# Chapter 10
# Radiopharmaceuticals for Prostate Cancer


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## General Considerations for Radiopharmaceuticals

Only physicians and facilities with experience and licensing to handle and use these medications should administer radiopharmaceuticals. The American College of Radiology has a practice standard for the administration of radiopharmaceuticals, but state and local regulations must be followed as well. Candidates for intervention with radiopharmaceuticals should be assessed directly by the physician who will be overseeing treatment. Informed consent should be obtained before patients undergo treatment with radiopharmaceuticals. Physicians should have detailed discussions with patients about the possible side effects, logistics, and alternative treatments.

## Strontium-89

Strontium-89 is a beta-emitting radioactive isotope with a half-life of 50.5 days. It was the first radiopharmaceutical approved by the FDA for the treatment of pain related to known bony metastatic disease [5].

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## *Mechanism of Action*

Strontium-89 acts in a way similar to calcium in the body and is deposited in bone with increased uptake in blastic lesions [5]. Strontium-89 then delivers radiation to the tissue by emitting beta particles. The beta particles have a maximum range of emission of 8 mm with a maximum energy of 1.463 MeV, so the effect on normal tissue is minimized [5].

## *Pharmacokinetics*

After administration, strontium-89 is cleared from the bloodstream quickly and taken up by primarily bone tissue [5]. Since strontium-89 acts like calcium in the body, it is taken up in much higher amounts in blastic metastatic bone lesions where the rate of osteogenesis is higher [5]. Strontium-89 has a half-life of 50.5 days; therefore, there is more exposure of both diseased and normal bone to radiation over time compared to other isotopes [5]. Strontium-89 remains in metastatic lesions for longer time periods than normal bone and over half of the injected doses is deposited in the bones after treatment [5]. Excretion is two-thirds renal and one-third fecal, and the urinary excretion is highest in the first 2 days after treatment [5].

## *Dosage and Administration*

Strontium-89 is given over IV push infusion over 1–2 minutes at a dose of 148 MBq, 4 mCi, or 1.5–2.2 MBq/kg, 40–60 μCi/kg body weight [5]. Repeat infusion can be considered but should only be done depending on how the patient tolerates the first infusion [5]. Infusions should not be given less than 90 days apart. Though there is no clear recommended alternative dosing for patients with renal insufficiency, caution should be taken in patients with decreased renal function given the high percentage of renal excretion [9].

## *Adverse Reactions and Warnings*

White blood cells and platelets are most often affected by strontium-89, and bone marrow effects are often seen. The prolonged half-life relative to radium-223 or samarium-153 has been associated with an extended delay in count recovery and, in some patients, a lack of full recovery. A complete blood count should be checked prior to administration and then should be checked every 2 weeks after injection [5]. Per the manufacturer's prescribing guidelines, caution should be used in patients

with a platelet count below 60,000 and a white blood cell count below 2400 [5]. However, more conservative baseline parameters such as platelet counts of at least 100,000 and WBC counts of at least 3000 at baseline should be considered. Many patients experience a 30% or greater decrease in platelet levels with strontium-89 [5]. Generally, the blood count nadir was found to be 12–16 weeks after infusion, and it may take up to 6 months for blood cell counts to recover after treatment [9]. Some patients have noticed an increase in bone pain within 36–72 hours after infusion, which usually resolves with analgesics [5]. Flushing has been seen in patients when there is a rapid administration of the drug [9]. Other reported adverse reactions that are less common include chills, fever, hot flashes, and septicemia [9]. Strontium-89, like all radiopharmaceuticals, may cause fetal harm and should not be given to pregnant women [5]. Patients should be advised to avoid pregnancy. There are no known contraindications, but caution should be used in any patients with underlying bone marrow suppression [5]. There are no known significant drug interactions.

## *Safety Precautions and Patient Education*

Strontium-89 should only be given in facilities and by physicians who are trained in using radiopharmaceuticals. The strontium-89 should be stored in its original lead container or have adequate radiation shielding during handling [9]. Given the renal excretion, patients who are incontinent of urine should be catheterized to avoid contamination and exposures [5]. Patients should be instructed to flush the toilet multiple times after use and practice good hand washing. Typical onset of pain relief is 7–20 days after infusion [5].

