OBJECTIVES

Upon completion of this program, the participant will be able to the following:

- Discuss the role of osteoclasts (bone-resorption cells) and osteoblasts (bone-forming cells) in the pathophysiology of bone metastases
- Identify the contributors of pain resulting from osseous metastases
- Define the nuclear characteristics of the therapeutic radiopharmaceuticals used for bone pain palliation
- Delineate the chemical characteristics of bone pain palliation radiopharmaceuticals
- Discuss the pharmacodynamics of these radiopharmaceuticals
- List the indications and dosage parameters of these radiopharmaceuticals
- Describe the monitoring parameters for patients receiving these therapeutic radiopharmaceuticals

INTRODUCTION

A major and frequent complication of cancer is bone metastases with a 70% occurrence in patients afflicted with advanced breast or prostate cancer.\(^1,2\) In addition, it is a major complication of other types of solid cancers, such as lung, kidney, and thyroid; but it is present most often with breast and prostate cancer.

Even though bone metastases can be clinically silent, they can result in bone pain, fractures, and hypercalcemia.\(^4\)

With advancing malignancy, bone pain is a frequent symptom and often dictates quality of life, and decreases performance status.\(^2,3\)

Bone pain as a result of metastatic disease is frequently considered a distinctive type of pain. In the beginning, the pain is dull or aching, that increases in intensity at night, but it improves with physical activity. However, the danger of impending fracture is greater if physical activity increases the pain.\(^2\)

The main mechanism of pain due to small metastases seems to be via chemical mediators (secretions from the tumor) stimulating the nerve endings in the endosteum, while larger bone metastases cause stretching of the periosteum (vascular membrane covering the bones), which results in pain.\(^1,2\)
Also, it has been considered that neuropathic pain can result since tumor growth may entrap and damage nerves.²

Numerous modalities are available for the long-term management of refractory pain caused by malignancies; however, a multidisciplinary approach is required involving the formation of close cross-specialty liaisons.³,⁴

Table 1, shown here, includes a list of modalities used in the management of bone pain:

<table>
<thead>
<tr>
<th>TABLE 1: MANAGEMENT OF BONE PAIN¹,²,⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conventional analgesics</td>
</tr>
<tr>
<td>• External beam radiation</td>
</tr>
<tr>
<td>• Radiofrequency (RF) ablation</td>
</tr>
<tr>
<td>• Chemotherapeutic agents (cytostatic and cytotoxic agents)</td>
</tr>
<tr>
<td>• Hormonal therapy</td>
</tr>
<tr>
<td>• Bisphosphonates</td>
</tr>
<tr>
<td>• Therapeutic radiopharmaceuticals</td>
</tr>
<tr>
<td>• Surgical intervention</td>
</tr>
</tbody>
</table>

To treat localized areas of involvement, perform either:

• Surgery,
• RF (radiofrequency) ablation, or
• External beam radiotherapy.

With more diffuse bone involvement, the options include:

• Therapeutic radiopharmaceuticals,
• Hormonal therapy, and
• Chemotherapeutic agents.²
It is unfortunate that the various non-radiotherapeutic modalities are not helpful in all patients, particularly in the disease’s late stage.¹

Usually, the first step in pain control is the use of analgesic pharmaceuticals via a 3-step approach.

1. The initial step involving the relief of mild to moderate pain is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen.
2. Therapy advances to the next step if the pain is persistent or increases while on NSAIDS and this step utilizes weak opioids such as codeine or hydrocodone.
3. If the pain persists or increases in severity, the third step calls for higher doses of the weak opioids or changing to more potent opioids such as morphine, hydromorphone, or fentanyl.

Significant side effects accompanying the more potent narcotic pharmaceuticals used in this 3 step approach, include: constipation, somnolence, nausea, and limitations in mental and physical status; thus, the result of their use is nearly unavoidable deterioration in the quality of life of a patient in the advanced stages of cancer.²⁵ Particularly frequent symptoms are constipation and lethargy.

