HOW I DO IT

Dosing, administration, and safety of radium-223: How I do it

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DAN TD, DOYLE L, RAVAL AJ, PRIDJIAN A, GOMELLA LG, DEN RB. Dosing, administration, and safety of radium-223: How I do it. *Can J Urol* 2016;23(3):8301-8305.

Radium-223 dichloride is a first-in-class bone-directed radiopharmaceutical that has been shown to prolong survival in men with metastatic castrate resistant prostate cancer (mCRPC). Unlike other radiopharmaceuticals, radium-223 uniquely uses alpha-emission to deliver high intensity, short range cytoxic treatments resulting in minimal myelosuppression. Following the results of the ALSYMPCA trial, radium-223 (Xofigo) was FDA approved in the United States in May 2013 and approved by Health Canada in December 2013 for the treatment of mCRPC with symptomatic bone metastases and no visceral disease. This "How I do it" article describes the background of radium 223 as well as the methods and techniques that our institution uses for safe and effective administration and notes the subtle differences when administering the drug in Canada.

Key Words: radium-223, alpharadin, metastatic prostate cancer, bone metastases

Introduction

Radium-223 dichloride (Ra-223, *alpharadin*) is a calcium-mimetic that is selectively taken up in areas high bone turnover, such as sclerotic bone metastases from prostate cancer. Unlike other radiopharmaceuticals that utilize beta and gamma emission, radium-223 takes advantage of the emission of high-energy, short range (< 100 µm) alpha particles, which deliver a higher radiobiologic effect. Once engaged, alpha-particle radiation induce double-stranded DNA breaks with very little chance for repair, creating a highly localized cytoxic effect on the growing metastatic foci in bone while limiting marrow exposure.[1] Due to its unique properties, radium-223 demonstrates a superior therapeutic ratio when compared to other radiopharmaceuticals such as samarium and strontium (primarily beta particle emitters), which have higher incidences of hematologic suppression without a demonstrated improvement in overall survival.[2]

In May 2013, the US FDA approved radium-223 (Xofigo) with approval by Health Canada in December 2013 for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Approval was based primarily on results of the international ALSYMPCA trial – a phase 3, double-blinded study that randomly assigned 928 men with painful bone metastasis from mCRPC to receive six intravenous doses of monthly radium-223 (50 kBq/kg) versus placebo. The trial was terminated early after interim analysis demonstrated significantly improved overall survival (median 14.0 months versus 11.2 months; hazard ratio, 0.70 p = 0.002).[3] In addition, improvement in overall survival was accompanied by significant quality of life (QoL) benefits, including a higher percentage of patients with meaningful QoL improvement and a slower decline in QoL over time.[4]

Patient selection

The FDA and Health Canada approved indication for radium-223 includes patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease. This heterogeneous group of patients includes those with varying comorbidities and exposure to a number of systemic agents, including marrow-suppressing cytotoxics. Despite this, in a pre-specified subgroup analysis, it was reported that radium-223 prolonged median overall survival irrespective of previous docetaxel use, however toxicity was higher in patients who had received chemotherapy.[5] Conversely, there exists limited data

Accepted for publication May 2016

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TABLE 1. **Checklist for administration in the United States and Canada noting significant differing country specific considerations (shaded)**

United States	Canada
Patient selection	
• Metastatic castrate resistant prostate cancer with symptomatic bone metastases	
• No visceral disease or evidence of cord compression	
• Determine hematologic parameters (CBC/differential/platelets) acceptable (see Table 2)	
Product supplied as	
• Pre-measured, ready-to-use syringes	• Single-use vials containing 6.6 MBq at the reference date
Scheduling	
• Radiation safety officer-approved radiation oncology staff orders radium-223	• Staff in Canadian Nuclear Safety Commission licenced location orders radium-223
• All injections ordered no later than Monday before the day of administration (typically Thursday)	• Tuesday 4:30 pm EST order deadline for a guaranteed delivery the following Tuesday
• All patients scheduled on single day, mid-week to reduce errors related to shipping delay or inclement weather	• Patients scheduled on Wednesdays, Thursdays or Fridays
• Monthly hematologic parameters (CBC/differential/platelets) determined prior to each administration (see Table 2)	
Receipt	
• Once package received, survey and verify dose in compliance with local regulations	
Dose	
• N/A	• Calculate volume to be administered • Draw into syringe • Confirm correct dose in dose calibrator
Administration	
• On day of procedure, injection surfaces are covered with disposable, protective material	
• Time out performed o Patient name prior to administration o Authorized user verifies the dose (activity per the written directive)	
• Slow intravenous injection into a peripheral vein over approximately 1 minute	
• Syringe is surveyed after administration	
• Unused product or exposed materials disposed per protocol (decay-in-storage)	
Follow up	
• Patient treatment calendar provided o Monthly injections o Laboratory prescriptions o Post treatment follow up	
• Patient provided with wallet card indicating radiation safety for travel	
• Precaution handout o Standard hygiene practices for at least 1 week after the last injection o Toilet should be flushed several times after each use o Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing o Contraception (i.e., condom) recommended for 6 months following treatment	

