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Editorial
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Radium-223 Therapy in the Set of Patients Affected by Bone Metastases

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Editorial

Bone-seeking radiopharmaceuticals permit targeted radiation treatment of the metastatic bone disease. Among bone-seeking radiopharmaceuticals, The beta- (β-) emitting Samarium-153-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP) has been used for palliation of pain from bone metastases with interesting results [1]: namely, a trial has found that patients who received ^{153}Sm experienced significant improvement in pain scores compared with those receiving placebo [2]. However, even if these agents allowed to reach palliative benefits, they showed no impact on survival [1,3]. Additionally, because of tissue penetration and track lengths, surrounding tissues can be damaged resulting in important adverse effects, in particular bone marrow toxicity. The new bone-seeking Radium-223 dichloride (^{223}Ra) is an alpha (α) emitting and calcium mimetic which selectively targets increased areas of turnover in bone metastases: it has demonstrated to reach not only bone pain relief but also improved survival in the set of patients affected by metastatic castration-resistant prostate cancer (mCRPC), receiving FDA approval in 2013.

^{223}Ra has a half-life of 11.4 days and decays to ^{207}Pb with the emission of four α-particles: these are heavy and highly ionizing particles which are able to deposit a large amount of energy over a short range in tissue (50–100 µm) due to the high linear energy transfer (100 keV/µm), rendering α-radiation more cytotoxic than that of β-emitters, but at the same time sparing the normal structures [1,3]. The penetration of alpha particles is approximately 40–100 µm (2–10 tumor cell diameters), while ^{89}Sr and ^{153}Sm show a tissue penetration of approximately 2.4 and 0.6 mm, respectively [4]. Alpha emission induces predominantly non-repairable DNA double-strand breaks in cells, with respect to DNA single breaks of other bone-seeking radiopharmaceuticals, allowing the antitumor peculiar features of ^{223}Ra [5].

After intravenous injection, ^{223}Ra is rapidly cleared from the blood: in fact, after 15 minutes, only about 20% of the injected activity is present in the blood. At 4 and 24 hours, about 4% and 1% of the injected activity remains in the blood; oppositely, the activity in bone at 4 hours ranges between 44 and 77%. Fecal excretion is the major way of elimination and only 5% is excreted through the urine.

^{223}Ra is indicated for the treatment of adult men with CRPC with symptomatic bone metastases and without known visceral metastases. ^{223}Ra is administered by intravenous injection at the therapeutic activity of 50 kBq/kg body weight, at four week intervals, for a total of six injections.

The ALSYMPCA trial was a randomized, double blind, phase III study that compared six injections of ^{223}Ra against placebo in men with CRPC and bone metastases who had received, were not eligible to receive, or had declined docetaxel chemotherapy [8]. In their study, Parker et al. [8] evaluated 921 patients with or without previous docetaxel administration, in a 2:1 ratio, to receive ^{223}Ra or matching placebo. All patients received the best standard of care. The primary end point was overall survival. The main secondary efficacy end points were the time to an increase in the total alkaline phosphatase level, total alkaline phosphatase response and normalization of the total alkaline phosphatase, the time to the first Symptomatic Skeletal Event (SSE) and the time to an increase in the Prostatic Specific Antigen (PSA) level. ^{223}Ra showed survival benefit and significantly improved overall survival. Evaluation of all main secondary efficacy end points also showed a benefit of ^{233}Ra with respect to placebo. Detailed analyses of SSEs were evaluated subsequently and the administration of ^{223}Ra demonstrated to prolong significantly the time to first SSE and reduce the need of external beam radiation therapy for bone pain and spinal cord compression, regardless of prior docetaxel therapy, baseline ALP level, or use of bisphosphonates [9]. The safety profile of ^{223}Ra

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can be obtained from data of more than 1000 patients treated in phase II and III studies [8,10,11].

^{223}Ra was well tolerated and associated with few adverse events. Although the difference was not significant, a slightly higher rate of diarrhea (25% v 15%) was seen with radium with respect to placebo. Other reported side effects were nausea, vomiting, peripheral edema, and hematologic abnormalities (mainly anemia, leukopenia, thrombocytopenia, neutropenia). An improvement in quality of life was also observed for ^{223}Ra with respect to placebo [8].

Unfortunately, there are no established data to support ^{223}Ra use in combination with other agents. Additional studies that combine ^{223}Ra with docetaxel, abiraterone, or enzalutamide are ongoing. Denosumab and zoledronic acid may not compete with ^{223}Ra for uptake in the bone and therefore may be used concomitantly [12-14].

Further studies could evaluate the efficacy of ^{223}Ra in patients with bone metastases from other tumor types and trials evaluating breast, thyroid and renal cancers metastatic to bone are ongoing. Recently, Takalkar et al. [15] reported a case of breast cancer with bone metastases and without visceral metastases who underwent surgery, chemotherapy, radiation and hormonal therapy, but still had extensive symptomatic secondary bone disease. She received ^{223}Ra, reporting an excellent response with significant pain relief and tumor markers decrease. Follow-up ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) and ^{18}F-sodium fluoride bone PET/CT scans confirmed improvement in the lesions.

PET/CT imaging (with choline or other radiotracers) can have an important impact on the management of mCRPC. Recently, Ahmadzadehfar H et al. [16] retrospectively evaluated the utility of ^{68}Ga-PSMA-11 PET for the management of ^{223}Ra therapy in patients affected by metastatic prostate cancer. They observed a significant correlation between the PSA changes and the therapeutic response according to follow-up PSMA-PET. They concluded that, considering PSMA-PET as the gatekeeper, radionuclide therapy with ^{223}Ra may be more effective and have more success regarding changes in the PSA. These new imaging modalities could certainly lead to more tailored and personalized therapy, especially in the set of patients with reduced PSA levels but with progression of disease on imaging. Namely, these patients may be conducted to a second line of systemic therapy, to radiotherapy on the non-responding lesions, or even to ^{223}Ra therapy.

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