Surgery and radiation therapy are utilized for the therapy of localized bone metastases in order to limit the dose of the narcotic pharmaceuticals.²

Wide-field, hemibody radiotherapy may be useful in patients with diffuse metastases; however, the potential benefit is frequently overshadowed by significant gastrointestinal and bone marrow toxicity.¹³

Osteoclast-mediated bone resorption is inhibited by bisphosphonates. and these pharmaceuticals also stimulate osteoblast differentiation as well as bone formation. Since these drugs encourage bone repair, their role in the therapy of painful bone metastatic lesions is increasing.²

Even though these agents decrease the rate of skeletal complications due to osteolytic (bone degeneration) metastases in breast cancer, their function in hormone-refractory prostate cancer is not as well determined.

In order to determine the optimal bisphosphonate, administration mode, dose, and duration of treatment, controlled trials are necessary.³

Since disseminated osseous metastatic lesions are frequently encountered, and some patients suffer with multifocal bone pain, systemic targeted therapy using bone-seeking radiopharmaceuticals is well-matched to the management of skeletal metastases after repetitive local treatment is no longer practical.²³

Because of the comparatively discriminating tumor targeting with these agents, there is a reduction in the possible toxicity via systemic administration.³ Radionuclide therapy for palliation of bone pain has been used successfully for decades.³⁴

Therapeutic radiopharmaceuticals developed for bone pain palliation use the radionuclides listed here:³²P, ⁸⁹Sr, ¹⁸⁶⁸Re, ¹⁸⁸⁸Re, ¹⁸⁵⁵Sm, ¹⁷⁷⁸Sn, ¹⁷⁷⁷Lu and ²²³⁶Ra.²³

Bone palliation success relies on matching a specific pharmaceutical carrier and optimal radionuclide to the physiologic characteristics of the target tissue.
Targeting of the bone is dependent on selective uptake as well as delayed retention in areas of increased osteoblastic activity.\(^5\) Dosimetry delivered to the *tumor and marrow* by these radiopharmaceuticals is difficult to determine for a variety of reasons.

The anatomic distribution of bone trabeculae (network of miniature strands of bone) is quite irregular; thus, the greater the thickness of these trabeculae, as found in osteoblastic lesions, the smaller the distance an emitted particle or photon can traverse.

In addition, the anatomic relationship as well as the distribution of tumor and marrow vary significantly and are occasionally intermixed.

It is not always possible to predict the biological half-life of the radiopharmaceutical, generally being considerably longer on woven or reactive bone in the region of the tumor as compared to normal cortical or trabecular bone.

The radiopharmaceutical’s deposition is never completely homogeneous, and the ratio of radioactivity in the tumor, to normal bone typically ranges from 2 to 5.

In the same patient, the radiation dosimetry of individual tumor lesions will be different due to differences in the target-to-non target ratios between the individual sites.\(^5\)

A therapeutic radiopharmaceutical must possess certain characteristics to be efficacious in alleviating bone pain.

The agent must have a high affinity to metabolically active bone and it must emit particulate radiation, such as \(^\alpha\) decay, beta particle or conversion electrons.

The radiation must be of ample energy to reach the pain causing cells, and the half-life of the radiopharmaceutical must be sufficient to deliver damaging or lethal radiation dosimetry to the cells.\(^6\)

**SODIUM PHOSPHATE\(^{32}\)P SOLUTION**

In 1950, Friedell was the first to use \(^{32}\)P-sodium phosphate for the palliation of intractable bone pain secondary to skeletal metastatic disease.\(^7\)

Phosphorus\(^{32}\)P has a physical half-life of 14.3 days and decays solely by negatron (\(\beta^-\)) emission. The \(\beta^-\) particle has a maximum energy of 1.71 MeV and a mean energy of 694.9 keV. Refer to Table 2.

