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Review Article

Optimal usage of radium-223 in metastatic castration-resistant prostate cancer

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Abstract Radium-223 is a first-in-class α-emitting radiopharmaceutical that targets bone metastases associated with metastatic castration-resistant prostate cancer (mCRPC). In the pivotal phase III trial ALSYMPCA, radium-223 significantly increased overall survival (OS), compared with placebo (median 14.9 vs 11.3 months; hazard ratio 0.70; 95% CI 0.58–0.83; $p < 0.001$), in patients with mCRPC and symptomatic bone metastases—with a comparable safety profile.

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prostate cancer;
Osteoblasts

To optimize treatment outcomes, selection of appropriate patients is important. As well as osteoblastic bone metastases, mCRPC patients should be well enough to receive six doses of radium-223 as this treatment duration has been shown to greatly improve OS outcomes compared with administration of four or fewer doses. Additionally, alkaline phosphatase and lactate dehydrogenase are emerging as important biomarkers during radium-223 treatment. Optimal concomitant standard-of-care therapies (such as abiraterone or enzalutamide) to be administered with radium-223 have yet to be defined as does the most efficacious dose and duration of radium-223 treatment.

In conclusion, radium-223 is an important addition to the mCRPC treatment landscape and marks a paradigm shift in the treatment of bone metastases.

Introduction

Stage IV prostate cancer is characterized by metastatic spread to bone, which occurs in up to 90% of patients.[1] Bone metastases are a substantial source of morbidity, in particular bone pain and skeletal-related events (SREs), and are a major cause of mortality, with the extent of osseous involvement being correlated with patient survival.[2,3] The formation of bone metastases associated with prostate cancer involves detachment of prostate cancer cells from the primary tumor and migration into the blood or lymph vessels, extravasation into the bone marrow and initiation of interaction with cells within the microenvironment as well as with osteoblasts within the bony matrix. Within the bone environment, osteoblasts promote growth of prostate cancer cells and osteoblast activity and proliferation is increased. This results in the formation of fragile abnormal osteoblastic (bone-forming) metastases (woven bone) and it is these metastases that radium-223 targets.[4,5]

Radium-223

Approval

Radium-223 [Xofigo®; Bayer, Whippany, NJ], a first-in-class α-particle-emitting radiopharmaceutical, was approved in May 2013 in the USA for the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients with symptomatic bone metastases and no known visceral involvement.[6] Approval soon followed in Europe (November 2013) and was recently granted in Taiwan (June 2015).[7,8] Radium-223 was the fifth agent to be approved for mCRPC since 2010 and is the only mCRPC therapy that extends overall survival (OS) by exclusively targeting bone metastases (See Table 1).

Mechanism of action

Radium belongs to the same group in the periodic table as calcium, the alkaline earth metal group, and therefore possesses calcium-mimetic properties. Consequently, following intravenous administration, radium-223 disperses preferentially to bone, in particular areas of new bone formation. Radium-223 then forms a complex with hydroxyapatite, a major constituent of the bone matrix, and is incorporated into the bony matrix (See Figure 1).[9] Radium-223 decays over six steps into lead-207, releasing four α particles and two β particles for each atom, with the almost all of the energy (95.3%) being emitted by the α particles.[10]

Compared with β-particles, α particles are larger, comprising two protons and two neutrons, and the resulting radiation, known as high-linear energy-transfer radiation, has a shallower penetration depth (40 μm–100 μm) but delivers a more intense and highly localized radiation dose.[9] One advantage of this type of radiation is that it mainly induces lethal double-stranded DNA breaks whereas radiation from older β-emitting radiopharmaceuticals such as strontium-89 and samarium-153 tends to induce single-stranded DNA breaks, which are more easily repaired.[11,12] Another advantage is minimal damage to surrounding soft tissue, including bone marrow. As a result, myelosuppression associated with radium-223 is mild and transient, and no dose-limiting hematological toxicities were observed in early-phase clinical trials.[13–15] This is in contrast with radiation from β-emitting radiopharmaceuticals, which can result in severe myelosuppression.[16,17]

Radium-223 in clinical trials

Early-phase clinical trials

In a first-in-human phase I trial conducted in patients with breast or prostate cancer and bone metastases, radium-223 demonstrated a favorable safety profile at single doses ranging from 46 to 250 kBq/kg.[13] Subsequent phase II trials in patients with mCRPC and bone metastases also showed good tolerability, as well as improvements in time to first SRE, time to prostate specific antigen (PSA) progression, bone alkaline phosphatase (bone ALP) levels, pain outcomes, and a trend towards improved OS was observed in one study.[18–20]

Results from a two-year follow-up of a phase II placebo-controlled trial that evaluated four doses of radium-223 (50 kBq/kg every four weeks) further suggested that radium-223 might improve survival. Median OS was 65 weeks in the radium-223 arm and 46 weeks in the placebo

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