## *Background and Clinical Considerations*

Strontium-89 has been evaluated in several clinical trials. In a small placebo-controlled trial of patients with castrate-resistant metastatic prostate cancer with painful bone metastases, patients were randomly assigned to receive either strontium-89 or placebo. After 5 weeks, patients were reassessed and a second injection could be given if the patient was still having pain. The patients' pain was evaluated with a scoring system and categorized as deteriorated, no significant change, some improvement, substantial improvement, or dramatic improvement [2]. The final analysis showed that only patients in the strontium-89 arm had full pain relief, and strontium-89 significantly reduced pain scores in more patients than those treated with placebo ($p < 0.01$) [2]. Strontium-89 was also evaluated in a phase III, randomized, placebo-controlled clinical trial to associate its effect as an adjunct treatment in patients with metastatic prostate cancer treated with external beam radiation therapy. A total of 126 patients with

castrate-resistant prostate cancer were treated with local radiation therapy plus strontium-89 or placebo as a single injection and then followed with tumor markers and pain assessments [19]. Patients in the strontium-89 arm had a greater decrease in the amount of pain medication they were taking, decreased new sites of pain (1.213 in the placebo arm vs 0.587 in the strontium-89 arm, $p < 0.002$), and improved quality-of-life indicators in the strontium-89 arm with decreased pain and improved physical activity found to be statistically significant ($p < 0.05$) [19].

Strontium-89 has been evaluated with chemotherapy in several trials, as well. In a small, randomized, phase II clinical trial, 103 patients with metastatic castrate-resistant prostate cancer and either increasing cancer-related symptoms or rising PSA were treated with induction chemotherapy with doxorubicin, ketoconazole, vinblastine, and estramustine [11]. Patients with stable or improved disease after two to three cycles of chemotherapy were then randomized to receive 6 weeks of doxorubicin with or without one dose of strontium-89 [11]. One limitation of the study however was the use of doxorubicin, which is now recognized as having limited efficacy in the treatment of prostate cancer. Patients who received strontium-89 along with chemotherapy were found to have an increased overall survival, with a mean survival of 27.7 months compared to 16.8 months in the chemotherapy alone arm [11]. The TRAPEZE trial involved 757 patients with castrate-resistant metastatic prostate cancer, who were randomized to receive treatment on one of four arms: docetaxel alone, docetaxel with zoledronic acid, docetaxel with strontium-89, or docetaxel with both zoledronic acid and strontium-89. Chemotherapy with strontium-89 had a mild effect on the time to clinical disease progression with an increase of approximately 1 month (HR, 0.85; 95% CI, 0.73–0.99; $P = 0.03$) but with no improvement in overall survival [20].

Strontium-89 can be a beneficial tool for the treatment of patients with painful bony metastatic disease. Patients should have imaging studies or biopsy confirming the presence of bone metastases before treatment. The high affinity for blastic metastatic bone lesions and low area of tissue penetration help to target areas of cancer while limiting the effect to healthy tissue. In addition, strontium-89 may also be helpful in managing patients who have had persistent pain despite other therapies. Patients should be alerted to the possibility of pain flare 36–72 hours after injection and a strategy to address pain flare, including adjustment in pain medication dose, put in place prior. Because most patients do not see an onset of pain relief until 7–20 days after administration, it may not be the ideal treatment for patients with a very short life expectancy. In addition, the cost of producing strontium-89 has made it one of the more expensive radiopharmaceuticals and may limit its overall use [15]. The prolonged half-life and associated less favorable hemodynamic side effect profile of strontium-89 as compared with samarium-153 EDTMP has led to a wider utilization of samarium-153 EDTMP in the management of diffuse, predominately osteoblastic metastatic bone pain.

## Samarium-153

Samarium-153 EDTMP is a radioactive isotope that emits medium-energy beta particles. The half-life of samarium-153 at 1.93 days is considerably shorter than both radium-223 and strontium-89. Samarium-153 EDTMP is indicated for patients with pain from metastatic osteoblastic bone lesions confirmed on nuclear bone scan imaging [6].

### *Mechanism of Action*

Samarium-153 EDTMP is taken up by bone metastases, and local radiation is delivered to the lesions. Alone, the samarium-153 does not have a high affinity for bone uptake, but when chelated to form a complex with EDTMP (ethylenediamine tetramethylene phosphonic acid), it becomes more targeted to bone [16]. The exact method by which the drug decreases pain from bone metastases is not clear [6]. Samarium-153 EDTMP decays much faster than other radiopharmaceuticals, such as strontium-89, so the radiation dose is delivered quickly over a shorter period of time.