The product is available as an intravenous dosage form having a concentration of 24.8 MBq (0.67 mCi) per milliliter (mL).\(^8\)

\(^{32}\)P-sodium phosphate was usually administered intravenously. However, in a few series, this radiopharmaceutical has been administered via the oral route with the absorption ranging between 40% and 80%, depending on the diet of the patient.\(^5\) In tissue, the mean \(\beta^-\) particle range is 3 mm, and the maximum range is approximately 8.5 mm.\(^2,3\)
Phosphate is incorporated into the inorganic matrix, hydroxyapatite, throughout the bone as well as being integrated into numerous intracellular compounds.\textsuperscript{2,5}

\textsuperscript{32}P has multiple potential mechanisms of action against metastatic cells. Since \textsuperscript{32}P localizes to a greater degree in more rapidly growing cells and in malignant tumor cells as opposed to normal cells, the result is that the tumor is irradiated by \textsuperscript{32}P accumulated within the tumor.

Also, considerable quantities of \textsuperscript{32}P-labeled phosphates are incorporated into new bone formation, resulting in irradiation of adjacent tumor cells.\textsuperscript{7}

Thirdly, \textsuperscript{32}P is incorporated into the structural backbone of RNA and DNA; and \textsuperscript{32}S, the decay product of \textsuperscript{32}P, may disrupt the chemical bonds which may be cytotoxic (causing destruction of cells).\textsuperscript{5,7} Also during this process, the cells producing pain modulators may be damaged.\textsuperscript{2}

The literature reports a range of fractionated treatment schedules, with administered activities ranging from 300MBq (8.1 mCi) to 740 MBq (20 mCi) over a time period of 7-40 days.\textsuperscript{3} However, there has not been a relationship established between \textsuperscript{32}P dosage and therapeutic response for breast or prostate cancer.\textsuperscript{5}

The administration of testosterone or parathormone in conjunction with \textsuperscript{32}P-sodium phosphate has been demonstrated to stimulate osteoblastic activity around metastases, enhancing the therapeutic ratio between tumor and normal bone. Unfortunately, the possible benefit of this methodology was outweighed by the risk of progression of soft tissue tumor in hormone-sensitive tumors.

After androgen priming, pain relief has been reported to range from 50% to 87% in metastatic prostate cancer patients administered between 200 MBq (5.4 mCi) to 800 MBq (21.6 mCi) of \textsuperscript{32}P delivered in daily fractionated doses of 20 MBq (0.54 mCi) to 80 MBq (2.16 mCi). Pain palliation occurred within 5 to 14 days, and the mean duration of response was 2 to 4 months.\textsuperscript{3} Calculations of the skeletal absorbed doses have ranged from 0.68 cGy/MBq (25.2 rad/mCi) to 1.733 cGy/MBq (64.1 rad/mCi).\textsuperscript{4}

Because of the distribution of \textsuperscript{32}P sodium in the inorganic matrix in addition to the cellular regions, it looks as though the normal marrow accumulates a high radiation dose relative to the tumor.\textsuperscript{4}
Thus, the major drawback of therapy with $^{32}\text{P}$ is the dose-limiting myelosuppression (inhibition in the process of blood cell and platelet production in bone marrow) with reversible pancytopenia (marked reduction in both red and white blood cells and platelets).

It appears that toxicity is cumulative and related to the radioactivity administered. Even though toxic deaths are very rare, in one study 9 out of 30 patients required transfusion support post treatment.\(^5\)

(Note: In August 2009 the sole commercial US manufacturer of $^{32}\text{P}$-sodium phosphate withdrew this radiopharmaceutical from the market.)

### STRONTIUM SR 89 CHLORIDE ($^{89}\text{SRCl}_2$) INJECTION

Strontium-89 has a physical half-life of 50.5 days and decays nearly 100% by $\beta^-$ particle emission with maximum beta energy of 1.463 MeV and a mean energy of 0.583 MeV.\(^6,10,11\) This $\beta^-$ particle has a maximum range in tissue of approximately 8 mm.\(^9\)

Strontium-89 decays by one of two $\beta^-$ particle emissions, one going to the excited level of $^{89}\text{Y}$ and the other to the stable state of $^{89}\text{Y}$.\(^12\)

Following the emission of the $\beta^-$ particle to the excited level of $^{89}\text{Y}$, a 910 keV gamma-ray is emitted with a percent abundance of 0.009%.\(^10,12\) Please refer to Table 3.

