Case Report



# Use of Radium-223 Dichloride in Patients With Osteonecrosis of the Jaw Induced by Zoledronic Acid: Report of 2 Cases

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## Clinical Practice Points

- Bisphosphonates, a group of inorganic pyrophosphate analogues that prevent the loss of bone density, are commonly used in patients with bone metastases; the calcium-mimetic α-emitter radium-223 dichloride (Ra223) is a bone-targeting therapy used in patients with metastatic castration-resistant prostate cancer (mCRPC)-related bone metastases. Both treatments reduce pain and disability; Ra223 is associated with significantly improved overall survival in mCRPC.
- Patients who receive bisphosphonate therapy are at risk of developing osteonecrosis of the jaw, especially in those who do not undergo an accurate oral evaluation and sanitation before the beginning of therapy, and in patients who present with conditions that facilitate the development of this problem, such as inadequate oral and dental care, lack of prophylactic antimicrobial mouth rinsing, patient comorbidity, or suboptimal suturing after tooth extraction. Although there is possible synergism between bisphosphonates and Ra223 therapy, there is no consensus about the use of Ra223 in patients with previous/current osteonecrosis of the jaw induced by zoledronic acid.
- However, our experience suggests that Ra223 therapy might not be contraindicated in patients with osteonecrosis of the jaw induced by zoledronic acid if an appropriate multidisciplinary approach is followed, and we report 2 cases of patients with current or previous osteonecrosis of the jaw induced by zoledronic acid, who were treated with Ra223 for mCRPC-related bone metastases.
- Multidisciplinary management, including accurate clinical and radiological evaluation before beginning therapy with Ra223, together with oral sanitation and periodic controls during treatment, allowed successful administration of Ra223 while reducing side effects, with absent or minimal worsening of osteonecrosis.

*Clinical Genitourinary Cancer,* Vol. 17, No. 3, e612-7 

**Keywords:** Bisphosphonate therapy, Bone metastases, Castration-resistant prostate cancer, Jaw necrosis, Ra-223

## Introduction

Deterioration of bone health, including osteoporosis and increased fracture risk, is an acknowledged side effect of long-term androgen deprivation therapy (ADT) in patients with prostate cancer,[1-5] and many patients with castration-resistant prostate cancer (CRPC) develop painful bone metastatic disease that is not amenable to chemotherapy.[6] The standard treatment for bone metastases related to solid tumors (for example prostate cancer or breast cancer) is the intravenous use of a bisphosphonate.[6,7]

The latest European Association of Urology, European Society for Radiotherapy & Oncology, and International Society of Geriatric Oncology guidelines on the treatment of relapsing, metastatic, and CRPC recommend that the bisphosphonate, zoledronic acid, or denosumab, a humanized monoclonal antibody directed against the receptor activator of nuclear factor κB ligand, may be offered to men with CRPC and skeletal metastases, to prevent skeletal-related complications.[6] The bisphosphonates are a group of inorganic pyrophosphate analogues used as antiosteoclastic agents to inhibit bone resorption in a number of clinical situations causing bone resorption, such as breast or prostate cancer-related metastatic bone

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Submitted: Feb 8, 2019; Accepted: Mar 5, 2019; Epub: Mar 13, 2019

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https://doi.org/10.1016/j.clgc.2019.03.002

disease, osteoporosis, hypercalcemia, and Paget disease.[8] Bisphosphonates decrease bone loss and increase bone mineral density, improving the biomechanical properties of the skeleton.[8]

Intravenous zoledronic acid 4 mg has been shown to reduce skeletal-related events in patients with CRPC and bone metastases ($P = .021$ vs. placebo)[9] while decreasing urinary markers of bone resorption and reducing pain. However, a survival benefit has not been shown. The only bone-targeting therapy with a demonstrated survival benefit in patients with symptomatic metastatic CRPC (mCRPC) and bone metastases is the calcium mimetic α-emitter, radium-223 dichloride (Ra223).[10] Furthermore, Ra223 also significantly prolongs time to first symptomatic skeletal event, reduces bone pain, and improves markers of bone formation and resorption markers.[10,11] Ra223 has been approved for use as monotherapy or in combination with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of adult patients with mCRPC and symptomatic bone metastases, and no known visceral metastases, who are in progression after at least 2 previous lines of systemic therapy for mCRPC (other than LHRH analogues), or who are ineligible for any available systemic treatment for mCRPC.[12]