### *Pharmacokinetics*

Samarium-153 EDTMP is cleared rapidly from the blood stream after injection [16]. The samarium-153 EDTMP complex has an affinity for bone and is taken up by osteoblastic lesions approximately five times more than normal bone [6]. More of the drug is taken up by patients with a higher number of osteoblastic skeletal lesions, and there is an unknown benefit to patients with osteolytic lesions [6]. The drug that is not taken up by bone is cleared quickly and excreted through the urine [16]. Samarium-153 EDTMP is excreted in urine as an intact complex with 34.5% (±15%) excreted within the first 6 hours after administration and urinary excretion of radioactive material takes place over approximately 12 hours after administration [6]. Beta particles of samarium-153 EDTMP travel a maximum of 3 mm in soft tissues and 1.7 mm in bone [6]. In clinical studies, the age of the patient, including advanced age, did not seem to affect the pharmacokinetics of samarium-153 EDTMP [6].

### *Dosage and Administration*

Dosage of samarium-153 EDTMP is 1 mCi/kg or 37 MBq/kg given by IV push over 1 minute through a secure catheter. The IV should be flushed with saline after administration. The patient should be given 500 mL of oral or IV hydration prior to

IV push to promote excretion. Caution should be used in calculating doses for patients that are very thin or very obese [6].

## *Adverse Effects and Precautions*

Bone marrow suppression is a significant but generally predictable potential side effect for patients treated with samarium-153 EDTMP. In clinical trials, up to 95% of patients had a decrease in white blood cell counts and platelets counts of up to 40–50% from the pretreatment levels, and nadir of the counts was found 3–5 weeks after administration [6]. Most patients had return of counts to baseline levels within 8 weeks of treatment [6]. Patients should have weekly blood work to assess for bone marrow function for at least 8 weeks after treatment. In clinical trials, there were deaths in patients with disseminated intravascular coagulation (DIC) when receiving beta-emitting particles, so patients should be monitored closely. Caution should be taken in any patients with evidence of bone marrow insufficiency prior to treatment. Patients should generally not receive concurrent chemotherapy or external beam radiation therapy while undergoing treatment with samarium-153 EDTMP due to the risk for significant myelosuppression unless the benefit outweighs the risk [6].

Hypocalcemia has been reported in patients undergoing treatment [7]. Other less common side effects include arrhythmias, hypertension, stroke, dizziness, ecchymosis, diarrhea, bone pain, spinal cord compression, hematuria, bronchitis, and epistaxis [7]. Samaraium-153 EDTMP can cause fetal harm, so women of childbearing age should have a negative pregnancy test prior to administration [6]. Patients should be advised to avoid pregnancy and use effective contraception after treatment. Samarium-153 EDTMP is contraindicated in any patients with a known hypersensitivity to the compound [6].

Increased hydration is recommended to promote urinary excretion of the compound, so caution should be used in patients with a history of congestive heart failure and renal insufficiency. There are no clear guidelines regarding dose adjustments for renal function, as adequate studies have not been performed [6]. Precautions should be taken to avoid contact with the urine of patients treated with samardium-153 EDTMP, as urinary excretion of radioactive material takes place over approximately 12 hours after administration. Patients should be encouraged to void frequently after treatment to decrease bladder exposure [6].

## *Patient Education*

Patients should be instructed to take precautions to avoid exposure to radioactivity in their urine for 12 hours after administration [6]. Toilets should be flushed several times after use. Any soiled linens should be cleaned separately. Alternatively, linens

can be stored for 1–2 weeks to allow for decay of the radioactivity [7]. Patients can use analgesics for any temporary bone pain that can be seen after treatment. The onset of pain relief is usually in 1 week with a full effect of pain relief within 3–4 weeks [6].

### *Background and Clinical Considerations*

The efficacy of samarium-153 EDTMP was evaluated in several clinical trials. In a randomized, double-blind study of 118 patients with bone metastases causing pain, patients received 0.5 or 1.0 mCi/kg versus placebo. The study found that 62–72% of patients who received 1.0 mCi/kg had some pain relief within the first 4 weeks after injections, while 31% reported "marked" or "complete" pain relief on patient-reported scores at 4 weeks after treatment [17]. Approximately 43% of patients who received the 1.0 mCi/kg dose also reported pain improvement 16 weeks after completion of treatment [17]. There were no grade 4 bone marrow adverse effects reported [17]. In another study, 152 men with metastatic castrate-resistant prostate cancer with bone metastases causing pain were enrolled in a randomized, double-blind clinical trial where patients were given either radioactive or nonradioactive samarium-153 complexes. Patients reported less pain with the radioactive samarium-153 compared with placebo within 1–2 weeks after administration [18]. Bone marrow suppression was also seen, but no grade 4 myelosuppression was noted [18].