The current method of production of $^{89}\text{Sr}$ is via neutron activation of enriched $^{88}\text{Sr}$, and the reaction is $^{88}\text{Sr}(n, \gamma)^{89}\text{Sr}$.\(^12\)

<table>
<thead>
<tr>
<th>TABLE 3: SR-89</th>
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<tbody>
<tr>
<td><strong>Physical Half-life</strong></td>
</tr>
<tr>
<td><strong>Beta (max)</strong></td>
</tr>
<tr>
<td><strong>Beta (mean)</strong></td>
</tr>
<tr>
<td><strong>Gamma/abundance</strong></td>
</tr>
</tbody>
</table>

In 1942, Pecher was the first to report the use of $^{89}\text{Sr}$ for the palliation of pain from prostate carcinoma metastases. And $^{89}\text{Sr}$ chloride injection received FDA approval in June 1993 for the indication of relief of bone pain in patients with painful skeletal metastases.\(^9,10,13\)

Since approval, $^{89}\text{Sr}$ chloride injection has lost its patent protection and is now available from two FDA approved manufacturers.
Strontium can be found in group II of the Periodic Table. After intravenous administration of $^{89}\text{SrCl}_2$, it follows the behavior of calcium analogs by rapidly clearing from the blood and selectively concentrating in bone mineral matrix. $^2,^9,^{14}$

Because $^{89}\text{Sr}$ is taken up by bone undergoing active osteogenesis (bone formation), primary bone tumors and sites of metastatic involvement (osteoblastic lesions) can amass considerably greater concentrations of $^{89}\text{Sr}$ as compared to the contiguous normal bone. $^2,^3,^9$

Biodistribution studies utilizing $^{85}\text{Sr}$, a $\gamma$ emitter, exhibited a therapeutic ratio of 10:1 for tumor to normal bone. $^3$

Strontium-89 has a biological half-life in normal bone of approximately 14 days while in osteoblastic lesions the half-life exceeds 50 days. $^3$

Strontium-89 not localized in the bone undergoes excretion via 80% renal (glomerular filtration) and approximately 20% through the gastrointestinal system. $^2,^3$

In patients having bone metastases, the pathways of excretion are two-thirds renal and one-third gastrointestinal. $^9$

The plasma renal clearance of strontium is significantly decreased in patients with bone metastases as compared to the International Commission on Radiological Protection standard man. $^3$

Following intravenous administration of $^{89}\text{Sr}$, renal excretion is greatest in the first two days. $^9$

Strontium-89 chloride is normally not indicated for patients with a life expectancy of less than 3 months and in patients having disseminated intravascular coagulation. $^6$

The recommended dosage for $^{89}\text{SrCl}_2$ is 148 MBq (4 mCi) administered by slow intravenous injection over a time period of 1 to 2 minutes.

An alternative method of dosing is based on body weight, using 1.5 – 2.2 MBq/kg (40 – 60 uCi/kg).

When a rapid injection has been used, patients have experienced a calcium-like flushing sensation.

Patients should be instructed that the onset of pain relief may require 1 to 3 weeks. Six months is the mean duration of relief. $^2$

During the first 2 to 3 days after treatment, the patients may experience a flare reaction (transient increase in bone pain), and it is readily treated with nonaspirin analgesics. $^2,^6$ A flare reaction is usually predictive of a good response to treatment. $^2$

Based on the individual patient’s response to $^{89}\text{SrCl}_2$, current symptoms, and hematologic status, retreatment is possible at 3 months. It is generally not recommended to repeat administration of this agent at intervals less than 90 days. $^9$

Radionuclides with avidity for bone are expected to have their principal adverse effect on the bone marrow’s hematologic precursor cells. When the bone marrow has already been infiltrated by malignant cells, the potential toxicity is greater. $^{14}$
Prior to the administration of $^{89}\text{SrCl}_2$, the patient’s white cell count should be greater than 2,400 and the platelet count greater than 60,000, since myelosuppression occurs with $^{89}\text{Sr}$.\textsuperscript{6}

The type of analgesic used to treat the flare reaction is important since anti-clotting analgesics, such as aspirin, can exacerbate the thrombocytopenia (decrease in platelets).\textsuperscript{6} Also, it is recommended that low hemoglobin levels be corrected prior to administration of $^{89}\text{SrCl}_2$.\textsuperscript{14}

