Several bone-seeking radionuclides can reduce pain caused by diffuse skeletal metastasis.

The Role of Bone-Seeking Radionuclides in the Palliative Treatment of Patients With Painful Osteoblastic Skeletal Metastases

Michael Tomblyn, MD, MS

Background: Pain from skeletal metastases represents a major burden of advanced disease from solid tumors. Analgesic medications, bisphosphonates, hormonal agents, cytotoxic chemotherapy, and external beam radiotherapy are all effective treatments. However, patients often suffer from diffuse painful metastases and respond poorly to these standard therapies. Bone-seeking radionuclides can specifically target osteoblastic lesions to offer palliation of pain.

Methods: This article offers a narrative review of bone-seeking radionuclides, examines the evidence of safety and efficacy for the treatment of painful skeletal metastases, and presents guidelines for their appropriate use in this patient population.

Results: Seven bone-seeking radionuclides have shown evidence of both safety and efficacy in reducing pain from diffuse skeletal metastases. $^{153}$Sm-EDTMP and $^{89}$Sr are most commonly used in the United States and have been safely utilized for both repeat dosing as well as concurrent dosing with cytotoxic chemotherapy.

Conclusions: Targeted bone-seeking radionuclides are underutilized in the treatment of painful diffuse osteoblastic metastases. Several new agents are in active clinical investigation, and the pending approval of the first alpha-emitting radionuclide ($^{223}$Ra) may offer a new class of agents that provide greater efficacy and less toxicity than those currently available for routine clinical use.

Introduction
Bone pain arising from symptomatic skeletal lesions is a common cause of morbidity in patients with metastatic cancer, and a majority of patients with diffuse disease require multiple treatment modalities for pain. The most common primary sites of solid tumors giving rise to such lesions are the breasts, prostate, lungs, and kidneys, together representing nearly 80% of all bony metastases.\(^1\) If undiagnosed or inadequately treated, skeletal metastases often lead to profound pain, compression of the spinal cord, hypercalcemia, and pathological fracture of involved bones. Multiple reports suggest a direct correlation between the burden of bony metastases and survival.\(^2\)

Most bone metastases are localized to the red marrow, thus the proclivity for the axial skeleton.\(^3\) Bone metastases are generally classified as osteoblastic (increased formation of bone matrix), osteolytic (increased destruction), or mixed. Although some malignancies give rise principally to blastic or lytic lesions (prostate cancer and multiple myeloma, respectively), most ma-
lignancies exhibit a mixed blastic-lytic phenotype.4 Recently, the interactions between tumor-expressed surface proteins and the bone microenvironment have been better elucidated. Prostate cancer cells often express transforming growth factor beta (TGF-β), which aids in the adhesion to bone matrix and can affect the maturation of osteoclasts.5-8 Epidermal growth factor (EGF) may also enhance metastasis by facilitating the migration of cancer cells from circulation and into bone.7

**Diagnosis of Bone Metastases**
The diagnosis of bone metastases can be made using several diagnostic imaging techniques. The most utilized technique is the 99mTc nuclear medicine bone scan; the radionuclide tracer, attached to an organophosphate (methylene diphosphonate), is specifically incorporated into the skeleton in areas of significant osteoblast activity, preferentially binding to hydroxyapatite within the bone matrix. Although this type of bone scan is useful for osteoblastic metastases (such as from prostate, lung, or breast tumors), primarily osteolytic lesions (myeloma, thyroid, renal cell), generally exhibit poor uptake. Plain films and computed tomography (CT) scans are sensitive for observing the destructive characteristics of such osteolytic metastases.8 Other imaging modalities, such as magnetic resonance imaging (MRI) and 18F sodium fluoride (NaF) positron emission tomography (PET), may also have utility in select patients.