Samarium-153 EDTMP has a shorter half-life than some other radiopharmaceuticals. For the majority of the radiation dose to be administered, it takes approximately 1 week for samarium-153, versus approximately 25 weeks for strontium-89 [16]. Repeat doses of samarium-153 EDTMP have been used in some patients who have had good pain control with recurrent symptoms after treatment and who have adequate bone marrow function [16]. Overall, samarium-153 EDTMP can be an effective tool in the treatment of pain from metastatic bone disease when patients are selected appropriately and monitored closely after treatment.

## Radium-223

Radium-223 is predominantly an alpha-emitting particle with a half-life of 11.4 days [14]. The energy emitted from radium-223 is 95.3% alpha particles, 3.6% beta particles, and 1.1% emitted as gamma-radiation [4]. Radium-223 is indicated for the treatment of bone metastases causing symptoms in castrate-resistant patients with no known visceral disease [4]. A key distinction of radium-223 is a defined survival advantage in the treatment of castrate-resistant prostate cancer.

## *Mechanism of Action*

The alpha-particle-emitting isotope radium-223 mimics calcium in the body, forming complexes with areas of new bone growth [10]. Alpha-emitting particles cause high linear energy transfer that causes breaks in double-stranded DNA to cause cell destruction; however, the range from radium-223 is less than 100 μm, so there is limited effect to surrounding healthy tissue [4].

## *Pharmacokinetics*

Radium-223 is quickly distributed from the blood to bone or excreted into the intestines. After 15 minutes, only 20% of the drug remains in blood circulation decreasing to only 4% at 4 hours [4]. In clinical trials, there was no significant uptake in organs such as the heart, liver, kidneys, urinary bladder, and spleen 4 hours after administration [4]. The highest doses absorbed by body organs include bone by osteogenic cells, red bone marrow, and the upper and lower large intestinal wall [4]. Radium-223 decays rather than undergoes metabolism through the body [4]. Approximately 63% of the radium-223 was excreted from the body within 7 days of infusion, which is mainly by fecal and urinary excretion [4]. Therefore, patients with slower gastrointestinal motility rates will experience higher radiation exposure to the intestines, but it is unclear if this causes an increase in gastrointestinal toxicities [4].

## *Dosing and Administration*

The dose of radium-223 is calculated based on the patient's body weight, dosage level, radioactivity concentration of the product, and decay correction factor to correct for physical decay of radium-223 [4]. The dose is 50 kBq/kg (1.35 μCi/kg). Administration of radium-223 is by IV push over 1 minute. The IV should be flushed with normal saline before and after injection. No dose adjustments are recommended for patients with moderate to severe liver dysfunction due to lack of clinical trial data but radium-223 is not metabolized in the liver or cleared through the bile, so hepatic impairment is unlikely to affect the body's ability to manage the drug [4]. There are also no dose adjustments recommended based on mild (creatinine clearance 60–89 mL/min) or moderate (creatinine clearance 30–59 mL/min) renal impairment [4]. There is insufficient data to recommend any dose adjustments for severe renal impairment (creatinine clearance less than 30 mL/min) [4].

## *Adverse Reactions and Warnings*

The most common side effects from radium-223, greater than 10%, include temporary bone marrow suppression, gastrointestinal side effects, and peripheral edema [4]. Less common side effects include renal insufficiency/failure, dehydration, injection site reactions, and rarely secondary malignant neoplasms [4]. Dehydration may be related to the gastrointestinal side effects from therapy. There was an increase in osteosarcomas in animal studies [4]. Radium-223 contributes to a patient's overall lifetime radiation dose, so this should also be taken into account when considering treatment.