Every other week a complete blood and platelet count should be acquired to monitor the hematologic toxicity. The lowest point of myelosuppression (nadir) typically occurs at 5 to 6 weeks after therapy.\textsuperscript{3,6}

Recovery is usually slow over the next 6 weeks, and it is determined by the extent of skeletal tumor and the reserve of bone marrow.\textsuperscript{3}

Even though the patient may qualify for retreatment after 90 days, it should be noted that greater marrow toxicity may occur after multiple therapies.\textsuperscript{2}

In a normal healthy adult, intravenously administered $^{89}\text{Sr}$ would deliver 63 cGy/37 MBq (63 rad/mCi) to the bone surface over time.\textsuperscript{6,9}

However, when osteoblastic metastases are present, there is considerably enhanced concentration of $^{89}\text{Sr}$ resulting in correspondingly greater doses to the metastatic sites as compared to normal bones and other organs.\textsuperscript{9}

The percentage of patients who will be free of pain is about 20%. Approximately 75% of patients will have some significant reduction pain; however in some series of studies, the reported percentage of patients experiencing some symptom relief was up to 90%.\textsuperscript{4}

**SAMARIUM SM 153 LEXIDRONAM INJECTION**

Samarium-153 has a physical half-life of 46.7 hours and decays by $\beta^{-}$ emission to stable $^{153}\text{Eu}$.\textsuperscript{12}

Refer to Table 4 for the information on primary radiation emissions. Per decay of $^{153}\text{Sm}$, the average energy emitted as beta particles is 0.233 MeV.\textsuperscript{12}

The 103 keV gamma emission can be used for bone imaging.\textsuperscript{4,6}

The production of $^{153}\text{Sm}$ is via neutron irradiation of isotopically enriched $^{152}\text{Sm}$ oxide. This method of production produces a high yield and purity.\textsuperscript{15}
TABLE 4: PRIMARY RADIATION EMISSIONS FOR $^{153}$SM

| Emissions | MeV* | Abundance |
|-----------|------|--|---|
| $\beta_{11}$ | 0.640 | 30% |
| $\beta_{13}$ | 0.710 | 50% |
| $\beta_{15}$ | 0.810 | 20% |
| $\gamma_{11}$ | 0.103 | 29% |

*Maximum energies are listed for the $\beta^-$ particles.

References: 12, 15

Samarium-153 lexidronam is composed of radioactive samarium and a tetraphosphonatechelator, ethylenediaminetetra methylene phosphonic acid (EDTMP) in a 1:1 complex.\textsuperscript{15,16}

This radiopharmaceutical received FDA approval in 1997.\textsuperscript{17} The product is supplied frozen, and it expires 56 hours after calibration time or 8 hours post thawing, whichever occurs first.\textsuperscript{15}

The recommended dosage of $^{153}$Sm lexidronam is 37 MBq/kg (1 mCi/kg) administered intravenously over a time period of one minute.\textsuperscript{12,15}

In very thin or very obese patients, caution should be used in the determination of the dosage.\textsuperscript{15} For an average 70 kg adult patient, the estimated absorbed radiation dose to the bone surfaces is 25 cGy/37MBq (25 rad/mCi).\textsuperscript{12,15}

In the presence of osteoblastic lesions, considerably enhanced concentration of $^{153}$Sm lexidronam will result, with correspondingly greater doses to the metastatic lesions in comparison to normal bones and other organs.\textsuperscript{15}

Samarium-153 lexidronam localizes in the skeleton, in proportion to osteoblastic activity.\textsuperscript{2} It binds to hydroxyapatite via both chemisorption as well as a hydrolysis reaction. In the hydrolysis reaction the samarium reacts with oxygen atoms present in both water and the hydroxyapatite molecule.\textsuperscript{5}

At 5 hours post intravenous administration of this radiopharmaceutical, less than 1% remains in the blood and approximately 65% of the administered activity remains in the skeleton. By 6 hours after administration, renal excretion is almost complete.

