Actas Urol Esp. 2018;42(4):227–237

Actas Urológicas Españolas

www.elsevier.es/actasuro

REVIEW ARTICLE

Radium-223 in the therapeutic sequence of metastatic castration-resistant prostate cancer☆

M. Unda-Urzaiz[a,b,*], R. Sousa-Campo[c], A. Rodríguez-Antolín[d], C. Silva-Marins[e], A. Juárez-Soto[f], B. Miñana-López[g], A. Figueiredo-de Castro[h], J.M. Cozar-Olmos[i]

[a] *Hospital Universitario Basurto, Bilbao, Spain*
[b] *CIBERONC, Madrid, Spain*
[c] *Hospital Beatriz Angelo, Loures, Portugal*
[d] *Hospital Universitario 12 de Octubre, Madrid, Spain*
[e] *Centro Hospitalar S. Joao, Porto, Portugal*
[f] *Hospital de Jerez, Cádiz, Spain*
[g] *Hospital Universitario Morales Meseguer, Murcia, Spain*
[h] *Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal*
[i] *Complejo Hospitalario Universitario de Granada, Madrid, Granada, Spain*

Received 3 May 2017; accepted 22 May 2017
Available online 31 March 2018

KEYWORDS
Prostate cancer;
Castration-resistant prostate cancer with bone metastases;
Treatment;
Metastases;
Radium-223

Abstract
Context: Radium-223 is an α-particle transmitter with specific action on bone metastases. The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study showed that radium-223 extended overall survival and delayed the onset of bone events in patients with symptomatic castration-resistant prostate cancer with bone metastases (mCRPC) and without visceral metastases, with a good safety profile.
Objective: To review the new scientific evidence on radium-223 based on prespecified and post hoc analyses of the ALSYMPCA study and on early-access programs after the publication of the ALSYMPCA study, thereby providing new data on the management of patients with mCRPC.
Acquisition of evidence: We searched for evidence on PubMed and in the abstracts of international urology and oncology congresses, as well as ongoing clinical trials (ClinicalTrials.gov).
Synthesis of the evidence: The results of the reviewed studies offer promising results that will broaden the therapeutic benefits of radium-223 to patients with mild symptoms and those with no symptoms. The results also provide preliminary evidence on the benefit of radium-223 treatment after the failure of docetaxel, enzalutamide or abiraterone or the combination of radium-223 with these agents or other therapeutic agents such as bone-targeted agents and immunotherapy.

☆ Please cite this article as: Unda-Urzaiz M, Sousa-Campo R, Rodríguez-Antolín A, Silva-Marins C, Juárez-Soto A, Miñana-López B, et al. Radio-223 en la secuencia terapéutica del cáncer de próstata resistente a la castración metastásico. Actas Urol Esp. 2018;42:227–237.

* Corresponding author.
E-mail address: jesusmiguel.undaurzaiz@osakidetza.eus (M. Unda-Urzaiz).

Conclusion: Radium-223 can be a treatment option for patients with mild symptoms and can provide a therapeutic benefit after failure of currently available treatments or in combination with these treatments. This evidence should be corroborated in clinical trials before being added to clinical practice.

PALABRAS CLAVE
Cáncer de próstata;
Cáncer de próstata resistente a la castración con metástasis óseas;
Tratamiento;
Metástasis;
Radio-223

Radio-223 en la secuencia terapéutica del cáncer de próstata resistente a la castración metastásico

Resumen

Contexto: El radio-223 es un emisor de partículas α con acción específica sobre las metástasis óseas. El estudio ALSYMPCA demostró que el radio-223 prolonga la supervivencia global y retrasa la aparición de eventos óseos en pacientes con cáncer de próstata resistente a la castración con metástasis óseas (CPRCm) sintomáticas y sin metástasis viscerales, con un buen perfil de seguridad.

Objetivo: Revisión de la nueva evidencia científica de radio-223 a partir de análisis preespecificados y *post hoc* del estudio ALSYMPCA y de programas de acceso precoz posteriores a la publicación del estudio ALSYMPCA, con el fin de aportar nuevos datos en el manejo de pacientes con CPRCm.

Adquisición de la evidencia: Búsqueda de evidencia en PubMed y en *abstracts* de congresos de urología y oncología internacionales, así como ensayos clínicos en marcha (ClinicalTrials.gov).

Síntesis de la evidencia: Los resultados de los estudios revisados ofrecen resultados prometedores que ampliarían el beneficio terapéutico de radio-223 a pacientes con síntomas leves e incluso asintomáticos. También aportan evidencia preliminar acerca del beneficio del tratamiento con radio-223 tras el fracaso a docetaxel o a enzalutamida o abiraterona o la combinación de radio-223 con estos u otros agentes terapéuticos como los dirigidos al hueso o inmunoterapia.

Conclusión: El radio-223 puede ser una opción de tratamiento en pacientes con síntomas leves y aportar un beneficio terapéutico tras el fracaso a tratamientos disponibles en la actualidad o en combinación con estos. Esta evidencia ha de ser corroborada en ensayos clínicos antes de ser incorporados en la práctica clínica.

Context

In the last decade, we have witnessed important advances in the development of treatments that have proved to increase the survival of patients with metastatic castration-resistant prostate cancer (mCRPC). These therapeutic alternatives, usually less toxic than docetaxel, allow to delay its use, which is maintained as a treatment option in patients with a high symptomatic metastatic load.

The optimal management of mCRPC in the current therapeutic scenario requires determining the appropriate sequence of the treatments available in specific patients. The absence of studies comparing these treatments and of biomarkers that can identify patients who could benefit from one treatment after failure to another, greatly hinders the establishment of therapeutic sequences. Another aspect still to be explored is which combinations of treatments could be the most beneficial in each type of patient.

Radium-223 is an α-particle emitter with specific action on bone metastases,[1] the main cause of death, morbidity, and reduction in the quality of life of patients with mCRPC.[2,3] Radium-223 was approved in 2013 for the treatment of patients with symptomatic mCRPC and with no known visceral metastases based on the results of the phase III, double-blind, multicenter, randomized ALSYMPCA study.[4] This study, carried out in 921 patients, showed that treatment with radium-223 dichloride was associated with a 30% reduction in the risk of death compared to placebo (Hazard ratio [HR] = 0.7; 95% confidence interval [CI]: 0.58–0.83; $p < 0.001$), prolonging overall survival in 3.6 months. Radium-223 dichloride also showed a benefit in other secondary efficacy variables, such as the risk of suffering a symptomatic bone event (HR = 0.66; 95% CI: 0.52–0.83 vs. placebo) or the time until the appearance of new events (15.9 vs. 9.8 months with placebo, $p < 0.001$). In this study, treatment with radio-223 dichloride was associated with a low myelosuppression and a lower rate of adverse events compared to placebo in the 12 weeks after the last injection,[4] a favorable safety profile that was maintained even up to 3 years after completion of the treatment.[5] The most recent treatment guidelines of the CRPC (2016) of the European Association of Urology (EAU),[6] of the National Comprehensive Cancer Network (NCCN)[7] and, in our country, the Protocol of action in patients with CRPC of the Spanish Association of Urology (AEU),[8] recommend treatment in 1st line with radium-223 of patients