In a clinical trial, 2% of patients experienced significant bone marrow suppression or ongoing pancytopenia compared to patients treated with placebo [4]. Patients to be treated with radium-223 should have an evaluation of blood counts prior to initiation of treatment and prior to each dose. Patients should have an absolute neutrophil count (ANC) greater or equal to $1.5 \times 10^9$/L, platelet count greater than or equal to $100 \times 10^9$/L, and hemoglobin greater than or equal to 10 g/dL [4] to begin treatment with radium-223. A complete blood count should be drawn prior to each dose of radium-223 and ANC should be greater than or equal to $1 \times 10^9$/L and platelet count greater than or equal to $50 \times 10^9$/L to continue treatment [4]. Treatment should be held if laboratory values are not adequate. If levels do not recover within 6–8 weeks, treatment with radium-223 should be terminated [4]. Chemotherapy should not be given concurrently outside of clinical trial [4, 8]. No comprehensive drug interaction studies have been done, but there have not been any clear interactions between radium-223 and bisphosphonates or calcium channel blockers in clinical trials [4].

## *Safety Precautions and Patient Education*

Precautions should be taken after administration of radium-223, and teaching should be done with patients and their families. Patients and family members should be advised to take precautions to avoid exposures for approximately 1–2 weeks after radium-223 injection. Patients should be instructed to remain well hydrated. Following micturition, patients should be instructed to flush toilets twice after each use and sit on the toilet for urination to avoid splashing of urine. Caregivers should wear gloves when handling bodily fluids, such as urine, feces, and emesis. Any clothing with bodily fluids should be washed immediately and separately. Patient should be instructed on good handwashing after urination. Radiation exposure is expected to be low given the low treatment activity range of radium-223, but precautions should be taken to minimize exposure in patient care. Men should be instructed to use condoms for sexual intercourse and female partners of childbearing age should use an effective contraceptive during radium-223 treatment and for

at least 6 months after treatment to avoid pregnancy. While there are no clear data on the fertility effects of radium-223, it has the potential to inhibit fertility [4].

## *Background and Clinical Considerations*

The ALSYMPCA trial was a phase III, double-blind trial designed to assess the clinical benefit of radium-223 versus best supportive care. The trial enrolled 921 patients with castrate-resistant metastatic prostate cancer with known bone metastases with or without prior docetaxel treatment and randomized them to either treatment with radium-223 or placebo. The study was closed early, as interim analysis showed a significant improvement in overall survival for the radium-223 arm (overall survival 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95% CI, 0.55–0.88; two-sided $P = 0.002$) [10]. Ultimately, the final analysis showed the median survival of patients receiving radium-223 was 3.6 months longer than those receiving placebo (14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58–0.83; $P < 0.001$) [10]. Patients treated with radium-223 also had a delay in symptomatic skeletal events, defined as symptomatic fractures, than patients treated with placebo [10]. There was no significant difference in adverse effects between the radium-223 and placebo arms of the trial. A subgroup analysis was later done to evaluate patients who had received docetaxel chemotherapy prior to radium-223 treatment. The analysis found that patients had improved overall survival regardless of prior docetaxel use and patients who had received prior docetaxel tolerated radium-223 well [13].

The ALSYMPCA trial was structured such that patients received six injections, though the optimal number of effective and tolerated doses has been in question. In a small study of 44 retreated patients with castrate-resistant metastatic prostate cancer with bone metastases who had previously undergone treatment with radium-223 without evidence of progression during treatment, the patients were given up to six additional infusions of radium-223 every 4 weeks. The retreated patients did not seem to have an increase in hematologic toxicities during therapy or for the 2 years of posttreatment follow-up [12]. Patients also had a low rate of radiographic progression [12]. Further studies are needed regarding retreatment or longer treatment durations with radium-223. Clinical trials are ongoing in diseases other than prostate cancer to see if radium-223 will be a benefit in patients with other tumor types, who have osteoblastic metastatic bone disease.

Studies have also been ongoing regarding combining radium-223 with other agents, including abiraterone, enzalutamide, docetaxel, olaparib, and immunotherapy [21, 22]. The ERA-223 trial was a large, double-blind, randomized, placebo-controlled phase III study in castrate-resistant metastatic prostate cancer patients with bone metastases, who were asymptomatic or mildly symptomatic and had not received prior chemotherapy that combined abiraterone and prednisone/prednisolone with radium-223 versus placebo [21]. This study was unblinded early due to interim findings of increased fractures and death [21]. It was determined that 28.6% of patients developed fractures in the radium-223 arm versus 11.4% in the placebo

arm, and there was also an increase in the number of deaths on the radium-223 arm (38.5% versus 35.5%) [4]. These findings led to an updated warning in the package insert for radium-223, as well as warnings from the European Medicines Agency (EMA) and Health Canada [3, 4]. Therefore, concurrent use of abiraterone and prednisone with radium-223 is not currently recommended outside of a clinical trial.