TABLE 2. **Hematologic monitoring for radium-223**[7]

Routine CBC/differential/platelets before first infusion and monthly during treatment

- Before initial infusion
  - o Absolute neutrophil count ≥ 1.5 x 10^9/L
  - o Platelet count ≥ 100 x 10^9/L
  - o Hemoglobin ≥ 10 g/dL
- Before subsequent administration of radium-223
  - o Absolute neutrophil count ≥ 1 x 10^9/L
  - o Platelet count ≥ 50 x 10^9/L
- Discontinue radium-223 if hematologic values do not recover within 6-8 weeks after that last administration despite receiving supportive care

regarding the use of next-generation anti-androgens in combination with radium-223. In our US based practice, due to non-overlapping side effect profiles, concurrent use of radium-223 and next-generation anti-androgens is frequently employed and appears to be well tolerated with similar toxicities to standard administration of radium-223 alone.[6] See Table 1, checklist for administration of radium-223 and also the subtle differences between the US and Canada in this process.

Clinical considerations

Patients should be maintained on androgen suppression therapy (medical or surgical) while using radium-223. While the safety profile of radium-223 is very good, myelosuppression can sometimes occur (approximately 2% compared to placebo in the ALSYMPCA trial). Standard hematologic monitoring hematologic parameters (CBC/differential/platelets) should be done before and during each treatment cycle, Table 2. Side effects generally are reversible. Bone is rapidly targeted with little or no redistribution from decay sites, little or no urinary excretion, and slow clearance via the gastrointestinal tract (GI) tract. The use of concomitant chemotherapy with radium-223 has not been established and should not be used outside of a clinical trial due to the risk of additive myelosuppression.

In the ALSYMPCA trial the most common hematologic abnormalities in radium-223 treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Other reported adverse reactions (≥ 10%) were nausea, diarrhea, vomiting, and peripheral edema.[7] The only officially noted contraindication to radium-223 is pregnancy.

$$\text{Vol of Ra-223 (mL)} = \frac{\text{Body Weight (kg)} \times \frac{55\ \text{kBq}}{\text{Bodyweight (kg)}}}{\text{Decay factor} \times \frac{1{,}100\ \text{kBq}}{\text{mL}}}$$

Figure 1. Equation to calculate prescribed activity utilizing the patient's most recent body weight.

Radium-223 dosing

Radium-223 is currently commercially available in the United States (US) in pre-measured, ready to use 10 cc syringes. In Canada, radium-223 is available in single-use vials which contain 6.6 MBq of activity at the reference date. Doses are ordered in monthly increments approximately 1 week prior to a patient's scheduled treatment date by the manufacturer. Prescribed activity is calculated using a simple equation utilizing the patient's most recent body weight, Figure 1. As previously discussed, the dosage in the initial clinical trial was 50 kBq/kg body weight. However, a re-evaluation of the primary standard of the isotope resulted in a revised dosage of 55 kBq/kg body weight as of April 2016. Details of this dose adjustment are beyond the scope of this article, but readers are referred to the manufacturer for more information.[7]

As a caveat, it should be noted that dosage recommendations are based primarily on patient selection criteria described in the ALSYMPCA study. Interestingly, in the initial dose-finding studies, there were no demonstrated relationships between dose and hematologic toxicity and the role of radium-223 dose-escalation remains an open question.[8]

Regulatory considerations

Logistical considerations when implementing a radium-223 program include licensing of the radioisotope, acceptance of radioactive material onsite (including appropriately trained personnel), calibrated dose assay

verification, appropriate administration facilities and trained personnel to execute the administration.

Given the population of patients suitable for treatment with radium-223, administration has emerged most often in nuclear medicine or radiation oncology departments.

US licensing requirements

Before implementing a new radium-223 program, an application must be submitted to the Nuclear Regulatory Commission (NRC) or appropriate agreement state agency (in our setting Pennsylvania Department of Environmental Protection Agency) that is responsible for licensing of the facility. This action is usually performed by the institution's radiation safety officer, but may be completed by other administrative officials. The next regulatory requirement includes identifying an authorized user that meets the criteria specified in 10CFR (Code of Federal Regulations) Part 35, Subpart E, 35.300. This includes physicians "who are approved for the use of any beta emitter or any photon-emitting radionuclide with a photon energy less than 150 keV" under 10CFR 35.390(b)(1)(ii)(G)(3), "training for use of unsealed byproduct material for which a written directive is required" or 10CFR 35.396(d)(2), "training for the parenteral administration of unsealed byproduct material requiring a written directive."[9]

Canadian licensing requirements

In Canada, the facility radiation safety office submits an application to the Canadian Nuclear Safety Commission in order to add radium-223 to the facility's therapeutic Nuclear Substances and Radiation Devices license.

Training

Personnel within the institution must be trained in hazardous materials to be able to receive radioactive material. Hazardous material training includes understanding of shipping and radioactive materials labeling, packaging requirements and acceptance protocols. Personnel must be able to perform wipe testing upon receipt of the package to confirm no contamination has occurred during transportation. Upon receipt of the radioactive material, the isotope quantity must be recorded. The isotope must be kept in a secured location until administered to the patient.