Biodistribution of $^{153}$Sm lexidronam is the same as bone-seeking agents such as $^{99m}$Tc-medronate.\textsuperscript{2} Depending on the skeletal tumor burden, the range of total skeletal uptake is between 55% and 75%.
The ratio of tumor-to-normal bone ranges from 4:1 to 7:1. The average path length of the β⁻ particle is 1.7 mm in bone and 3.1 mm in soft tissue. When taking into account the dose to normal bone marrow, the short range of the β⁻ of $^{153}$Sm should be beneficial.

The noteworthy toxicity that has been demonstrated is thrombocytopenia (reduction in platelets) and neutropenia (reduction in neutrophils) with bone marrow suppression increasing with higher radioactivity. Usually the rapid drop in the number of platelets did not occur until after 2 weeks had elapsed. Once this occurred, the platelet count remained steady for the following two weeks; two to four weeks after the nadir, the platelet count recovered to the pretreatment levels. Another reference reported that the nadir for platelet counts did not occur until 3 to 5 weeks, and recovery occurred by 8 weeks.

The nadir (as in Ralph nadir) for leukocytes has been observed to occur at an average of 24 days after the administration of $^{153}$Sm lexidronam, and the median time to recover to pretreatment levels was 44 days. In 87% of the patients, there was hematologic recovery to baseline levels. Of those who did not recover, bone marrow was replaced by either cancer or radiation therapy for progressive disease.

Using the standard dosing of 37 MBq/kg (1 mCi/kg) of $^{153}$Sm lexidronam, bone pain relief was noted in 35% of the patients 1 week post administration of the radiopharmaceutical. By 4 weeks after injection, the percentage of patients experiencing relief of bone pain was 70%. Even at 16 weeks, 39% of the patients were still reporting effective relief of bone pain.

The duration of response has been reported to be usually 8 weeks with the range being 4 to 35 weeks. Retreatment with additional $^{153}$Sm lexidronam doses has been demonstrated to be both efficacious and safe.

With $^{153}$Sm there is the benefit of providing a high dose rate over a brief time period due to the short physical half-life of 46.7 hours. This possibly explains the early onset of palliation of bone pain.

According to Pandit-Taskar et al, $^{153}$Sm lexidronam is the most extensively used radiopharmaceutical for the palliation of pain in the United States.

### RADIUM RA 223 DICHLORIDE INJECTION

Radium-223 has a physical half-life of 11.4 days. The first α particle emitting radiopharmaceutical, $^{223}$Ra dichloride is indicated for treating men with symptomatic, metastatic, castration-resistant prostate cancer that has spread to bones but not to other organs.

It is intended for use in men whose prostate cancer has metastasized to the skeleton after receiving medical or surgical therapy to lower testosterone. The fraction of energy emitted from $^{223}$Ra and its short-lived daughters as α radiation is 95.3% (energy range of 5-7.5MeV).

As illustrated here in Table 5, small fractions of β⁻ (3.6%) and γ (1.1%) emissions with different energies occur during decay.
TABLE 5: $^{223}\text{Ra}$

<table>
<thead>
<tr>
<th>Physical Half-life</th>
<th>11.4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha $\alpha$</td>
<td>5.56 MeV (max)</td>
</tr>
<tr>
<td>Beta $\beta$</td>
<td>0.492 MeV (max)</td>
</tr>
<tr>
<td>Gamma $\gamma$</td>
<td>1.27 MeV</td>
</tr>
</tbody>
</table>

Radium-223 dichloride is a simple salt form of the radionuclide approved on May 15, 2013 under the FDA Priority Review program.

It is supplied as a ready-to-inject, clear, colorless, isotonic, sterile solution for IV administration.

It should be stored in the original container at room temperature until use. Each vial contains 6mL with 1,000 kBq (27 μCi) per mL at the calibration date/time.

