alpha particles travel less than 100 micrometers (less than 10 cell diameters), which minimizes damage to normal surrounding tissue.

EFFICACY

Radium-223 dichloride (223-Ra) efficacy has been assessed in 921 patients in a phase III clinical trial (BC1-06, 15245 or ALSYMPCA) and in 286 patients included in three phase II clinical trials (BC1-02, BC1-03, BC1-04). Patients had to be diagnosed with castration-resistant prostate cancer with bone metastases.

The ALSYMPCA study was a multi-center, randomized, double-blind trial where radium-223 dichloride (223-Ra) and the best standard of care was compared with placebo and the best standard of care, with best standard of care being defined as local external beam radiation therapy or treatment with bisphosphonates, corticosteroids, anti-androgens, estrogens, estramustine or ketoconazole. The study demonstrated that the treatment with radium-223 prolonged the time to a first symptomatic skeletal event, reduced alkaline phosphatase, improved quality of life, and was well tolerated. A PSA decrease was observed in a minority of patients.

SAFETY

Safety data are essentially based on 600 patients of the ALSYMPCA trial who had to be treated with a total of six intravenous injections of 50 kBq/kg of radium-223 dichloride (223-Ra) at four-week intervals between administrations.

In this study, treatment mean duration was 141 days for the radium-223 dichloride (223-Ra) group and 128 days for the placebo group patients, with a mean number of doses of 5.1 and 4.5, respectively.

The most common adverse reactions reported with radium-223 dichloride (223-Ra) include nausea (36%), diarrhea (25%), vomiting (19%), thrombocytopenia (12%), neutropenia (5%), and leukopenia (4%).

CASE PRESENTATION

This is the case of an 83-year-old male patient with a history of prostate adenocarcinoma with bone metastasis (lumbar) diagnosed in 2011. He was treated with hormone blockade for two years, and experienced progression of the disease at the bone level in 2013, demonstrated by scintigraphy (hip, lumbar spine, and shoulder), which was defined as castration-resistant prostate cancer. The patient was therefore initiated on abiraterone therapy in 2014 but showed progressive elevation of the tumor marker (PSA) and bone progression, as well as bone pain without visceral disease. In view of this, treatment with radium-223 dichloride (223-Ra) was indicated in January 2015. The patient received four administrations, with an important improvement in symptoms such as bone pain and alkaline phosphatase and PSA levels, with no data consistent with hematologic toxicity being found.

DISCUSSION

Radium-223 dichloride (223-Ra) is indicated for the treatment of male adult patients with castration-resistant pros-