**Treatment Options**

Pain from bone metastases generally exhibits two distinct components. The first is a chronic, baseline level of pain caused by local effects of bone remodeling and the inflammatory reaction around the metastatic foci. The second component is often elicited by physical activity or with certain positions. It is more acute and severe and is often referred to as “breakthrough pain.”9,10

Beyond nonsteroidal and narcotic analgesics, external-beam radiotherapy (EBRT) is the most common form of palliation for pain arising from bone metastases. The American Society for Radiation Oncology recently published comprehensive evidence-based guidelines for the use of palliative EBRT for bone metastases.11

Although traditional forms of radiotherapy are effective for palliation of symptoms associated with bone metastases,12 many patients present concurrently with painful lesions in several distinct areas of the skeleton. Large-field radiotherapy such as hemibody radiation therapy is effective,13 but it has been largely abandoned due to concerns over the toxicity of radiating such large fields,14 the technical challenges of providing hemibody radiation therapy, and the time-consuming nature of such a technique. For patients with diffuse symptomatic skeletal involvement, a systemic approach is often necessary. Intravenous bisphosphonates play an important role in the reduction of skeletal events in these patients.

<table>
<thead>
<tr>
<th><strong>Indications</strong></th>
<th><strong>Relative Contraindications</strong></th>
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<tbody>
<tr>
<td>Diffuse skeletal metastases visualized on nuclear medicine bone scan</td>
<td>Uncontrolled extraskeletal disease burden</td>
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<tr>
<td>Painful skeletal metastases inadequately treated by analgesics</td>
<td>Asymptomatic skeletal metastases</td>
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<td>Intolerance to prescribed analgesics</td>
<td>Skeletal lesions limited to fewer than three sites</td>
</tr>
<tr>
<td>Hormone-insensitive disease (for metastatic prostate cancer)</td>
<td>Purely osteolytic lesions (no uptake on bone scan)</td>
</tr>
</tbody>
</table>

**Absolute Contraindications**

- Presence of epidural spinal cord compression
- Pending or active pathological fracture of weight-bearing bone
- Renal failure
- Pregnancy
- Breast-feeding

**Radionuclide Therapy**
Over the past few decades, several radiopharmaceuticals have been developed with bone-seeking properties that provide palliation of pain to multiple areas of the skeleton simultaneously without the significant soft-tissue toxicity and technical complications of large-field EBRT. These agents are generally delivered intravenously and quickly localize specifically to sites of active bone reaction and remodeling. Excess radionuclides not deposited in these areas of remodeling are typically eliminated quickly from the body, either through the genitourinary or gastrointestinal system. Specific indications and contraindications to bone-seeking radionuclide therapy are summarized in Table 1.

To date, seven bone-seeking radiopharmaceutical agents have shown evidence of safety and efficacy in the medical literature (Table 2). Most are beta-emitters, releasing highly energetic electrons that deposit their energy over up to several millimeters in the surrounding tissues. The energies of emitted beta particles are generally not sufficient to elicit a significant cytotoxic response. Radium-223 (223Ra), a recently developed alpha-emitter, releases a large helium nucleus, causing more biologic damage but over a much shorter path length and with the possibility of killing tumor cells and reducing tumor burden. Other beta-emitting radionuclides have been proposed for the treatment of bone metastases, with preclinical animal evidence of targeting to the stroma surrounding these lesions. Following is a review of the evidence for their use in patients with diffuse skeletal metastases.
Mechanism of Uptake Into Bone

Radiopharmaceuticals intended for the treatment of bone metastases are incorporated into bone by one of two major mechanisms. Radionuclides residing in family IIA of the periodic table carry the same divalent charge as elemental calcium and are incorporated into bone matrix directly. Most other radionuclides are not efficiently targeted to bone naturally and instead are chelated to organic phosphates, which are incorporated into the matrix. Several of the therapeutic agents emit small amounts of gamma radiation, allowing for a scintigraphic visualization of uptake, and the patterns of skeletal uptake of the therapeutic agents are congruent with those seen with the diagnostic bone scan.

Approved Radionuclides

**Phosphorus-32 (32P):** Although no longer in common use, the beta-emitter 32P, in the form of a sodium orthophosphate, was the first systemic radionuclide to be used for the treatment of bone metastases. It exhibits a physical half-life of 14.3 days, with an average beta particle energy of 695 keV, a mean path length of 3 mm, and a mean range in bone of 1.7 mm.15 32P is incorporated into hydroxyapatite and decays to sulfur-32 (32S), the isotope likely responsible for the agent’s efficacy. Significant myelosuppression16 led to the abandonment of 32P, as newer radionuclides were developed.