Administration

Prior to administration, the radioactivity contained within in the syringe (which is provided ready-to-use in the US and prepared on-site in Canada) should be confirmed through an independent assay. This requires a dose calibrator, also referred to as a well chamber, calibrated for radium-223. This measurement is performed by placing the 10 cc syringe into the dose calibrator and recording the activity. There are additional quality assurance requirements for commissioning and recurring tasks at quarterly and annual intervals for ensuring functionality of the dose calibrator system. These activities should be performed by trained personnel, such as a nuclear medicine technologist or medical physicist. The assay is time sensitive given the short half-life of radium-223 and must be decay corrected to compare to the vendor assay.

A written directive or prescription must also be documented prior to administration and include elements dictated by regulation, such as patient identifiers (name, date of birth, medical record number), treatment date and time, isotope, prescribed activity and route of administration. The activity injected in the patient should be confirmed by assaying the syringe and miscellaneous delivery equipment (IV, tubing, etc.) following the injection. This process accounts for the possibility of any residual isotope remaining in the delivery system.

Radium-223 is administered by slow intravenous injection into a peripheral vein over approximately 1 minute. The injection should take place in an appropriately equipped treatment room. The area surrounding the injection site should be prepared with disposable material to aid in clean up in the event any material is spilled. Wipe tests should be performed in the area of source storage, assay, preparation and administration to ensure none of the isotope escapes the syringe during these activities. The patient should be surveyed with an appropriate survey meter prior to and after injection to confirm a minimal radiation exposure rate and declare the patient safe for discharge. Patients are provided with educational material to assist in the event they need to explain their medical procedure to other medical professionals or throughout the course of travel (such as TSA screening).

In the US the actual administration of the radioactive dose must be performed by an authorized user that meets regulatory standards and is approved on the radiation license of the facility. In our practice, an IV is placed by nursing staff, checked for venous return, flushed, and capped. Radium-223 is subsequently delivered by the authorized user. Other clinical personnel involved in the procedure should be educated on radiation safety procedures and the proper techniques for handling the syringe and providing care to patients following the administration of radium-223. In Canada, individual users are not specifically named on the facility's Nuclear Substances and Radiation Devices license. Instead, the facility's radium-223 protocol dictates who can

administer the dose in the licensed location. Typically, a nuclear medicine physician administers the first dose and subsequent doses are administered by a nuclear medicine technologist.

Radiation safety

Due to the nature of the radium-223 decaying primarily via emission of alpha particles, the radiation safety precautions are minimal compared to other radiation therapy isotopes such as strontium and samarium that are beta emitters. Alpha particles are attenuated (or stopped) by millimeters of virtually any material. The best illustration is the fact that a single sheet of paper is sufficient to shield most alpha particles with skin thick enough for self-shielding. There are minimal components of beta and photon radiation in the decay chain of radium-223, comprising most of the radiation detected in the process of dose assay and radiation survey. While no radiation shielding precautions are necessary during administration, clinicians may prefer to use a syringe holder, made of less than 1 centimeter of plastic material to surround the pre-filled syringe. Patients should be provided with basic information regarding radiation safety procedures to minimize the possibility of radiation exposure to others however there are no specific restrictions regarding contact with other people after receiving radium-223. These instructions should include recommendations to flush the toilet several times after use, avoid contact with urine, feces or other bodily fluids and wash contaminated clothing separately from other pieces. Gloves (followed by hand-washing) act as a sufficient barrier to protect caregivers from any possible exposure.[7]

Assessment of response

At the current time, there does not appear to be a universally utilized assay to track treatment response to radium-223. Although serial prostate-specific antigen (PSA) monitoring is typically done following administration, PSA control following radium-223 treatment has been variable. In the ALSYMPCA trial, a 30% or greater reduction in PSA blood levels at week 12 was achieved in 16% of patients in the radium-223 group and in 6% of patients in the placebo group ($p < 0.001$). This reduction was sustained 4 weeks after the last injection in 14% of patients in the radium-223 group and in 4% of patients in the placebo group ($p < 0.001$).[3] However, earlier phase studies did not find a strong concordance with radium-223 and PSA control.[10] In our experience, particularly in patients receiving third line of treatment or later, there does not appear to be a strong association between PSA control and administration of radium-223.[6] Future areas of active investigation include the use of nuclear medicine studies in combination with markers of bone turnover to measure radium-223 response.

Conclusions

In summary, radium-223 is a safe and effective bone-directed therapy that can provide patients with mCRPC better quality of life and extend overall survival. It takes advantage of alpha-emission to deliver high-energy, short range cytoxic treatments while minimizing myelosuppression. Treatment is logistically favorable with therapy given at monthly intervals, and manufacturer-provided dosing based on body weight. With proper licensing, personnel, monitoring and facilities, use of radium-223 can be performed safely in a variety of clinical settings. □

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