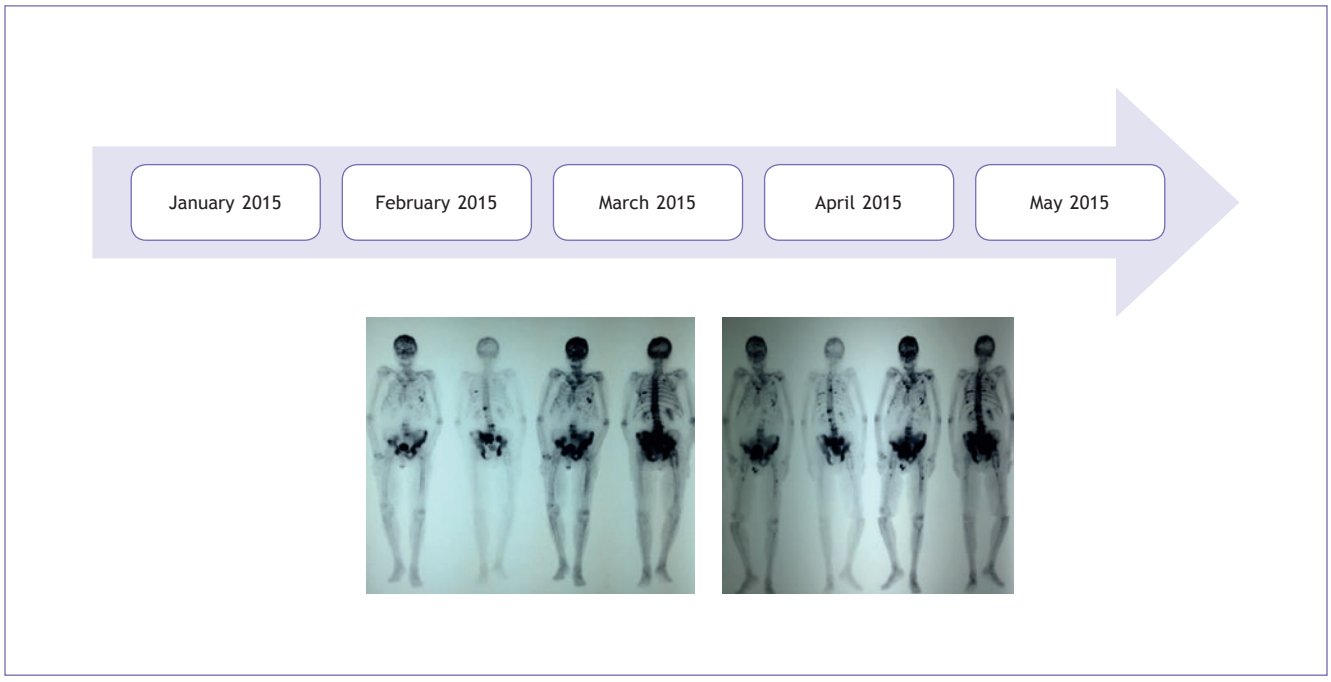

Figure 1. Evolution by imaging in the course of the treatment with radium-223 dichloride (223-Ra).

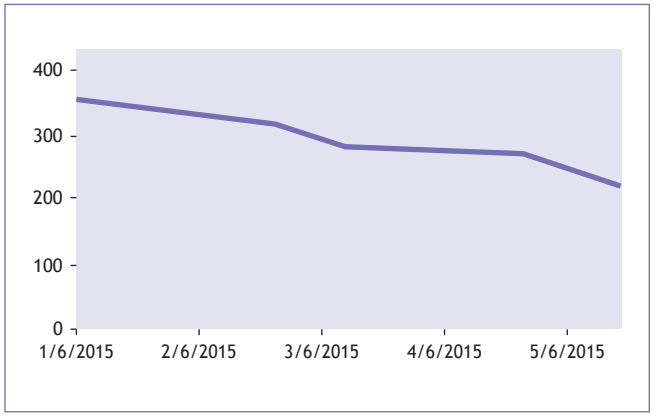

Figure 2. Alkaline phosphatase.

tate cancer, symptomatic bone metastases, and without known visceral metastases. Therefore, this indication suggests that it can be administered both in patients with no previous treatment with chemotherapy and in patients who have failed to respond to first-line chemotherapy.

There are a total of seven clinical trials available to support radium-223 dichloride (223-Ra) efficacy and safety (including pharmacokinetics), although no study so far has been positive for overall survival. However, there are sufficient data to support that the administration of this treatment helps to improve symptoms associated with symptomatic metastatic bone disease such as pain, with an adequate toxicity profile at the hematologic level, as in the present case. There was no PSA-associated therapeutic response, but an important symptom improvement was maintained. Median treatment duration was 118 days, with an important decrease in alkaline phosphatase and adequate

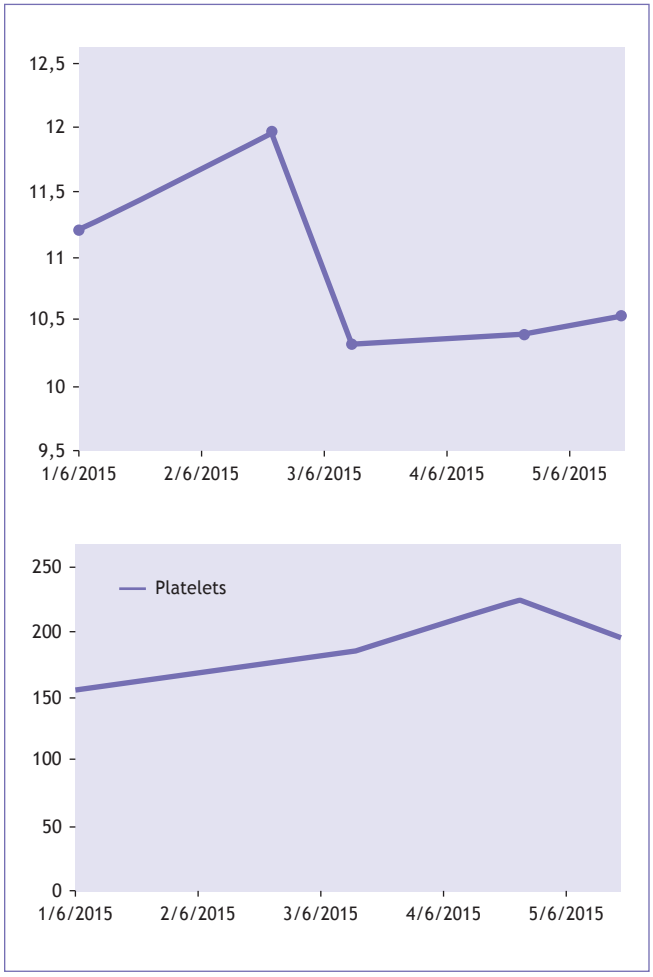

Figure 3. Hemoglobin.

