Radiopharmaceuticals: When and How to Use Them to Treat Metastatic Bone Pain

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Bone pain due to osseous metastasis constitutes the most frequent type of pain in cancer patients. It is significantly related to poor quality of life in the final stages of the disease. Although it is most commonly seen in the advanced stages, patients can often present with bone pain as the first symptom of cancer, particularly in prostate and breast cancers. The prevalence of painful osseous metastases varies among the different types of cancers. Approximately 65% of patients with prostate or breast cancer and 35% of those with advanced cancers of the lung, thyroid, and kidney will have symptomatic skeletal metastases. Breast and prostate cancers are responsible for more than 80% of cases of symptomatic bone metastases in any oncologic practice.[1,2] This type of pain is distinct from neuropathic, visceral, or other types of somatic pain, such as inflammatory and arthritic pain, and presents with certain features during its course: initially, it is dull and of low intensity and progresses to a chronic state with intermittent severe breakthrough episodes of acute pain. Generally, the bone pain exacerbates at the end of dose of the analgesic, and it is often difficult to treat without being accompanied by significant, unwanted side effects. The pathophysiology is not well understood, and multiple mechanisms are postulated.[3] Tumor-induced cytokines, stimulating factors released by tumor cells, and direct nerve injury have all been proposed as mechanisms that mediate skeletal pain. Infiltration of bone trabeculae and matrix by tumor-causing

Abstract Bone pain due to skeletal metastases constitutes the most common type of cancer-related pain. The management of bone pain remains challenging and is not standardized. In patients with multifocal osteoblastic metastases, systemic radiopharmaceuticals should be the preferred adjunctive therapy for pain palliation. The lack of general knowledge about radiopharmaceuticals, their clinical utility and safety profiles, constitutes the major cause for their underutilization. Our goal is to review the indications, selection criteria, efficacy, and toxicities of two approved radiopharmaceuticals for bone pain palliation: strontium-89 and samarium-153. Finally, a brief review of the data on combination therapy with bisphosphonates or chemotherapy is included.

osteolysis also generates skeletal pain, which is supported by the inhibitory osteoclastic effect of bisphosphonates in the treatment of bone pain.[4] Peripheral nerve endings are also triggered by various substances produced by cells in response to the tumor (eg, prostaglandin E, interleukins, substance P, transforming growth factor) and by the tumor cell itself (tumor necrosis factor); these molecular signals lead to sensitization of the peripheral nervous system, causing allodynia and hyperalgesia.[5]

The appearance of bone involvement may be the first and only sign of solid tumor spread, detected in many instances before the primary site. Due to a high prevalence of osseous metastasis, screening whole-body bone scintigraphy has been part of the initial staging algorithm of prostate and breast cancers. Also, when osseous metastasis is suspected clinically or detected by other imaging modalities, bone scintigraphy helps to delineate the extension and severity of skeletal involvement and classify lesions as predominantly osteoblastic, lytic, or mixed type, which will be crucial in the correct treatment plan, as discussed later in this article.[1]

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The Challenge of Managing Bone Pain

The appropriate management of painful skeletal metastasis is complicated and expensive and should be carried out by a multidisciplinary approach.[6] The current treatment strategy for cancer pain palliation involves a variety of modalities.

Most of the therapies targeted to destroy the tumor itself are effective methods of pain control, like chemotherapeutic agents, external beam radiation (XRT), radiofrequency ablation (RF), and surgery. However, they sometimes can be invasive (ie, surgery and RF) or arduous to administer (ie, chemotherapeutic regiments), can provide incomplete pain control, or can be accompanied by unwanted side effects, particularly in patients with extensive metastatic disease. Medications without tumoricidal effect targeted to diminish the pain associated with metastasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opiates, are equally useful but also have dose-limiting side effects.

Despite a large armamentarium of available analgesics, it has been reported that at least 45% of cancer patients have insufficient and undermanaged pain control, due to a poor estimation of the patient's pain by the physician, inadequate pain assessment, treatment-associated side effects, and lack of knowledge of all treatment options.[7] Symptomatic pain assessment must be performed with standardized measurement tools administered at appropriate intervals. Consistent pain measurement and systematic recording of analgesic use across clinical trials would enhance comparability of findings and facilitate the development of evidence-based guidelines for the management of metastatic bone pain. For instance, a consensus on palliative end-point measurements in bone metastases has been in use for XRT trials and can be used as a reference in future trials of other palliative modalities.[8]

Furthermore, the physician caring for these cancer patients should understand that no single method is capable of offering adequate pain control for most individual cases and frequently a combination of systemic and local treatment is necessary, particularly to avoid debilitating side effects. At this time, curative options do not exist for multiple skeletal metastases, and all described treatments are palliative.

