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Continuing Education

Radium-223 in the treatment of bone metastases in patients with castration-resistant prostate cancer. Review and procedure☆

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ABSTRACT

Bone metastatic disease is the main cause of morbidity/mortality in patients with prostate cancer, presenting frequently as bone pain, pathological fractures or spinal cord compression, which requires early and timely therapy. Although, for the moment, the therapeutic window for its use has not been definitively established, radium-223 (^{223}Ra), an alpha particle emitter, has proved to be an effective therapeutic tool, pre or post-chemotherapy, in patients with castration-resistant prostate cancer with symptomatic bone metastases and absence of visceral metastases, significantly modifying the prognosis of the disease.

It is therefore imperative to define the ideal scenarios and the correct protocol for the use of this therapy and thus offer the greatest possible clinical benefit to the patient.

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Radio-223 en el tratamiento de metástasis óseas en pacientes con cáncer de próstata resistente a la castración. Revisión de la literatura y procedimiento

Palabras clave:
Cáncer de próstata resistente a castración
Metástasis óseas
Terapia radiometabólica
^{223}Ra

RESUMEN

La enfermedad metastásica ósea es la principal causa de morbimortalidad en pacientes con cáncer de próstata, presentándose frecuentemente como dolor óseo, fracturas patológicas o compresión medular, lo que requiere la instauración de una terapia precoz y oportuna. Aunque, por el momento, no se ha establecido de manera definitiva la ventana terapéutica para su utilización, el radio-223, fármaco emisor de partículas alfa, ha demostrado ser un arma terapéutica eficaz, pre o posquimioterapia, en pacientes con cáncer de próstata resistente a la castración con metástasis óseas sintomáticas y ausencia de enfermedad visceral, modificando de manera significativa el pronóstico de la enfermedad.

Resulta, por tanto, imperativo definir los escenarios idóneos y el correcto protocolo para el empleo de esta terapia y así ofrecer el mayor beneficio clínico posible al paciente.

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Introduction

According to the International Agency for Research on Cancer of the World Health Organization, prostate cancer is the most commonly diagnosed neoplasm in Spanish males, and it is the second cause of death by cancer, with its morbimortality mainly being associated with the presence of bone metastasis.[1]

Following the diagnosis of prostate cancer the probability of the patient being disease free after local treatment can be predicted based on the prostate specific antigen (PSA) value, the Gleason score and the T stage. Three prognostic groups have been defined: low, intermediate and high risk (Table 1). All this information conditions the therapeutic approach (active surveillance, surgery, radiotherapy and hormone therapy).

Approximately 20–30% of patients with prostate cancer present advanced disease at diagnosis. On the other hand, patients who

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Table 1
Prognostic groups.

Low risk	PSA <10 ng/ml, Gleason ≤6 and T1c or T2a. >85% patients disease-free at 5 years after treatment with surgery or radiotherapy
Intermediate risk	PSA 10–20 ng/ml, Gleason 7 or T2b. 50–70% patients disease-free at 5 years after surgery or radiotherapy
High risk	PSA >20 ng/ml or Gleason ≥8 or T2c 33% patients remain disease-free after local treatment

Source: Guidelines on prostate cancer. European Association of Urology 2017.[10]

Teaching point
The main cause of morbimortality in patients with prostate cancer is bone metastasis and its complications.

present localized tumors in the initial phase may present disease relapse after intention to cure treatment, at which time the disease is advanced.[2,3]

Up to 30% of patients present bone metastases at diagnosis, being observed in 90% of patients who die from prostate cancer.[4] Bone metastases are often accompanied by pain, pathological fractures or spinal cord compression requiring the implementation of early, adequate therapy.

According to the current recommendations of the European Society of Urology, the usual initial management of advanced disease includes androgen deprivation therapy. The effectiveness of this approach is high, being initially estimated at 80%. However, the duration of the benefit is limited over time, with a median of 18–24 months after which the disease progresses in most patients to a situation denominated "resistance to castration".[5] The reason why the treatment becomes ineffective is mainly due to adaptation of the tumor cells to the hostile environment of androgen deprivation, with the cells generating testosterone and sensitizing the androgen receptors to better exploit the low androgen levels.[6]

Teaching point
Up to 30% of the patients present bone metastases at diagnosis, reaching 90% in patients who die from this disease.