There are suggestions that zoledronic acid and Ra223 might work synergistically,[7,10] and the concurrent use of zoledronic acid and Ra223 is permitted, because trials and clinical practice experience suggest benefits from their use together.[7,13]

Osteonecrosis of the jaw (ONJ) is a painful and potentially disabling side effect that can appear in patients during current or previous treatment with an antiangiogenic agent or antiresorptive therapy, characterized by exposed bone or an intraoral or extraoral fistula lasting for 8 weeks or more without a history of metastatic disease or radiation therapy in this structure.[14] Bisphosphonate-related ONJ is a recognized side effect of antiresorptive therapy with bisphosphonates, more commonly after intravenous administration with zoledronic acid or pamidronate.[15]

Currently, no consensus exists regarding the use of Ra223 in patients with ONJ induced by bisphosphonates. We report our experiences of 2 patients with current or previous ONJ induced by zoledronic acid, who were treated with Ra223 for mCRPC-related bone metastases.

## Cases

### *Case 1*

A 79-year-old man was diagnosed with prostate cancer in 2008. He had bone metastases at the diagnosis, precluding surgery, and he was treated from the beginning with ADT. From May 2012 to March 2013, the patient underwent first-line chemotherapy with docetaxel; the systemic therapy was suspended because of progression of bone disease shown at 11C-choline-positron emission tomography (PET)/computed tomography (CT) scan in April 2013.

From May 2013 to February 2014 he received a second-line therapy with abiraterone acetate associated with zoledronic acid 4 mg (May 2013 to September 2014; no documents available about clinical and radiological examination before the beginning of the therapy); an 11C-choline-PET/CT (April 2014) showed bone progression disease, so the systemic therapy was stopped.

At the end of April 2014, the patient started third-line chemotherapy with cabazitaxel, which was continued until September 2014, when he underwent an 11C-choline-PET/CT scan that showed bone disease progression.

Afterward, the patient received 2 other lines of therapy: a fourth-line chemotherapy with cyclophosphamide 50 mg per day that was interrupted in November 2014 because of biochemical progression (a prostate-specific antigen [PSA] value increase from 390 ng/mL to 539 ng/mL); and a subsequent fifth-line treatment with enzalutamide, that was interrupted because of radiological and biochemical progression of disease, observed on an 11C-choline-PET/CT scan (February 2015; Figure 1A) and an increased of PSA value (767 ng/mL).

Because of clinical-instrumental progression, the patient was eligible for Ra223 therapy. Before starting the treatment, he underwent a bone scan (April 2015; Figure 2) that showed increased uptake in multiple metastatic bone lesions, and in the right jaw of uncertain origin.