**Strontium-89 (89Sr):** Strontium is a member of family IIA of the periodic table and carries the same divalent charge as calcium. The body is unable to distinguish between the two elements, so the clinically utilized isotope 89Sr is provided as a simple chloride salt and is directly incorporated into bone. 89Sr is a beta-emitter, with a half-life of 50.5 days. The mean energy of the beta particles is 580 keV, with an average range in soft tissue of 2.4 mm and an effective range of 5 to 6 mm.17 Less than 0.01% of the emissions are gamma rays,18 so postinjection imaging is not performed. Osteoblastic bone metastases take up 89Sr specifically in areas of osteoblastic bone metastases, with approximately 5-fold greater uptake compared to normal bone.19 89Sr not incorporated into bone is eliminated from the body through both the genitourinary (80%) and gastrointestinal (20%) systems. The standard prescribed dose for 89Sr is 4 mCi for all patients.

89Sr can be effective at palliating pain from bone metastases, particularly for metastatic prostate or breast cancer, with pain relief reported in 60% to 92% of patients.20-24 Relief typically begins by the second or third week following the injection, with a median duration of approximately 6 months. One study showed a significant improvement in quality of life in patients with prostate cancer due to a reduction in skeletal pain following administration of 89Sr.25 A brief but self-limited flare of bone pain lasting 24 to 48 hours is not uncommon following treatment with 89Sr. However, patients experiencing this complication may have a superior long-term palliative response compared with those who do not have a “pain flare.”

A dose-response relationship for relief of pain exists for 89Sr for patients with metastatic prostate cancer.26 However, dose escalation up to 10.8 mCi does not affect overall survival.27 Combining 89Sr with chemotherapy appears to improve pain response28,29 and may affect survival in patients with metastatic prostate cancer.30 Two randomized trials of 89Sr vs EBRT alone showed similar responses for pain relief in patients with androgen-independent prostate cancer metastases, but there seemed to be a greater freedom from developing new painful sites with 89Sr, and the US Food and Drug Administration (FDA) approval of 89Sr was granted for this reason.31,32 However, overall survival was superior in the EBRT arm of a randomized trial by the European Organisation for Research and Treatment of Cancer (EORTC), and radiotherapy was less costly to deliver.

**Samarium-153 (153Sm):** Samarium is a member of the lanthanide family of the periodic table, with several dozen isotopes described. The clinically utilized iso-

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<table>
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<th>Radionuclide</th>
<th>Half-life (days)</th>
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<th>Average Energy (keV)</th>
<th>Average Path Length (mm)</th>
<th>Gamma Emission</th>
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</table>

β− = beta particle, CE = conversion electron, α = alpha particle
The isotope is $^{153}\text{Sm}$, a beta-emitter with a half-life of 1.9 days. Since $^{153}\text{Sm}$ has no inherent bone-seeking properties, the isotope is chelated to ethylene diamine tetramethylene phosphonate (EDTMP), which targets the bone matrix as a polyphosphonate. The mean energy of released beta particles is 235 keV, with an average range in soft tissue of 0.5 mm and an effective range of 2 to 3 mm. $^{153}\text{Sm}$ also releases gamma radiation (29%, 103 keV), which allows for direct scintigraphy of the administered radionuclide.

In fact, scintigraphic studies of patients with metastatic prostate cancer have shown identical patterns of skeletal uptake after administration of technetium-99m-methylene diphosphonate ($^{99m}\text{Tc-MDP}$) and $^{153}\text{Sm-EDTMP}$. Approximately two-thirds of the injected dose is incorporated into the skeleton, and urinary excretion of unincorporated tracer is essentially complete within 6 hours.

The standard specific activity of $^{153}\text{Sm}$ prescribed for patients with bone metastases is 1 mCi/kg to a maximum of 150 mCi. Several studies have shown the radionuclide to be effective at palliating pain from bone metastases. Palliation of pain occurs in approximately 60% to 80% of patients within 1 week of administration of $^{153}\text{Sm}$, with a clear dose response in dose escalation studies. A randomized trial using 0.5 mCi/kg vs 1.0 mCi/kg of $^{153}\text{Sm}$ in patients with bone metastases from a variety of primary tumors showed significant pain improvement with the higher dose as well as superior survival in the patients with breast cancer treated with the higher dose.

