Skeletal Metastases Therapy:  
The Curies’ Radium

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Learning Objectives

• Describe the “ideal” therapeutic radiopharmaceutical
• Explain how radiation interaction with matter can be used to treat disease
• Provide a summary of the treatment modalities for painful osseous metastases
• List the radiopharmaceuticals for use in the treatment of painful osseous metastases
• List the properties of radium Ra-223 dichloride
Self-Assessment Questions

1. Which of the following best describes the amount of cell destruction associated with 1 MeV of α, β, and γ radiation?
   a. γ > β > α
   b. β > α > γ
   c. α > β > γ
   d. β > γ > α

2. Which of the following is considered the “ideal” Tp of a radionuclide for use in radiopharmaceutical therapy?
   a. Tp measured in minutes
   b. Tp measured in days
   c. Tp measured in weeks
   d. Tp matches the biological clearance patterns and rates of the chemical carrier

3. Which of the following IS NOT a calcium mimetic or bone-seeking element?
   a. Sm
   b. Ra
   c. Sr
   d. P

4. Which of the following are the most common adverse reactions observed/reported in patients who participated in the clinical trials with Ra-223 dichloride?
   a. nausea, vomiting and diarrhea
   b. renal insufficiency and failure
   c. secondary malignant neoplasms
   d. erythema, pain and edema at the injection site

5. According to the prescribing information (P.I.) for Ra-223 dichloride, which of the following is the recommended total number of administrations for a bone pain palliation patient?
   a. one
   b. four
   c. six
   d. eight

Radiopharmaceuticals for Therapy

- Involves oral, intra-cavity, intravenous or intra-arterial administration of a radiopharmaceutical to treat or reduce the symptoms of a particular disease.
- Therapy with radiopharmaceuticals utilizes unsealed sources of radioactivity capable of internally irradiating the target tissue or organ involved with disease.
Therapeutic Radiopharmaceuticals

Radium-223 dichloride represents the most recent addition to the available therapeutic radiopharmaceuticals.

Palliation—relief without cure.

Therapeutic Radiopharmaceuticals for Bone Pain Palliation

- Except for skin malignancies, prostate cancer is the most common cancer among men in the U.S. (American Cancer Society, Cancer Facts and Figures 2016)
- Almost 20% of prostate cancer cases include metastatic spread to nearby or distant areas of the body. (American Cancer Society, Surveillance, Epidemiology, and End Results Stat Facts: Prostate; Survival & Stage, 2002-2008)
- Palliation—relief without cure.
- Radium-223 (Ra-223) and Radionuclide Therapies of Bone and Visceral Metastases (Ra-223 and Iodine-131) (American Cancer Society, Surveillance, Epidemiology, and End Results Stat Facts: Prostate; Survival & Stage, 2002-2008)
- Palliation—relief without cure.
- Radium-223 and 131I were both investigated as therapies for primary and metastatic cancer of the bone early in the use of radioactive drugs (1940s)
- Renewed interest in Radium-223 as treatment of the pain associated with metastatic malignancies led to FDA approval in 2013.
- Stimulated interest in other “bone seeking” radioactive compounds for further improvement of bone pain palliation.
Strontium Sr-89 Chloride Metastron™-GE Healthcare

- Strontium is a member of the alkaline earth family of elements along with beryllium (Be), magnesium (Mg), calcium (Ca), barium (Ba) and radium (Ra). All are “bone seekers”.
- Chemical form is the dichloride salt, $^{89}\text{SrCl}_2$.
- Distributes to bone tissue where it undergoes ion exchange with the existing calcium to form strontium hydroxyapatite as reactive bone is being laid down in disease sites.
- Large radiation dose is delivered to cortical bone without much radiation damage to bone marrow.
- $T_p$ of 50 days, $\beta_{max}$ of 1.4 MeV, patient dosage is 4 mCi I.V.

Metastron (Strontium-89 Chloride Injection) is indicated for the relief of bone pain in patients with painful skeletal metastases.
Samarium Sm-153 Lexidronam Quadramet®-EUSA Pharma

- Lanthanide series of elements which are highly reactive metals—especially with oxygen containing compounds
- Sm-153 is produced by an (n,γ) reaction using Sm-152 as the target
- Biological distribution and mechanism of localization is similar to Tc-99m phosphonates such as medronate-MDP.
- Tp of 46.3 hours and βmax of 0.81MeV (103keV γ photon), patient dosage of 1mCi/kg
Alpha Particles for Therapy

- Alpha particles are a form of radiation emitted from the nucleus of mostly large atomic mass radionuclides (Bi-212, At-211, Pb-212, Ra-223).
- The alpha particle consists of 2 protons and 2 neutrons bound together into a single particle.
- Similar to a helium nucleus, the particle is 7000 times the size and mass of beta particles.