Among available therapies, systemic radiopharmaceuticals are the least understood and used by clinical oncologists and pain specialists. Our major goal is to increase awareness of available radiopharmaceuticals for bone pain palliation. We will review the current indications, patient selection criteria, efficacy, and toxicity profile of two radiopharmaceuticals which are currently approved for bone pain palliation: strontium-89 chloride (Sr-89) and samarium-153 lexidronam (Sm-153). Finally, the available data on combination therapy of radiopharmaceuticals with bisphosphonates or chemotherapy will be discussed. The use of other available palliative treatment options, including pharmacological, surgical, and hormonal modalities, is beyond the scope of this article. However, since XRT is the main alternate modality to radiopharmaceuticals for the treatment of painful osseous metastasis, a short discussion of this method will be provided below.

External Beam Radiation for Pain Control

The therapeutic purposes of XRT for bone metastases are pain relief as measured by reduced pain intensity scores, elimination or reduction of analgesic usage, functional improvement such as increased ambulation, and reduction in the risk of fracture in weight-bearing bones. Extensive data from large multicenter, randomized trials conducted by the Radiation Therapy Oncology Group (RTOG) have demonstrated that 80%–90% of patients receiving radiation therapy for osseous metastases will experience complete or partial pain relief, typically within 10–14 days of the initiation of therapy with minimal side effects.[9] Patients with metastases from slowly-proliferating tumors such as prostate cancer may respond less rapidly. The overall proportion of patients receiving pain relief rises to approximately 90% in 3 months; and 70% of the patients experiencing pain relief do not develop recurrent pain in the treated region. Sustained local pain relief for one year is noted in almost two-thirds of patients. Therefore, it is indisputable that patients with localized painful osseous metastasis accessible to XRT should initially receive such therapy for palliation.

However, XRT has limited use in extensive multifocal osseous metastasis or in metastatic sites included in previously treated radiation fields. Also, it does not preclude the development of other metastatic foci away from or nearby sites that were treated for disease. Although hemibody or total-body radiation can sometimes be utilized, the total delivered dose is limited due to its high risk of inducing severe bone marrow suppression. In addition, patients must be hospitalized and given extensive supportive care. Studies have shown that approximately 80% of patients may be successfully treated with sequential whole-skeleton radiation, in which 6–7 Gy is administered as a single fraction to either the upper and lower parts of the body, followed by a second dose of 6–8 Gy, given 4–6 weeks later, to the remainder of the body.[10] Although the expected response is within 24–48 hours, depending on the location of the radiation treatment field, 60% of patients experience adverse side effects such as diarrhea, nausea, lymphedema, fatigue, radiation pneumonitis, and hair loss, all of which can be quite challenging.[7,11] Also, the total cost of this treatment is significantly higher than conventional single or fractionated localized XRT.

Therefore, patients with widespread metastatic bone disease or osseous lesions within previously treated radiation fields may be ideal candidates for treatment with systemic radiopharmaceuticals. The possibility of combining radiopharmaceuticals and localized XRT is exciting, although limited data are available.[12]

Targeted Systemic Radionuclide Therapy with Bone-Seeking Radiopharmaceuticals

Systemic radionuclide therapy has shown its value in the management of painful bone metastasis in current clinical practice.[1,7,13,14] However, radionuclide therapy remains a relatively unknown treatment modality for many physicians,

Table 1

Comparison Between Clinically Used Bone Seeking Radiopharmaceuticals

RADIOPHARMACEUTICAL	HALF-LIFE (DAYS)	STANDARD DOSE (SI)	GAMMA-ENERGY (keV) (%)	BETA-ENERGY (MeV) (MAXIMUM)	MAXIMUM PENETRATION IN TISSUE (AVERAGE)	REMARKS
Sr-89 chloride	50.5	4 mCi (148 MBq)	910 (0.01%)	1.46	6 mm (2.4 mm)	Longest half-life
Sm-153 lexidronam	1.9	1 mCi/kg (37 MBq/kg)	103 (28%)	0.81	2.5 mm (0.6 mm)	Most common agent used in United States
Re-186 HEDP	3.8	35 mCi (1,295 MBq)	137 (9%)	1.07	4.5 mm (1.1 mm)	Approved only in Europe

Adapted from Paes et al.[1]

even those working in the fields of oncology and pain palliation.

Radioactive isotopes of phosphorus-32 (P-32) and Sr-89 were the first bone-seeking radiopharmaceuticals approved for the treatment of painful bone metastases. These elements preferentially incorporate into the sites of osteoblastic bone metastases at rates 2–25 times greater than in normal metabolic active bone. The clinical use of P-32 has decreased since the 1980s in favor of Sr-89 and newer radionuclides. These newer beta-emitting isotopes were developed for palliation of cancer-induced bone pain and are currently administered using multidentate chelate complexes with more efficient pharmacokinetics, better decay properties, and a shorter beta range (Table 1).