Serafini et al. performed a double-blind, randomized controlled trial of $^{153}\text{Sm-EDTMP}$ (at 0.5 and 1.0 mCi/kg) vs placebo in patients with skeletal metastases from solid primary tumors. Efficacy was measured using a standard subjective visual analog scale (VAS), a blinded physician’s global assessment of pain (PGA), and a record of daily use of opioids. Patients receiving the higher dose of $^{153}\text{Sm}$ reported significant pain responses based on VAS at all time points (weeks 1–4) compared with placebo, whereas patients given the lower dose had improved VAS scores only at week 1. Two-thirds of patients treated at the higher dose with significant pain relief at week 4 were judged by the PGA to be responders at week 16. Significant reduction in opioid use was seen at the higher dose level only, compared with placebo.

Sartor et al. completed a double-blind (2:1), randomized controlled trial of 1.0 mCi/kg of $^{153}\text{Sm-EDTMP}$ vs placebo in patients with metastatic prostate cancer. Patients randomized to receive $^{153}\text{Sm}$ reported significant improvement in subjective pain response compared with those receiving placebo in weeks 2 to 4 following injection. They also used significantly fewer opioids than patients who were given placebo.

Repeat dosing with $^{153}\text{Sm}$ is both safe and effective. Two reports of patients with symptomatic bone metastases receiving multiple doses of $^{153}\text{Sm}$ showed no significant differences in pain reduction or in myelosuppression after a second or third treatment.

Several early-phase clinical trials combining $^{153}\text{Sm}$ with cytotoxic chemotherapy for patients with metastatic prostate carcinoma have been reported. Morris et al. performed a phase I study of escalating doses of docetaxel (65–75 mg/m²) and $^{153}\text{Sm}$ (0.5–1.0 mCi/kg) in 28 men with androgen-independent disease. No maximum tolerated doses were reached, and 15 patients exhibited a decline in prostate-specific antigen (PSA) level of more than 50%.

Tu et al. performed a dose-escalation study of two 28-day cycles of low-dose weekly docetaxel (25–35 mg/m²) on days 1, 8, and 15 with $^{153}\text{Sm}$ (1.0 mCi/kg) on day 1 of each cycle. The maximum tolerated dose was not reached in this study of 18 patients. Five patients (28%) had a decline in PSA level of at least 50%.

Fizazi et al. reported a phase II trial of 43 patients with androgen-independent metastatic prostate cancer who exhibited a clinical response to 4 cycles of docetaxel and estramustine chemotherapy. Patients received weekly docetaxel (20 mg/m²) for 6 weeks with $^{153}\text{Sm}$ (1.0 mCi/kg) at week 1. A further reduction in PSA level was seen in 77% of patients, with a reduction in pain in 69%. The regimen was well tolerated, with 81% receiving at least 5 of the 6 planned cycles of docetaxel. Grade 3 hematologic toxicity (thrombocytopenia) occurred in 2 patients. The median survival was 29 months, with 1- and 2-year survival rates of 77% and 56%, respectively.

### Investigational Radionuclides

**Rhenium-186 ($^{186}\text{Re}$) and Rhenium-188 ($^{188}\text{Re}$):**

Rhenium is a transition metal with two clinically important isotopes: $^{186}\text{Re}$ and $^{188}\text{Re}$. Both are radionuclides attached to hydroxyethylidene diphosphonate (HEDP) for bone targeting. $^{186}\text{Re}$ has a half-life of 3.7 days. Its beta emission exhibits a mean energy of 3.49 keV and an average range in soft tissue of 1.1 mm (maximum range, 4.5 mm). $^{186}\text{Re}$ also emits a small gamma component (9%, 137 keV), allowing for postadministration imaging of biodistribution. The short half-life and path length of $^{186}\text{Re}$ could potentially be useful in patients with poor bone marrow reserve.

One study of bone metastases from breast cancer showed palliation of bone pain in more than 90% of patients treated with $^{186}\text{Re-HEDP}$. Similar efficacy has been seen with this agent in patients with metastatic prostate cancer. The maximum tolerated dose of $^{186}\text{Re-HEDP}$ appears to be 65 mCi.