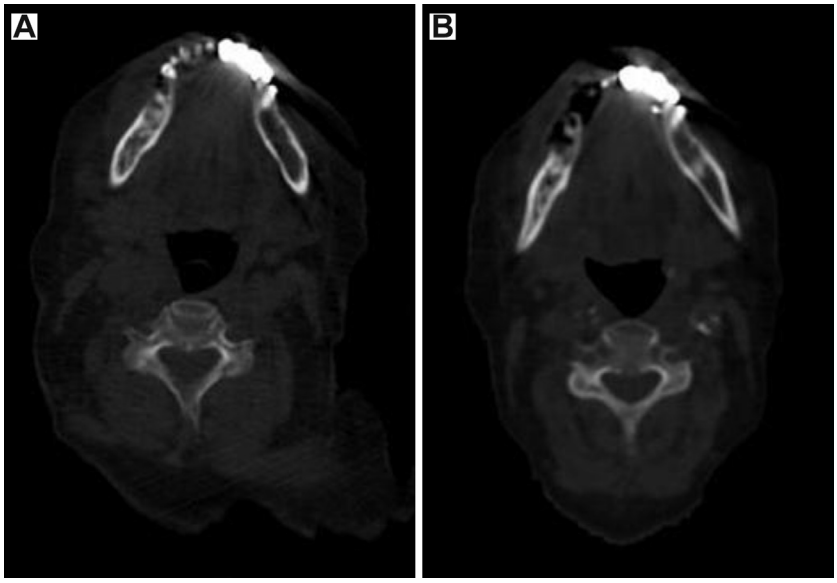
On May 2015 he received the first injection of Ra223; then subsequently started complaining about jaw pain. After a few days, he underwent a CT scan that displayed a bone-thinning area in the right jaw (at the level of first and second premolars), with periosteum thickening, more marked at the front but also present at the back. In June 2015, he received the second dose of Ra223; he subsequently reported a tenderness of the jaw. In July 2015, some days after he received the third dose of Ra223, a maxillofacial examination was performed, with the diagnosis of ONJ. However, the patient received a fourth and fifth dose of Ra223, in July 2015 and September 2015, respectively, with persistent jaw pain. The last dose of Ra223 was administered in October 2015. Further bone scans performed after all Ra223 administrations showed uptake in the jaw. However, no images are available.

One month later, a CT scan confirmed osteo-structural alterations of the right jaw with osteolytic areas, interruption of cortical bone and periosteum reparative reaction. The CT images were slightly worse than those obtained in May 2015. After a new maxillofacial examination, the patient was determined to be a candidate for surgery. In November 2015 the patient was in good general condition, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and numeric rating scale score of 0. Blood tests showed stable alkaline phosphatase values and an increase of PSA value. In November 2015, an 11C-choline-PET/CT scan (Figure 1B) showed increased bone uptake and progressive disease. A further CT scan in October 2016 showed brain metastases, with a deterioration of deambulation (ECOG performance status of 2). The patient died in 2017.

### *Case 2*

A 66-year-old man underwent radical prostatectomy for prostate cancer (Gleason score 3+2) in 1996, followed by adjuvant ADT. In September 2012, after increasing PSA levels, prostate cancer bone metastasis was detected at bone scan. The patient initially underwent ADT, before starting systemic therapy with docetaxel from February 2014 to June 2014. Because he was a candidate for bisphosphonate therapy because of the presence of bone metastases, he underwent an orthopantomography of the dental arches (Figure 3A), followed by oral sanitation. Therefore, he was treated with a monthly intravenous infusion of zoledronic acid 4 mg from March 2013 to September 2014. On September 2014 he

**Figure 1** 11C-Choline-Positron Emission Tomography/Computed Tomography Scan (Patient 1) on February 26, 2015 (A) and November 25, 2015 (B)




underwent a new orthopantomography of the dental arches, which led to a diagnosis of ONJ induced by zoledronic acid (Figure 3B).

Because of disease progression, he also started second-line therapy with abiraterone acetate and prednisone. From October 2014 to February 2015, he underwent therapy with amoxicillin-clavulanic acid, metronidazole, and clarithromycin for the ONJ. In February 2015, the patient developed a fistula; antimicrobial therapy was changed and continued until May 2015. The new CT scan of his inferior dental arches in June 2015 (Figure 4A) showed a comminuted pathologic fracture of horizontal branch of the right