Alpha Particle Ranges

<table>
<thead>
<tr>
<th>Radiation Type</th>
<th>Compound of</th>
<th>Range in air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha α</td>
<td>Helium nucleus</td>
<td>A few inches (several centimeters)</td>
</tr>
<tr>
<td>Beta β</td>
<td>Electrons</td>
<td>Several feet (many centimeters)</td>
</tr>
<tr>
<td>Gamma γ</td>
<td>Electromagnetic waves (photons)</td>
<td>Many yards (many meters)</td>
</tr>
</tbody>
</table>

Radiation ranges (i.e., distances over which energy is deposited): γ >> β > α

Alpha Particle Shielding

- Shielded by:
  - Tissue paper, skin
  - Aluminum foil, plastic
  - Centimeters - inches of lead, tungsten

Ease of shielding: α > β >> γ
Alpha Particles Interaction with Matter

- Large, heavy particles with a +2 charge
- Travel in a straight line (not scattered)
- High Linear Energy Transfer (LET) leading to a short path length
- Short path length in tissues (<100 µm) and high LET (~100 keV/µm) creates a large number of ion pairs per unit path length
- The ion pair creation (ionization) leads to cell death.

Biological Effects of Alpha Particles

- α particles are stopped by the top layer of skin and therefore not dangerous relative to external exposure.
- Taken internally, α emitting radionuclides cause a tremendous amount of tissue destruction.
- Depending on the tissue it is passing through, estimates of 10-1000 times greater damage compared with an equivalent amount of gamma or beta radiation.


Why alpha particles?

- α particles have high energy, but short path length - which minimizes damage to healthy tissue surrounding the cancer cells
- In contrast, β particles - used in bone pain palliation agents in g. Metastasis, Quadrantex - produce low energy radiation and a longer track length

<table>
<thead>
<tr>
<th>Relative biological effectiveness</th>
<th>26</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial energy (MeV)</td>
<td>2-4</td>
<td>0.1-2.5</td>
</tr>
<tr>
<td>Range in tissue (µm)</td>
<td>40-100</td>
<td>56-700</td>
</tr>
<tr>
<td>Linear energy transfer (keV/µm)</td>
<td>10-30</td>
<td>0.005-0.1</td>
</tr>
<tr>
<td>Oxygen enhancement factor</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>LET</td>
<td>100-1000</td>
<td>1-10</td>
</tr>
<tr>
<td>Dose in cell kill</td>
<td>0.1</td>
<td>0.1-0.01</td>
</tr>
<tr>
<td>Relative biological effectiveness</td>
<td>26</td>
<td>1</td>
</tr>
</tbody>
</table>

The perspectives of overkill allow:
- Localized cell killing - high radiation dose in a smaller area
- Irradiation of a smaller area and better targeting
- Minimal non-target toxicity (e.g. bone marrow)
This is not the Curies radium!

- Radium was discovered in 1898 by Pierre & Marie Curie.
- Radium-226 was the radionuclide isolated by the Curies, used in medicine in the 1920s & 1930s as a cancer treatment.
- Radium-226 is also the isotope found in self-luminous paints for watches, nuclear panels, aircraft switches, clocks, and instrument dials.
- The first to learn of the hazards of radioactive sources, Ra-226 caused the burns on Becquerel and an ulcer on Pierre Curie’s hand that would not heal.
- In 1902, the Curies published a scientific paper that announced that, when exposed to radium, tumor-forming cells were destroyed.


Radium Ra-223 Dichloride
(Xofigo®-Bayer HealthCare Pharmaceuticals)

Ra-223 dichloride is the first-in-class, alpha particle-emitting therapeutic radiopharmaceutical for the treatment of patients with castration-resistant prostate cancer symptomatic bone metastases and no known visceral metastatic disease.

Found to extend overall survival by 11-14 months compared with placebo.

Approved by FDA in May, 2013, Xofigo® was originally known as Alpharadin by the developer, Algeta.

Xofigo® (radium Ra-223 dichloride) injection prescribing information. Bayer HealthCare Pharmaceuticals

Indication
Xofigo (radium Ra 223 dichloride) is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Important Safety Information
In clinical trials, the most common adverse drug reactions (≥10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic laboratory abnormalities (≥10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

Measure blood counts prior to treatment initiation and before every dose of Xofigo. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after treatment. Monitor patients with compromised bone marrow reserve closely. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care measures.

For full prescribing information, please refer to the package insert or visit www.xofigo.com

To report suspected adverse reactions, contact Bayer HealthCare Pharmaceuticals at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
Radium-223 decay

Ra-223 is predominantly an α-emitter (95.3%, energy range of 5 – 7.5 MeV) with low abundance of β- (3.6%) and γ (1.1%) emissions.

The T₁/₂ of 11.4 days provides a reasonable time frame from manufacture to patient administration.