The PLACORHEN randomized controlled trial of $^{186}\text{Re-HEDP}$ vs placebo showed a significantly higher rate of pain responders (65% vs 36%, respectively). The number of patients in this study requesting palliative EBRT was higher in the placebo group than in the treatment group (67% vs 44%). Repeat administration of $^{186}\text{Re-HEDP}$ appears to be both safe and effective in select patients.
Since \(^{188}\text{Re}\) is easily produced using an inexpensive generator, it has primarily been investigated in the developing world. \(^{188}\text{Re}\) has a half-life of 0.7 days, a mean beta particle energy of 2120 keV, and an average range of 3 mm in soft tissue (maximum, 11 mm). The higher beta energy for this isotope offers the potential for lethal insults to tumor cells in the region of decay. Relatively high doses (up to 70 mCi) have been given to patients with metastatic prostate cancer, with good efficacy of pain relief. The safety and efficacy of repeat dosing of \(^{188}\text{Re}\)-SnHEDP have also been described.

**Tin-117m (\(^{117}\text{Sn}\)):** Tin is a main group metal on the periodic table and has the greatest number of stable isotopes of all the elements. The metastable isotope \(^{117m}\text{Sn}\), chelated to diethylenetriamine pentaacetic acid (DTPA), is under investigation as a possible therapeutic radionuclide for the treatment of bone metastases. \(^{117m}\text{Sn}\) has a half-life of 13.6 days and emits low-energy conversion electrons, with an effective path length measured in micrometers. Tin is a natural bone-seeker, but its highest specificity for bone occurs when the element is in its quatrivalent state (\(4+\)). DTPA stabilizes tin in this preferred \(4+\) state, protecting it from competing redox reactions in vivo.

A comparison of dosimetric models of potential bone-seeking radionuclides performed by Bouchet et al suggests that the low energy and short range of the emitted conversion electron may provide an optimal therapeutic window. In clinical studies, pain relief with \(^{117m}\text{Sn}\) in patients with metastatic prostate cancer has been promising, with a low risk of myelosuppression. A comparison of dosimetric models of potential bone-seeking radionuclides performed by Bouchet et al suggests that the low energy and short range of the emitted conversion electron may provide an optimal therapeutic window. In clinical studies, pain relief with \(^{117m}\text{Sn}\) in patients with metastatic prostate cancer has been promising, with a low risk of myelosuppression.65,66

**Radium-223 (\(^{223}\text{Ra}\)):** Radium is also a member of family IIA and may be best known for its discovery in 1898 by Marie and Pierre Curie. The propensity for ingested radium to be deposited directly into bone has been recognized for nearly a century, first appreciated when workers using luminous radium-based paint began to exhibit cancers of bone and leukemias. \(^{223}\text{Ra}\) (provided as a radium chloride salt solution) is an alpha-emitting isotope, with a half-life of 11.4 days and a mean path length of less than 0.1 mm in soft tissue. Its mean alpha particle energy is 5850 keV. This limited range and high linear energy transfer of the emitted alpha particle allow for potentially lethal insults to surrounding tumor cells, with minimal exposure to the nearby bone marrow.

Early experience with this investigational agent suggests a low incidence of clinically significant myelosuppression, even with repeated dosing. A phase II clinical trial of \(^{223}\text{Ra}\) in patients with symptomatic, hormone-refractory prostate cancer showed an improvement in survival, PSA levels, and alkaline phosphatase levels compared with placebo, with no differences in hematologic toxicity.66

Based on these early encouraging data, an international double-blind, placebo-controlled randomized trial (alpharadin in symptomatic prostate cancer [ALSYMPCA]) was performed to compare \(^{223}\text{Ra}\) with placebo (2:1 randomization) in patients with symptomatic, androgen-independent prostate cancer with skeletal metastases. Patients had received docetaxel, were ineligible for the chemotherapy, or refused it. The study was stratified based on alkaline phosphatase levels at registration, bisphosphonate use, and prior treatment with docetaxel. A total of 922 patients from 19 countries were enrolled in this trial, with the primary endpoint of overall survival.