**Figure 2** Bone Scan of Patient 1 in April 2015 Showing Uptake in the Right Jaw (Arrow)

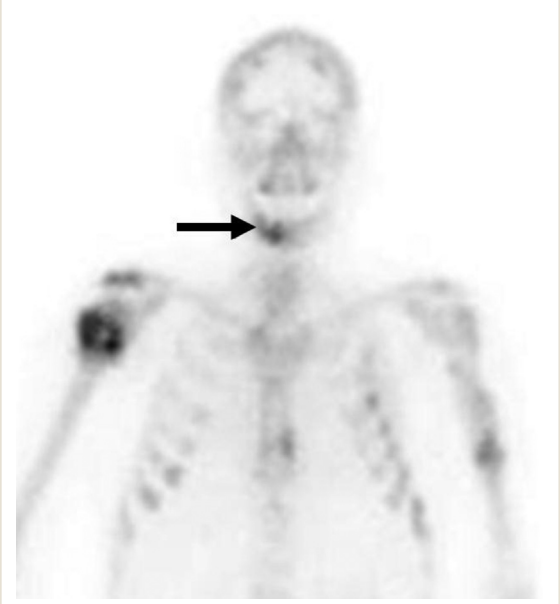


**Figure 3** Orthopantomography (Patient 2) in February 2013 (A) Before the Beginning of Therapy With Zoledronic Acid and (B) in September 2014 After the End of Therapy With Zoledronic Acid

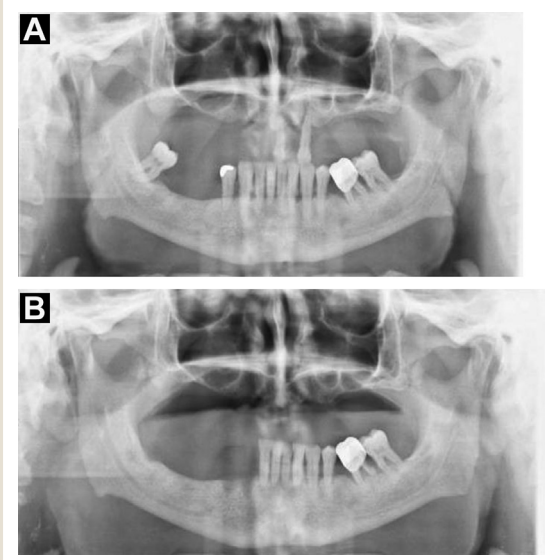
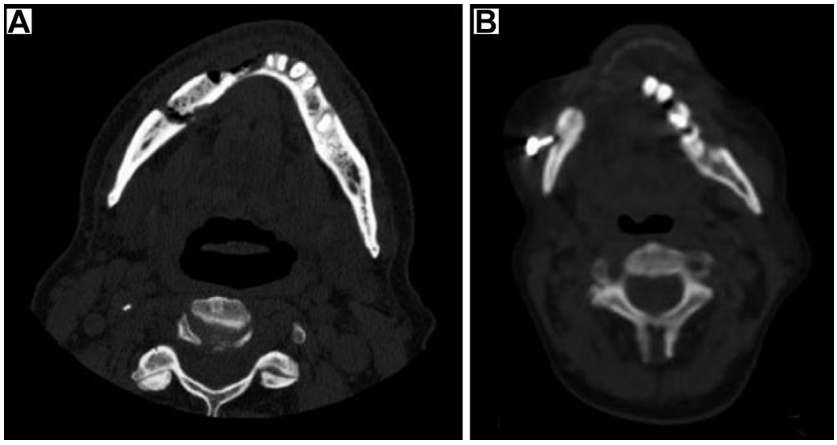


**Figure 4** Computed Tomography (CT) Scan of the Inferior Dental Arches of Patient 2 in June 2015 (A) and 11C-Choline-Positron Emission Tomography/CT Scan in July 2016 (B)




mandible. Over the following months, he was treated with other antibiotics, such as azithromycin, and analgesics, followed by 10 sessions of gaseous ozone to induce bone healing.