Formation of Ra-223

- Radium-223 occurs naturally, but for medical use, a byproduct material is used, thus, radium-223 is a byproduct material.
- The radium-223 source used was produced by neutron irradiation of radium-226 in a reactor.
- Actinium-227 decays to radium-223 through thorium-227 (T₁/₂ = 31.77 years).
- The production process of the drug product is a purification of radium from a mixture of actinium-227, thorium-227 and radium-223 and does not involve chemical synthesis.

Xofigo Production Process

The A-generator contains the starting material, Actinium-227, which decays to Radium-223 and other radionuclides. The Radium-223 drug substance is removed from the A-generator vial using a solvent and finally purified to make the drug product, radium-223 dichloride (Xofigo).
Actinium-227 (A-generator)

Ac-227 is supplied by Bayer as the A-generator as it is used repeatedly for the production of Ra-223. Typically, the Ra-223 is removed from the A-generator every 3 weeks. A-generator contains 270mCi of Ac-227 and lasts 3-6 months.

Ra-223 Dichloride

- Sterile, isotonic aqueous solution of radium-223 chloride, $^{223}$RaCl$_2$
- Dosing regimen is 50 kBq per kg body weight (95 μCi for a 70 kg patient) given at 4 week intervals for 6 cycles
- Acts as a calcium mimic, naturally targets new bone growth in and around bone metastases

Ra-223 Dichloride Patient Dosage

Recommended dosage of Ra-223 dichloride is 50 kBq/kg (1.35 μCi/kg) given at four week intervals for six administrations. The standard, 70 kg patient, would receive a total of 95 μCi or 3.5 MBq. Safety and efficacy for more than six injections has not been proven.

Slow (up to one min.) IV injection recommended. A patient-specific volume for injection, calculated using the formula below, is withdrawn directly from the vendor-provided Ra-223 dichloride vial.

The decay factor is the fractional decay factor for the time interval from the date/time of calibration of the Ra-223 dichloride to the date/time for the patient administration.
Properties of Bone Pain Palliation
Radiopharmaceuticals

Table 4. Properties of Radiopharmaceuticals Used for Bone Pain Palliation

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Radiation</th>
<th>Emission Energy (MeV)</th>
<th>T1 (h)</th>
<th>Range in Tissue (mm)</th>
<th>Tissue to Normal Tissue Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra-223 Diphosphonate</td>
<td>alpha 1.78</td>
<td>11.4</td>
<td>&lt;.1</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Sr-89 Cloidronate</td>
<td>18.8</td>
<td>1.0</td>
<td>3</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Sr-89 Chloride</td>
<td>1.5</td>
<td>56.5</td>
<td>4</td>
<td>1.6</td>
<td></td>
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<tr>
<td>P-32 Sodium Phosphate</td>
<td>1.71</td>
<td>14.3</td>
<td>10</td>
<td>1.6</td>
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ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase 3 Study Design

Enrollment: 321 patients with symptomatic CRPC and skeletal metastases
136 centers in 19 countries (7 centers in the US) enrolled patients

Probability of Survival

Xofigo demonstrated improved median survival from 11 to 14 months compared to placebo.
Ra-223 Dichloride Pharmacology

- Similar to Sr-89, Ra-223 mimics calcium and selectively targets bone
- Binds to hydroxyapatite found in reactive bone
- Rapid clearance from blood with bone uptake seen within 10 minutes
- Radioactivity levels in skeleton ranged from 44-77% at 4 h. post administration
- Eliminated via the urinary system

Ra-223 Dichloride Clinical Experience

- Safety/efficacy proven in Phase 1 & 2 trials involving 255 patients. Measurements showed decline in serum levels of PSA and bone alkaline phosphatase as well as prolonged survival compared with placebo.
- A large double-blind, placebo-controlled study totaling 922 patients demonstrated a significant reduction in the risk of death compared with the placebo-controlled arm.
- In summary, more than 1,000 prostate cancer patients have received Ra-223 dichloride therapy in clinical trials resulting in significant PSA declines and prolonged survival benefit without dose-limiting myelotoxicity or other normal-tissue related toxicities.

Adverse Effects

- Most common adverse effects (> 10%) reported include nausea, vomiting, diarrhea and peripheral edema
- Most common hematologic laboratory abnormalities (> 10%) reported were anemia, leukopenia, neutropenia, lymphocytopenia and thrombocytopenia
- Measure blood counts prior to treatment initiation and before every dose of Xofigo
- Contraindicated in women who are or may become pregnant (can cause fetal harm).


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Xofigo® Ordering and Distribution Process

- Treating facility calls Xofigo Access Services® at 1-855-6XOFIGO (1-855-696-3446) to order Xofigo
- Xofigo Access Services Access Counselor will collect initial information for the patient order
- Provide Referring Physician information to facilitate follow-up care with Xofigo (bloodwork, etc)