The recommended dosage of $^{223}\text{Ra}$ dichloride is 50 kBq/kg (1.35 μCi/kg) administered intravenously over one minute.\textsuperscript{19}

For the standard 70 kg man, the dosage of $^{223}\text{Ra}$ dichloride would amount to less than 100 μCi. However, the estimated absorbed radiation dose to the osteogenic cells (outer surface) of the bone is much higher than that reported for other commercially available bone pain palliation radiopharmaceuticals as shown here:

- 4,263 rad/mCi for Ra-223,
- 63 rad/mCi for Sr-89, and
- 25 rad/mCi for Sm-153.

As in the case of other agents, reactive bone concentrates Ra-223 to a higher degree than normal skeleton.\textsuperscript{19}

Ra-223, like other bone seeking elements, mimics calcium and forms complexes with the bone mineral hydroxyapatite which is found in higher concentrations in areas of increased bone metabolism such as bone metastases.

The high specific ionization or linear energy transfer associated with $\alpha$ particle emission leads to a high number of double-strand DNA breaks in bone tumor and adjacent cells and cytotoxic effects.

The $\alpha$ particle range of Ra-223 is < 100μm (less than 10 cell diameters) which limits damage to surrounding normal bone tissue and bone marrow.
At 4 hours post intravenous administration of Ra-223 dichloride, less than 4% of the injected radioactivity remains in the blood decreasing to < 1% at 24 hours. Corresponding uptake in the skeleton was 61% at 4 hours with the majority of remaining radioactivity found in the intestine.\(^\text{19}\)

Comparison of the bone surface to red bone marrow dose ratio for the three commercially available bone pain palliation agents indicated Ra-223 was highest at 10.3 followed by Sm-153 at 4.4 and Sr-89 at 1.6.\(^\text{20}\)

During Ra-223 dichloride clinical trials, the most common adverse reactions (≥ 10%) included nausea, diarrhea, vomiting and swelling of the leg, ankle or foot.

The most common abnormalities (≥ 10%) observed in blood testing included low levels of most blood cells (RBCs, lymphocytes, WBCs and platelets).

This bone marrow suppression, observed with all bone pain palliation radiopharmaceuticals, should be monitored closely with baseline \textit{hematologic evaluation performed prior} to dose administration and prior to every subsequent dose of Ra-223 dichloride.

Although effects on quality of life with pain reduction have yet to be reported for the large, Phase III randomized double-blind placebo controlled trial with Ra-223 dichloride (ALSYMPCA TRIAL), pain palliation was reported in smaller numbers of patients involved in Phase I and II studies.

More than half of the patients reported reduction in bone pain with 52% reporting improvement at 1 week, 60% at 4 weeks and 56% at 8 weeks.\(^\text{21}\)

Prolonged pain reduction can be realized with patients receiving up to 6 injections given at 4 week intervals. Safety and efficacy beyond 6 injections have not been studied.\(^\text{19}\)

The Phase III ALSYMPCA trial involving over 800 men was designed to measure overall survival compared with placebo.

An interim analysis of the results showed an extended overall survival benefit of 44% with patients living about 14 months longer in the group that received Ra-223 dichloride versus 11 months for those who received placebo.

In addition to prolonged survival, those treated with the α particle emitter also experienced delayed onset of complications due to bone metastases including pathologic bone fracture and spinal cord compression leading to the need for external beam radiation therapy or surgical intervention.\(^\text{22}\)

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**CONTRAINDICATIONS**

When considering the use of therapeutic radiopharmaceuticals for the treatment of bone pain palliation, there are few, but significant, relative contraindications for their use. They are listed here:

- Patients with significant myelosuppression are not suitable candidates.
- Patients with disseminated intravascular coagulation must not receive these radiopharmaceuticals.
Radiopharmaceuticals for Bone Pain Palliation

Patients with actual or impending spinal cord compression or pathologic fractures of other bones require urgent or emergent radiotherapy or surgical intervention; thus, treatment with therapeutic radiopharmaceuticals is not appropriate.

A relative contraindication to the use of $^{89}$Sr-strontium chloride, and $^{153}$Sm-lexidronam is renal failure because these agents undergo renal excretion.

Since there is not enough data concerning their utilization in patients with renal insufficiency, caution should be exercised in deciding whether or not to use these radiopharmaceuticals for this group of patients.