Sm-153, rhenium-186 (Re-186), and rhenium-188 (Re-188) are categorized as newer bone-seeking radioisotopes[15,16] and have been extensively studied in the treatment of painful bone metastasis. Sm-153 has been approved for use in the United States and Europe for more than one decade, whereas Re-186 has been approved only in Europe. Re-188 is still an investigational agent which shows a promising availability profile since it can be obtained from a generator.[15,17]

Although all the beta-emitting radioisotopes differ significantly in their physical properties, they seem to have the same clinical efficacy in most trials for bone pain palliation conducted with these agents. The bone-seeking agent of choice has not yet been determined. Since all the commonly used radiopharmaceuticals have similar efficacy profiles, the agent should be selected in a case-based fashion, taking into consideration the availability, toxicity, and goal of therapy.

Different indications for clinical use of these agents, besides pain palliation, have also been studied in recent clinical trials, which include radioisotope treatment of hemophilic arthropathy,[18,19] conditioning therapy prior to bone marrow transplantation in acute leukemias,[20–22] and radioimmunotherapy using radiolabeled antibodies against different tumors.[23–26]

Indications for Radionuclide Therapy in Bone Pain Management

Intravenous injection of Sr-89 chloride, Sm-153 lexidronam, and Re-186 etidronate is approved for the treatment of bone pain due to osteoblastic or mixed osseous metastasis from prostate and breast carcinomas (most common indications) and any other tumor presenting with painful osteoblas-

tic lesions documented by whole-body bone scintigraphy performed within eight weeks prior to therapy.[1,14,27,28] The pain described by the patient should correlate to the areas of abnormal radiotracer accumulation in the bone scan. Most patients treated with radionuclide therapy have failed chemotherapy and other pharmacological therapy or have developed limiting side effects from these agents and are not candidates for XRT for reasons previously mentioned. Although these bone-seeking radioisotopes have been typically reserved for the treatment of diffuse osseous metastasis late in the course of the disease, an effort should be made to administer them early in the metastatic phase, to increase the rate of therapeutic response.[29] The paradigm of using systemic radionuclide therapy as a last resort should be avoided because its earlier use has been proven safe and effective for bone pain therapy in most clinical scenarios.[30] A common misconception is that the use of radiopharmaceuticals will preclude or limit the use of systemic chemotherapy or XRT in the patient with metastatic disease.[31] If treated early, such patients can still be treated with systemic or localized therapies without significant side effects. Another theoretic advantage of early bone-targeted radionuclide treatment is that radiation can be delivered selectively to subclinical tumors and to metastases that are too small to be imaged and treated by surgical excision or local XRT.[32]

The appropriate choice of radiopharmaceutical is based on physical characteristics of the radioisotope in relation to the extent of the disease, bone marrow reserve, and its availability in different countries. The clinically used radioisotopes have comparable efficacy with diverse biophysical properties and pharmacokinetic profiles, as will be discussed later (Tables 1 and 2).[1,13,33]

Patient Selection, Expected Effect, and Contraindications

Theoretically, any patient with documented osteoblastic bone metastasis by bone scintigraphy with associated uncontrolled pain is a candidate for radiopharmaceutical therapy for pain palliation. However, in practice, it has been used in patients with more extensive metastatic bone disease that could not be controlled by localized XRT. Two important absolute contraindications for therapy with bone-seeking agents are pregnancy and breastfeeding. A pregnancy test should be obtained for all female patients of reproductive age. They should also be advised against conceiving for at least six