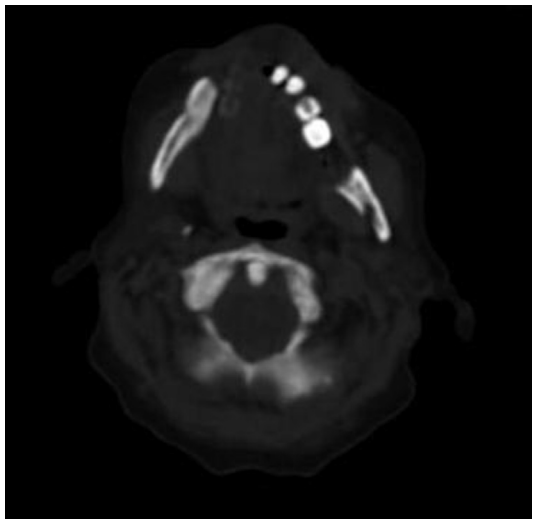
In August 2015, he underwent 2 segmental mandibular resections and reconstruction with a metallic plate. In October 2015 he again started therapy with azithromycin because of fistula recurrence. In November 2015 ONJ recurrence was observed, and the patient underwent oral surgery. In February 2016, he again had fistula recurrence, and antibiotic therapy was started and continued until February 2017. In June 2016, therapy with abiraterone acetate was stopped because of a documented radiological progression at bone scan and an increase in PSA value (27.19 ng/mL). Therefore, the patient was a candidate for Ra223 treatment of symptomatic bone metastases.

The patient underwent Ra223 treatment from August 2016 until January 2017. A post–Ra223-injection bone scan using radium223 gamma emission was performed 2 hours after every administration of Ra223, with no evidence of any significant uptake of the tracer in the mandibular region. In April 2017, the mandibular metallic plate was removed because of a fistula in the region of the right mandibular body. A bone scan in March 2017 and 11C-choline-PET/CT in April 2017 showed disease progression of the bone. At the time of writing, the patient was in follow-up with progressive disease and was a candidate for treatment with enzalutamide and cabazitaxel (Figure 5). The patient is currently in systemic therapy with enzalutamide (started on August 29, 2018), with good clinical tolerance. A radiological exam has not yet been performed.

## Discussion

Estimates of the incidence of ONJ in cancer patients with bone metastases treated with bisphosphonate or denosumab range between 1% and 2%[16] and 7% to 10%,[17] rising as high as approximately 15% in patients who have received bisphosphonates and denosumab.[17] Patients with exposed and necrotic bone might remain asymptomatic for weeks, months, or years.[18] Usually, the lesions are symptomatic due to phlogosis of surrounding tissues. ONJ can manifest with pain, mobility, and loosening of teeth, swelling, or erythema or ulceration in the mucosa of the oral cavity, halitosis, anesthesia of the associated branch of the trigeminal nerve, with decreased quality of life.[19,20] The exact pathophysiology of ONJ is unknown; in particular, it is unclear if necrosis precedes or follows infection. However, dental disease is an important risk factor for ONJ, with infection and inflammation involved in the multifactorial pathogenesis.[21] Other important factors that can speed the development of ONJ are the use of other drugs that can influence bone health, such as glucocorticoids, surgical procedures on jaws, the duration of bisphosphonate therapy, poor oral hygiene and

**Figure 5** Gallium-68 Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography Scan (Patient 2) in May 2018



other comorbidities.[14,15] ONJ is diagnosed according to clinical evidence, history, physical exam, and radiological exams. There are some recommendations to reduce the risk of ONJ, such us oral surgery before the beginning of bisphosphonate therapy if it is necessary, use of antibiotics in the case of infections, good oral hygiene, and mouth rinsing with antimicrobial products.[22]

Most patients with mCRPC and bone metastases have decreased quality of life and increased disability.[10] Ra223 is a targeted alpha emitter that emits high-energy particles of short range (<100 μm) that are localized in areas of increased bone turnover, especially in the areas where there are osteoblasts or in the presence of metastases.[23,24] This radiation might induce breaks in the DNA of malignant cells, with cytotoxic effect on malignant cells but with minor effects on normal cells.[25] Ra223 reduces pain and disability, with minimal toxicity on bone marrow,[26] and a pivotal trial has documented a survival benefit in patients with bone metastases related to prostate cancer that is resistant to chemical castration.[11]

Among the different types of therapy for the prevention and treatment of bone fragility in patients with mCRPC, it has been suggested that there might be a synergism between zoledronic acid and Ra223.[7] Whether therapy with a bone-targeting α-emitter, such as Ra223, has to be interrupted when a patient develops ONJ is unclear.[27] Furthermore, an increased risk of developing ONJ in patients treated with a bisphosphonate and Ra223 cannot be excluded.