The decision for these cases should only be made after an appropriate risk analysis has been undertaken.\(^\text{17}\)

**INVESTIGATIVE RADIOPHARMACEUTICALS**

Other radioactive agents have been investigated for use in palliation of painful osseous metastases.

The therapeutic radionuclide rhenium-186 (Re-186) stably attached to the bone seeking chemical etidronate (HEDP) has been studied in patients for bone pain reduction.

Re-186 has a physical half-life of 3.7 days and decays by $\beta^-$ (1.07 MeV max) and $\gamma$ (137 keV) emission.\(^\text{2}\)

Uptake in skeletal lesions is thought to be due to chemisorption in reactive bone.\(^\text{6}\)

The metastable isomer tin-117m (Sn-117m) has a physical half-life of 13.6 days and decays by isomeric transition emitting a $\gamma$ (159 keV).

The $\gamma$ undergoes conversion producing conversion electrons (127, 129 and 152 keV energies) that have potential for destroying cancer cells where the radionuclide localizes.\(^\text{2}\)

The chemical form used in clinical studies was the simple pentetate (DTPA) chelate which carries the Sn-117m to the bone surface where it undergoes hydrolysis and is deposited in bone as the hydrated oxide.\(^\text{6}\)

**SUMMARY**

For more than 30 years, therapeutic radiopharmaceuticals have been successfully employed in the palliation of bone pain.\(^\text{3}\)

Three FDA-approved, commercially available radiopharmaceuticals offer clinicians options for treating their patients with bone pain from metastatic disease.

For successful results regarding safety and efficacy, it is critical to carefully select the radiopharmaceutical that best meets the clinical needs of the patient, monitor patients for evidence of adverse effects and provide supportive therapy as needed.
QUIZ

**QUESTION #1**

Concerning bone metastases:

- 85% occurrence in patients afflicted with advanced breast or prostate cancer
- Bone pain is always present
- In the beginning, pain increases with physical activity
- Main mechanism of pain due to small metastases seems to be via chemical mediators

**QUESTION #2**

It is not appropriate for a patient with __________ to receive therapeutic radiopharmaceuticals for the relief of bone pain associated with metastatic bone disease.

- Nausea
- Alopecia
- Disseminated osseous metastases
- Impending spinal cord compression

**QUESTION #3**

Which radionuclide decays by alpha particle emission?

- $^{32}$P
- $^{89}$Sr
- $^{153}$Sm
- $^{223}$Ra

**QUESTION #4**

Which of the following radionuclides emits radiation with the shortest range in tissue penetration?

- $^{32}$P
- $^{89}$Sr
- $^{153}$Sm
- $^{223}$Ra
QUESTION #5
Which therapeutic radiopharmaceutical is only indicated for use in prostate cancer patients?

- $^{32}$P sodium chloride
- $^{89}$Sr chloride
- $^{223}$Ra dichloride
- $^{153}$Sm lexidronam

QUESTION #6
Which statement is true concerning a flare reaction?

- Recommended treatment is aspirin
- Refers to temporary decrease in pain
- Occurs during first 2 to 3 days after treatment
- Related to rapid injection of the radiopharmaceutical

QUESTION #7
Which radiopharmaceutical(s) has/have the standard dosing of 37 MBq/kg?

- $^{89}$Sr chloride
- $^{153}$Sm lexidronam
- $^{32}$P sodium phosphate
- $^{223}$Ra dichloride

QUESTION #8
The clinical trials with _________ showed a prolonged survival compared with placebo?

- $^{89}$Sr
- $^{223}$Ra
- $^{153}$Sm
- $^{32}$P
QUESTION #9

Which statement is FALSE concerning $^{153}$Sm lexidronam?

- Localizes in the skeleton in proportion to osteoblastic activity
- Binds to hydroxyapatite solely by chemisorption
- Ratio of tumor-to-normal bone ranges from 4:1 to 7:1
- Expires 72 hours after calibration

QUESTION #10

Onset of pain relief with $^{89}$Sr chloride occurs:

- Less than 1 week
- 1 to 3 weeks
- 21 to 50 days
- 50 to 90 days

REFERENCES