At the time of the planned interim analysis, the improvement in overall survival exceeded the predetermined boundary, and the independent data monitoring committee stopped the trial. The data were presented in part at the 2011 European Multidisciplinary Cancer Congress meeting, and the authors reported a significant reduction in the risk of death for patients randomized to the \(^{223}\text{Ra}\) arm (hazard ratio [HR], 0.695; \(P = 0.00185\)), with a median overall survival of 14 vs 11.2 months. The overall survival benefit was seen across all subgroups. The time to a skeletal-related event was also significantly longer for patients in the \(^{223}\text{Ra}\) arm (13.6 vs 8.4 months; \(P = 0.0046\)). The time to disease progression based on PSA and alkaline phosphatase levels was significantly superior in the \(^{223}\text{Ra}\) arm. The patients randomized to \(^{223}\text{Ra}\) tolerated treatment well, with no grade 3 or 4 side effects that occurred more often with \(^{223}\text{Ra}\) than with placebo.

Based on the results of this pivotal trial, regulatory approval of this novel agent is expected in late 2012. In the interim, an expanded-access protocol is currently open for enrollment of patients with symptomatic metastatic androgen-independent prostate cancer. Additionally, a 60-patient phase I/II protocol examining the combination of \(^{223}\text{Ra}\) with docetaxel chemotherapy for this patient population is currently open for accrual in the United States. A phase II study of \(^{223}\text{Ra}\) in patients with metastatic breast cancer recently closed to accrual in Europe.

**Potential Future Radionuclides**

**Lutetium-177 (\(^{177}\text{Lu}\)):** A beta-emitter, \(^{177}\text{Lu}\) is currently used for radioimmunotherapy and peptide receptor radionuclide therapy. Due to its 6.7-day half-life, maximum beta energy of 497 keV, and reliable gamma emission for imaging, \(^{177}\text{Lu}\) has been considered for a number of therapeutic roles. Preclinical studies of \(^{177}\text{Lu}\)-EDTMP have shown specific accumulation within the bones of rats. \(^{177}\text{Lu}\)-EDTMP use has been reported in humans for imaging purposes. Results of clinical trials have yet to be reported.

**Thulium-170 (\(^{170}\text{Tm}\)):** This beta-emitter is produced by thermal neutron bombardment of thulium oxide and has recently been proposed as a potential therapeutic radionuclide. \(^{170}\text{Tm}\) has a long half-life (128 days), a high maximum beta energy (968 keV), and sufficient gamma emission for imaging. Investigators...
from India prepared $^{170}$Tm-EDTMP, which was shown to specifically accumulate in bone and reside for at least 60 days following administration in rats.$^{71}$ No human use has been reported to date.

**Potential Uses of Radionuclides**

**Metastatic Breast Cancer**

Most of the published evidence supporting the use of bone-seeking radionuclides in patients with skeletal metastases has focused on androgen-independent adenocarcinoma of the prostate, especially given its typical osteoblastic bone lesions, the usual absence of extraskeletal metastases, and the paucity of effective cytotoxic chemotherapeutic options for these patients. However, many patients with widespread bone metastases from breast cancer harbor painful lesions exhibiting uptake on bone scans. Three major randomized controlled trials of bone-seeking radionuclides allowed for inclusion of 126 patients with breast cancer.

Baczyk et al.$^{72}$ reported the results of a randomized controlled trial comparing $^{89}$Sr and $^{153}$Sm in patients with metastatic prostate cancer ($n = 60$) and breast cancer ($n = 40$). There was no difference in pain relief between the radionuclides, but patients with a mixed blastic/lytic pattern of metastases experienced less pain relief than did patients with purely blastic disease. All patients tolerated the radionuclide treatments well.

Reshe et al.$^{73}$ compared 0.5 and 1.0 mCi/kg of $^{153}$Sm-EDTMP for patients with painful bone metastases. A total of 36 of the 114 patients had breast cancer. A clear dose response was described for pain relief, and the patients with the best pain relief and overall survival were those with breast cancer receiving the higher dose.

The only published randomized controlled trial of radionuclides for metastatic breast cancer was performed by Sciuto et al.$^{74}$ Patients were randomized to receive either $^{89}$Sr or $^{186}$Re-HEDP. Pain response and duration were similar between the groups. However, patients receiving $^{186}$Re-HEDP obtained pain relief more quickly and recovered from transient myelosuppression significantly faster than did patients treated with $^{89}$Sr.