Patients should have a baseline or updated nuclear medicine bone scan or sodium fluoride PET scan done prior to initiation of radium-223 to assess the state of the bony disease. Generally, patients with metastatic castrate-resistant prostate cancer, who have two or more bone metastases that are symptomatic, would be eligible for treatment with radium-223. Symptoms from bone disease could include pain or fracture. Patients with visceral disease, considered to be any evidence of cancer in the abdominal organs, lung, or brain, should not be considered for radium-223 therapy. In addition to blood work and side effect assessment, pain should be assessed at the start of therapy and monthly through the duration of therapy to assess for changes.

## New Directions and Conclusions

As discussed above, there are ongoing clinical trials assessing the use of radiopharmaceuticals in combination with other medications for metastatic prostate cancer, as well as investigations into radiopharmaceutical use in other cancers. There have also been new radiopharmaceuticals in development for the treatment of prostate cancer. Lutetium-177 PSMA radioligand is a medium-energy β-emitting radionuclide bound to a protein that binds with PSMA, which is a transmembrane glycoprotein highly expressed on prostate cancer cell membranes [22, 23]. PSMA has been found to be overexpressed in prostate cancer cells. Therefore, Lutetium-1777 PSMA radioligand targets both bone and soft tissue disease. It is also found in some other organ tissues, such as the small intestine and salivary glands, so there is the possibility of some radiation dose to these areas, as well [24]. The Lutetium-177 PSMA radioligand binds to PSMA on the cell surface and is taken into the cell where it emits radiation therapy causing DNA damage and cell death [23]. In early studies, Lutetium-177 PSMA has been found to decrease prostate-specific antigen levels, though measures such as overall survival have been limited to date due to the trials done [23]. The Lutetium-177 PSMA side effect profile so far has been favorable with some hematologic toxicities and mild nausea, fatigue, and xerostomia [23]. Thorium-227-labeled PSMA antibody is another alpha-emitting radionuclide that is beginning clinical trials and has shown promise in early preclinical studies [22].

Radiopharmaceuticals can play an important role in the treatment of bone metastases. Radium-223 is a treatment with category 1 evidence to support improvement in pain relief from prostate cancer with bone metastases and overall survival in men with bone metastases without known visceral involvement. The short active range of the alpha particles in radium-223 gives a higher dose of radiation to a more localized area than other radiopharmaceuticals, thereby decreasing the activity on

normal tissue and myelosuppression. Radium-223 should not be used with combined chemotherapy or abiraterone and prednisone outside of clinical trials. Strontium-89 and samarium-153 have been shown to improve pain for bone metastases for patients who are not good candidates for traditional radiation therapy but have not shown any survival benefit. Because of the longer half-life of strontium-89, higher rates of myelosuppression are often seen in comparison to samarium-153. Myelosuppression with some of these agents may be prolonged, therefore inhibiting the ability to use chemotherapy options in the future. However, radiopharmaceuticals can be an effective means of treating pain related to bone metastases.

There are several considerations for the advanced practice provider (APP) related to radiopharmaceuticals in the treatment of bone metastases. While the APPs will not be involved in prescribing or administering these medications, often APPs are involved in the management of patients as they progress through treatment, as well as follow-up after treatment. Monitoring of labs prior to and after treatment is important in helping to identify patients who may not tolerate treatment or may be having adverse effects. APPs should be aware of the possible side effects of radiopharmaceuticals, as well as the precautions that patients should take immediately after administration. APPs can play an important role in patient education and reinforcement of teaching.

**Pearls for the Advanced Practice Provider**

- Only physicians and facilities with experience and licensing to handle and use these medications should administer radiopharmaceuticals.
- Strontium-89 and samarium-153 EDTMP have been shown to improve pain related to bone metastases in patients with metastatic cancer. Samarium-153 is generally the preferred of these two agents given its shorter half-life with better hematologic toxicity profile.
- Radium-223 has been shown to improve overall survival in patients with metastatic castrate-resistant prostate cancer to bone.
- Radium-223 should not be used with abiraterone and prednisone outside of clinical trial due to the increased risk for bone fracture and death. Use with other new-generation anti-androgen agents should likewise be limited to clinical trials.
- Blood counts should be monitored closely in patients receiving radiopharmaceuticals due to the risk for myelosuppression. The risk is highest with strontium-89.
- Advanced practice providers can play an important role in patient education regarding radiation safety after administration, possible side effects, and expectations around symptom management for patients undergoing treatment.

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