Resistance to castration is defined as suppressed testosterone levels (less than 50 ng/dl) during androgen deprivation treatment, with at least one of the following: (a) biochemical progression with 3 consecutive upswings in PSA value at determined time points separated by at least one week, with 2 increases of 50% over the nadir value and with a PSA >2 ng/ml, or (b) radiological progression with the appearance of 2 or more new lesions in the bone scintigraphy (BS) or a lesion in the soft tissue according to the Response Evaluation Criteria in Solid Tumors criteria.[7–10] Resistance to castration affects up to 20% of patients with prostate cancer followed for 5 years. In addition, the median survival of patients with castration-resistant prostate cancer with bone metastases (CRPCm) is of 2–3 years.[11]

The main objectives of the management of patients with CRPCm are to palliate the pain, reduce and/or delay the appearance of bone events and reduce the associated morbimortality.

The current management of CRPCm includes systemic treatment with androgen receptor inhibitors (abiraterone, enzalutamide), immunotherapy and chemotherapy with taxanes (docetaxel and cabazitaxel).[5]

In the last decade treatments shown to increase the survival of patients with CRPCm have been developed. These therapeutic alternatives are generally less toxic than docetaxel and delay its use, leaving this drug as a treatment option in patients with an elevated symptomatic metastatic load.[12]

According to the current clinical guidelines of the European Association of Urology (EAU),[10] the National Comprehensive Cancer Network (NCCN)[7] and the Spanish Association of Urology (AEU)[6] for the management of CRPCm, radiometabolic therapy with Radium-223 (^{223}Ra) is one of the first line options recommended in symptomatic patients without visceral metastases. It has been suggested that this radiopharmaceutical increases patient survival in contrast to beta emitters such as ^{153}Sm or ^{89}Sr. Likewise, it reduces the symptomatology derived from metastatic bone disease which leads to an increase in the consumption of analgesics, reducing the quality of life and increasing disease-related costs.[13]

Teaching point
According to the guidelines of the EAU, NCCN and the AEU for the management of CRPCm*, radiometabolic therapy with ^{223}Ra is one of the recommended first line therapeutic options in symptomatic patients without visceral metastases.*

Radiopharmaceutical: ^{223}Ra-dichloride

Healthy bone tissue surrounding the metastasis is often characterized by accelerated remodeling which makes this an ideal target for bone-targeted radiopharmaceuticals.

As a radium isotope, ^{223}Ra is a chemical element which belongs to the alkaline earth metals group (group 2 in the periodic table). Likewise, it is an alpha particle emitter with a half-life of 11.4 days. ^{223}Ra is a calciomimetic agent which deposits in areas with increased bone remodeling such as bone metastases, forming complexes with the mineral hydroxyapatite (the inorganic matrix of bone).

The high transference of linear alpha energy generated during its decay (80 keV/micrometer) leads to the rupture of the double DNA chain in the adjacent tumor cells, with a subsequent a potent cytotoxic effect.[14] Likewise, the radium has an effect on the tumoral microenvironment, including osteoblasts and osteoclasts, thereby contributing to its efficacy *in vivo*.

The penetration of the alpha particles of ^{223}Ra into the soft tissue is less than 0.1 mm (approximately the diameter of 10 cells), determining a highly localized effect and thereby mimimizing harmful effects to the surrounding healthy tissue.

The fraction of energy emitted by ^{223}Ra as alpha particles is 95.3% (energy range of 5.7.5 MeV). It also emits a small fraction of beta particles of 3.6% (average energy of 0.445 MeV and 0.492 MeV) as well as minimum gamma radiation of 1.1% (energy range of 0.01–1.27 MeV). The energy of total decay is 28 MeV.[15]

Teaching point
^{223}Ra is an alpha emitter with a range of soft tissue penetration of less than 0.1 mm, thereby minimizing damage to surrounding healthy tissue.

Fifteen minutes after its administration, approximately 20% of the dose can be found in the blood and activity begins to appear in the bone and intestine. The main via of excretion is intestinal.[16]

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