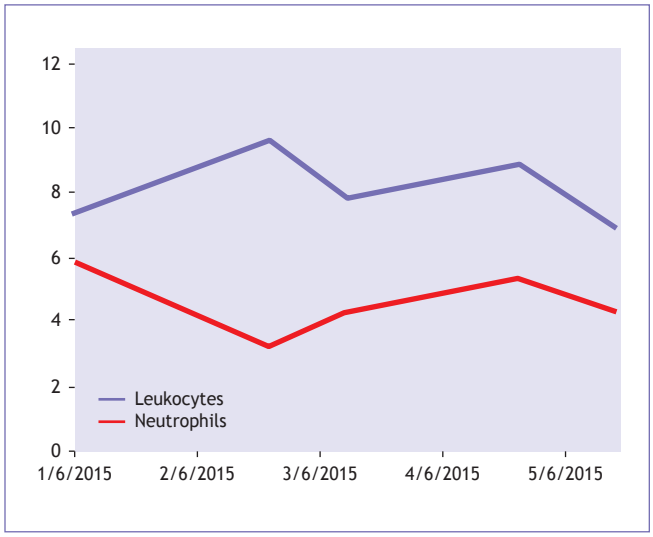

Figure 4. Leukocytes and neutrophils.

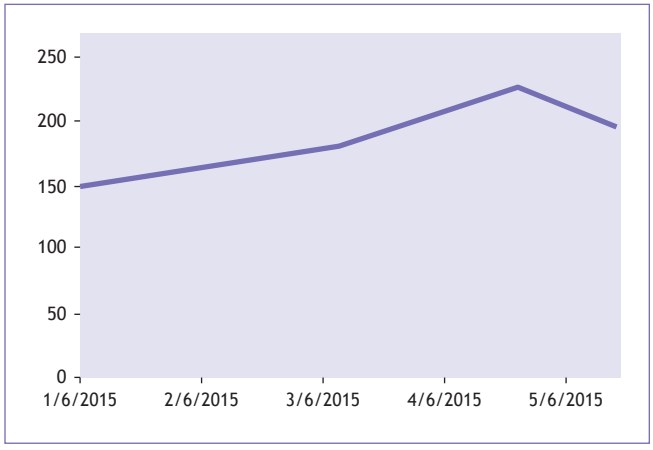

Figure 5. Platelets.

pain control, and even with a decrease in opioid medication support, most of which are clearly dose-limiting and sometimes can elicit undesirable effects that further deteriorate patient quality of life.

CONCLUSION

Treatment with radium-223 dichloride (223-Ra) is yet another alternative for patients diagnosed with castration-resistant metastatic prostate cancer with bone tumor activity and associated pain. Radium-223 dichloride (223-Ra) therapy offers an acceptable toxicity profile, with an impact on our patient's quality of life.

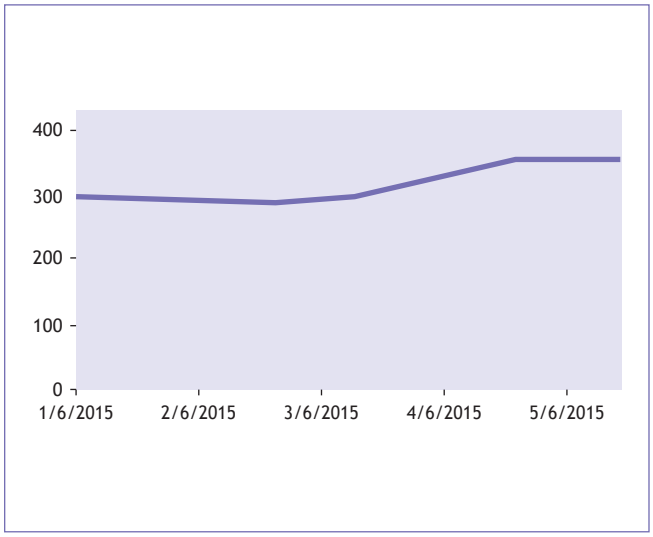

Figure 6. Prostate-specific antigen.

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