Christensen and Petersen$^{75}$ recently performed a systematic review of the evidence for the use of radionuclides for patients with breast cancer and painful bone metastases. In addition to the three randomized controlled trials previously mentioned, they found 16 case series that included patients with metastatic breast cancer and used $^{89}$Sr, $^{153}$Sm, or $^{186}$Re with palliative intent. They concluded that there is a significant lack of high-level evidence supporting the use of bone-seeking radionuclides in this patient population and that randomized controlled trials are needed.

**Prior to EBRT**

Although most studies have evaluated either modality alone, investigators have examined the role of combining focal radiotherapy to large symptomatic sites with subsequent systemic radionuclides to address the more diffuse skeletal disease. Investigators from Turkey examined this therapeutic combination in 33 patients with diffuse, symptomatic bone metastases from a variety of solid tumors. In this nonrandomized study, the addition of either $^{153}$Sm-EDTMP or $^{186}$Re-HEDP provided additional pain relief beyond that reported after focal radiotherapy alone.$^{76}$

Two placebo-controlled randomized trials examining adjuvant $^{89}$Sr following EBRT reported the opposite conclusions as to the additional pain relief provided by the radionuclide.$^{75,76}$ However, the study by Smeland et al.$^{77}$ closed early due to poor accrual, lacking the power to determine a significant difference between the arms.

**Administration and Side Effects of Radionuclides**

In the United States, bone-seeking radionuclides are generally administered in the outpatient setting, as the lack of significant gamma emission makes radiation precaution isolation procedures unnecessary. In other countries, regulatory authorities may require patients to remain in the hospital for hydration and observation for several hours or overnight after the administration. Following informed consent, the patient is identified through two or more identifiers. Intravenous access is obtained and flushed prior to the procedure. Patients often are hydrated prior to the injection, either orally or with up to 500 mL of normal saline, to allow for an efficient elimination of radionuclide not incorporated into bone.

The authorized user administers the radionuclide injection through the intravenous access over approximately 1 minute. The line is flushed with 20 to 30 mL of normal saline, and the access is removed by the procedure nurse. The patient is then given discharge instructions as well as recommendations to drink and urinate frequently for the first several hours. Typically, the injection is followed with weekly blood counts for up to 8 weeks to monitor the predictable transient decline and recovery of platelet and leukocyte counts.

The principal side effect of bone-seeking radiopharmaceuticals is transient myelosuppression. Thrombocytopenia is the most common form, with platelet counts generally exhibiting a nadir at 40% to 60% from baseline. In most patients, this event will lead to only grade 1 or 2 toxicity. Significant problems with neutropenia and anemia are even less common. Approximately 5% to 10% of patients will experience a “flare reaction,” with a transient and self-limited increase in bone pain. This event is more common in patients with a significant burden of bone metastases visualized on bone scan. Other uncommon side effects may include nausea, loose stools, asymptomatic hematuria, and heart palpitations.
Bone-Seeking Radionuclides and Bisphosphonates

Given the deposition of most agents in this class of radionuclides, many physicians may express concern over patients receiving both bone-seeking radionuclides and bisphosphonate therapy. A European group has reported the results of a prospective study of combined 153Sm-EDTMP and zoledronic acid in 20 patients with metastatic, hormone-refractory prostate cancer.27 They found no effect of zoledronic acid on the uptake of 153Sm-EDTMP, considering combined treatment to be both safe and effective.

Conclusions

Bone-seeking radionuclides are safe and effective agents to relieve pain in patients with osteoblastic bone metastases from solid tumors, and a recent update of a Cochrane systematic review28 supports the use of these agents for palliation of bone pain in this population, albeit with the risk of transient myelosuppression. Good candidates are those with multiple sites of symptomatic disease visualized on a nuclear medicine bone scan, with adequate baseline blood counts and pain not well controlled with analgesics. 153Sm-EDTMP and 89Sr are two FDA-approved agents in general clinical use in the United States. Both have been shown to be safe and effective with repeat dosing. In early-phase clinical trials, both were shown to offer additional promise when used together with cytotoxic chemotherapy, without adding significant additional hematologic toxicity. Other agents in this class are under active clinical investigation and have shown similar efficacy in early-phase clinical trials. The most promising investigational agent is 223Ra, an alpha-emitting bone-seeking radionuclide, which led to superior overall survival in a recently reported placebo-controlled randomized clinical trial.

References


