Castration-resistant prostate osseous metastases can be challenging to treat. There is a new era of clinical advancement with the Food and Drug Administration approval of radium-223 for use in these patients. Radium-223 is the only clinically used therapeutic radiopharmaceutical that emits alpha particles, making it extremely safe for therapeutic purposes for the patient as well as close contacts. This review discusses radium-223’s mechanism of action, pharmacokinetics, indications, and safety profile, as well as findings of concluded clinical trials.

Prostate cancer is the most common malignancy in men in the United States and Europe and is the third leading cause of cancer-related death in men. Nearly 14% of men will be diagnosed with prostate cancer at some point in their life. In 2014, prostate cancer accounted for 24% and 27% of all new male cancer cases in Canada and the US, respectively (1, 2). About 85% of cases present with localized disease, but nearly 40% progress to metastatic cancer. Bone metastases can be present in more than 90% of patients with advanced prostate cancer, leading to significant morbidity and mortality (3, 4). Patients are initially treated with either chemical or surgical androgen deprivation therapies. However, there is inevitable progression to castration-resistant prostate cancer (CRPC), which develops despite castration levels of testosterone. When this disease presents with detectable macroscopic metastases, patients are considered to have metastatic CRPC (mCRPC), which has a poor prognosis and an expected survival of 18 to 20 months. Complications include significant bone pain, skeletal-related complications such as pathologic fractures, malignant hypercalcemia, bone marrow suppression, and spinal cord compression (5–7).

MECHANISM OF ACTION AND RADIOBIOLOGY OF RADIUM-223

Radium 223 dichloride (radium-223), an alpha-emitting radionuclide, was the first agent of its kind to be approved by the US Food and Drug Administration (FDA) following the 2013 ALSYMPCA trial for treatment of bone pain in patients with mCRPC. It has a half-life of 11.4 days. Radium-223 decays to 4 alpha particles for every atom. It is a calcium mimic that binds to hydroxypatite and induces double-stranded breaks in DNA (8, 9). The short range of particles emitted and the high linear energy transfer lead to intensive killing in a small tissue volume, thereby sparing more of the normal bone (10). Its effect is a combination of decreased pathologic bone turnover and tumor irradiation (11). Other bone-seeking radiopharmaceuticals like the beta-emitting strontium-89 and samarium-153 ethylenediamine tetramethylene phosphonic acid have also been used for bone therapy, but have not been found to increase overall survival (12, 13).

PHARMACOKINETICS

Radium-223 is taken up primarily by bone tissue and bone metastases rapidly after intravenous injection. Most of the agent (95%) is eliminated from the body by the fecal route; ~5% is excreted in urine. Therefore, any changes in intestinal transit can affect the elimination rate of radium-223. It is not metabolized by the liver (1).

SAFETY PROFILE

Data collected from more than 1000 patients in phase 2 and 3 trials comprise the basis for the drug’s safety profile (1). Data from a 3-year follow-up study have also shown that radium-223 therapy is both safe and well tolerated (14). However, combining radium-223 with chemotherapy is not recommended because of potential additive effects of bone marrow suppression. The most common adverse reactions observed were nausea, vomiting, diarrhea, and peripheral edema. Radium-223 can cause hematologic abnormalities like anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Anemia and thrombocytopenia were the most common reasons for discontinuation of the drug (15). Concurrent administration of
radium-223 with antiandrogen therapies such as enzalutamide or abiraterone is well tolerated (16).

**CLINICAL TRIALS**

The first-in-human trial was conducted in 2000 by Nilsson et al to study the safety and tolerability of radium-223. They concluded that radium-223 was tolerated well at therapeutic dosages, with pain relief and positive effects on serum markers as indications of its anticancer effect (17).

The BC1-02 was the second clinical study conducted in 2002. It was a randomized double-blind placebo-controlled multicenter phase 2 trial. This study showed that adverse events, including serious adverse events, were more common when patients were not treated with radium-223 (18). Two additional randomized, double-blinded phase 2 trials were conducted (BC1-03 and BC1-04) before starting the ALSYMPCA (Alpharadin in SYMptomatic Prostate Cancer) trial (19). The ALSYMPCA trial, which concluded in 2013, was a randomized, double-blind, multinational phase 3 trial. Testing a total of six injections of radium-223 per patient, the trial showed a significant improvement in overall survival rates and improved quality of life with treatment (20). The trial also showed delayed development of skeletal complications and a significant reduction of the risks of spinal cord compression and requirement for external beam radiation therapy (4). There were no clinically significant differences in hematologic adverse events with radium-223 treatment (4).

**INDICATIONS**

Radium-223 is indicated for use in the management of adult men with CRPC with symptomatic metastases to the bone and no other visceral metastases. It is given intravenously over 1 minute at 50 kBq/kg body weight every 4 weeks for a total of 6 injections. There is no need for dose adjustment in the elderly and those with renal or hepatic impairment (1). The main adverse event to look for after administration is bone marrow suppression. This requires a baseline hematological investigation, with follow-up studies before and after each dose (1). Interval investigation of hematologic abnormalities is typically done 1 week before each injection. The gap between each injection can be extended up to 8 weeks if laboratory values are abnormal, to allow for repeat evaluation. If at 8 weeks the patient continues to experience a hematologic abnormality, treatment is halted.

**DISCUSSION**

Current treatment guidelines for mCRPC include hormonal agents like abiraterone acetate and enzalutamide, the chemotherapeutic agent cabazitaxel, the immunotherapeutic agent sipuleucel-T, and radium-223 (19, 21).

Radium-223 has been studied in comparison with other treatment modalities (19). Other bone-targeted therapies, apart from radiopharmaceuticals, include osteoclast inhibitors like the bisphosphonate zoledronic acid and the RANKL inhibitor denosumab. However, neither showed improvement in disease progression or overall survival (2). According to Hoskin et al, radium-223 is well tolerated and effective in patients with symptomatic mCRPC, irrespective of previous docetaxel use (22). Also, chemotherapy following treatment with radium-223 is feasible and appears well tolerated, irrespective of prior docetaxel use (23). According to Finkelstein et al, the hematologic safety profile of radium-223 with concomitant EBRT was similar to that without concomitant EBRT. Therefore, EBRT can be used additionally with radium-223 for pain palliation (24). There were no statistical differences when the treatment was combined with bisphosphonates (4). Trials studying the feasibility and efficacy of combining radium-223 with other endocrine modalities are currently ongoing (19).

**CONCLUSION**

Radium-223 is a first-of-its-kind FDA-approved bone-targeting therapeutic agent that positively impacts overall survival, delay in symptomatic skeletal events, and quality of life. Various clinical trials and their post hoc analyses have proved its safety and efficacy in treating mCRPC with bone metastases. However, its role in managing micro bone metastases in early mCRPC is still ambiguous. Ongoing research and trials are attempting to address various combination therapies and treatment sequencing strategies. They are also exploring use of radium-223 for treatment of other cancers like breast cancer, renal cancer metastases to bone, and thyroid cancer (1, 19) with osseous metastasis.


24. Finkelstein SE, Michalski JM, O’Sullivan JM, Parker C, Garcia-Vargas JE, Sartor AO. External beam radiation therapy (EBRT) use and safety with radium-223 dichloride (Ra-223) in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) from the ALSYMPCA trial. J Clin Oncol 2015;33(7 Suppl):182.