In phase III studies in the development program of Ra223, ONJ was reported in 0.67% of patients treated with Ra223 and in 0.33% of patients who received placebo.[12] Patients who developed ONJ were all exposed to previous or concomitant bisphosphonates (eg, zoledronic acid) or chemotherapy (eg, docetaxel).

We evaluated the cases of 2 patients who developed mandibular lesions before beginning Ra223 therapy. The first patient was treated with surgery after Ra223 therapy, and a CT scan showed a slight worsening condition of the jaw lesion compared with images observed before the beginning of the therapy. The other patient was treated with surgery before and after Ra223 therapy. In both cases, adequate control before the beginning of Ra223 therapy, with oral sanitation and periodic controls during therapy, appeared to reduce the possible side effects.

In a recent case report, Herlofson et al reported findings in contrast with our experience.[28] They described a 72-year-old patient with mCRPC and bisphosphonate-related osteonecrosis of the mandible who had deterioration of ONJ after Ra223 was started. Zoledronic acid therapy was not discontinued, although the dosing interval was extended to 3 months. The patient had rapid pain relief at bone-metastatic sites from the first administration of Ra223, but the mandibular pain worsened. However, the scheduled 6 cycles of Ra223 were completed, at which point bisphosphonate therapy was also discontinued. The ONJ continued to deteriorate, and a pathologic fracture was diagnosed 6 months after Ra223, and zoledronic acid therapy ended. Although not able to clearly evaluate the effect of Ra223 in their patient, who had ONJ of >2 years' duration before Ra223 therapy was started, Herlofson et al considered that their experience should raise awareness among clinicians for the need to consider the possible cumulative effects of combined Ra223 and long-term bisphosphonate administration and suggested that Ra223 be contraindicated in patients with active ONJ.[28]

We observed that multidisciplinary management of the patients, with radiological and clinical evaluation, mandatory maxillofacial examination before the start of the therapy with experienced surgeons is the best options for these patients. Also, it is important that patients have dentists that are well aware of the management of people undergoing bisphosphonate therapies. However, if there is no evidence of fractures or risks of fracture, the patient can start the treatment with Ra223 and, after all 6 cycles of therapy are completed, should then undergo a new evaluation.

If the patient has a jaw lesion at high risk of fracture before the beginning of the treatment with Ra223, the patient should undergo surgery before the treatment and postpone the treatment with Ra223. However, if there is no evidence of fractures or risks of fracture, the patient can start treatment with Ra223 immediately, and, after all 6 cycles of therapy are completed, undergo a new maxillofacial evaluation.

In these cases, Ra223 can cause a little worsening of osteonecrosis, which is, however, negligible compared with the positive effects induced by Ra223 therapy on bone health and overall survival.

## Conclusion

Our 2 cases suggest that there are no significant contraindications to the use of bone-target therapies in patients with ONJ. Patients with bone metastases related to mCRPC can benefit from therapy with Ra223 and zoledronic acid, which might have a synergistic effect in terms of therapeutic effect and improvement in the quality of life. We observed that patients with previous or current ONJ induced by zoledronic acid, without any clinical and radiological evidence of fracture, can be treated with Ra223 with absent or minimal clinical and radiological worsening of osteonecrosis, but adequate oral sanitation before the beginning of therapy and some precautions during the treatment are necessary.

## Acknowledgments

The authors thank Ray Hill, an independent medical writer, for English language editing and medical writing support before submission. This assistance was supported by Health Publishing & Services Srl, Italy.

## Disclosures

The authors have stated that they have no conflicts of interest.

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