Table 2

Summary of Efficacy Studies on Sr-89 and Sm-153

REFERENCES	YEAR	PATIENTS (N)	DOSE (SI)	CANCER	PAIN RELIEF
SR-89 CHLORIDE					
Fuster et al.[52]	2000	40	4 mCi (148 MBq)	Breast	92%
Kraeber-Bodere et al.[29]	2000	94	4 mCi (150 MBq)	Prostate	78%
Turner et al.[53]	2001	93	4 mCi (150 MBq)	Prostate	63%
Dafermou et al.[39]	2001	527	4 mCi (148 MBq)	Prostate	59.80%
Ashayeri et al.[54]	2002	27	4 mCi (150 MBq)	Prostate and breast	81%
Zorga et al.[55]	2003	33	4 mCi (148 MBq)	Prostate, breast, bladder, and renal cell	82%
Baczyk et al.[56]	2003	70	4 mCi (148 MBq)	Prostate	88%
Gunawardana et al.[57]	2004	13	4 mCi (148 MBq)	Prostate	57%
Liepe et al.[58]	2007	15	4 mCi (148 MBq)	Prostate and breast	72%
Ma et al.[59]	2008	116	40–60 μCi/kg (1.48–2.22 MBq/kg)	Prostate	83.60%
Sm-153 lexidronam					
Serafini et al.[60]	1998	118	0.5–1 mCi/kg (18.5–37 MBq/kg)	Prostate, breast, others	62%–82%
Tian et al.[61]	1999	105	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	84%
Dolezal et al.[62]	2000	33	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	70%
Wang et al.[63]	2003	9	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	78%
Sapienza et al.[64]	2004	73	1 mCi/kg (37 MBq/kg)	Prostate, breast	76%
Etchebehere et al.[65]	2004	58	1.0–1.6 mCi/kg (37–59.2 MBq/kg)	Prostate, breast, others	78%
Sartor et al.[66]	2004	152	1 mCi/kg (37 MBq/kg)	Prostate	65%
Tripathi et al.[67,a]	2006	86	1 mCi/kg (37 MBq/kg)	Prostate, breast, others	73%
Ripamonti et al.[69]	2007	13	1 mCi/kg (40 MBq/kg)	Prostate	61.50%
Liepe et al.[58]	2007	15	1 mCi/kg (37 MBq/kg)	Prostate and breast	73%
Dolezal et al.[68]	2007	32	1 mCi/kg (37 MBq/kg)	Prostate	75%

Adapted from Paes et al.[1]

[a] Response rates were 80.3% and 80.5% in breast and prostate cancers, respectively. One case each of Wilms tumor, ovarian cancer, germ cell tumor testis, multiple myeloma, primitive neuroectodermal tumor, and esophageal cancer did not respond to therapy.

months after a single therapeutic dose, even though there are no scientific data about related congenital abnormalities. It is also required to entirely discontinue breastfeeding before the radiopharmaceutical is administered.[27]

The presence of cytopenia constitutes a relative contraindication since bone-seeking radiopharmaceuticals can cause further myelotoxicity, aggravating previous low blood cell counts. Blood transfusion and granulocyte colony-stimulating growth factors (G-CSFs) may be used either prior to or following radionuclide therapy in some situations. In those cases, the purpose is to salvage and stabilize patients until such time as bone marrow recovery occurs spontaneously.[13,34–36] Most centers use the following blood cell count values as dose-limiting: hemoglobin (Hb) less than 9 mg/dL; absolute white blood cell (WBC) count less than 3,500 and platelet (PLT) count less than 100,000. These values must be stable for at least two to three weeks prior to therapy. Even patients with stable lower absolute WBC count ($>$2,400) and PLT count ($>$60,000) may be given consideration to receive systemic radionuclide therapy. However, the total injected activity may be reduced or fractionated in these cases.[1,13,34]

Bone marrow involvement is not considered a contraindication by itself, unless the blood counts are significantly low. The appearance of the bone scintigraphy provides information which helps to describe the extent of bone marrow involvement. The presence of a "superscan" appearance suggests limited bone marrow reserve, but it does not constitute an absolute contraindication for therapy. As long as the blood counts are stable above the described ranges, these patients can be treated with radiopharmaceuticals. As previously described, patients with mildly compromised bone marrow reserves also have two possible therapeutic options: be treated at lower dose levels or be treated with fractionated smaller doses.

The plasma clearance of these agents is dependent on renal function. Patients with impaired renal function (glomerular filtration rate [GFR] $<$30 mL/min) should not receive the radiopharmaceuticals due to a higher risk of myelotoxicity. Although there are no clinical data on patients undergoing dialysis, the risk of contamination and radiation exposure in the dialysis unit make it an absolute contraindication for the therapy, mostly due to logistic issues. By consensus, patients with moderate renal failure (GFR $>$30 and $<$50 mL/min) should have their dose lowered by 50%. In patients with impaired renal function, Sm-153 lexidronam and Re-186 etidronate are the preferred radiopharmaceuticals due to their lower physical half-lives, even though there are currently no significant data regarding their safety and toxicity. The pa-

Table 3

Checklist before Therapy with Radiopharmaceuticals and Contraindications

Clinical information and imaging findings
Recent positive bone scintigraphy within 8 weeks
Positive correlation between osteoblastic lesions and painful sites
Severe pain despite analgesics or analgesic side effects
Not a candidate for local control with external beam radiation (XRT)
No chemotherapy or large field XRT in the past 4–12 weeks
Incontinence: place urinary catheter
Life expectancy more than 4 weeks
Signed informed consent
Cervical spine involvement—consider steroid use prior to injection
Laboratory data
Hemoglobin >9.0 mg/dL
Absolute WBC >3,500/dL (may consider in >2,400/dL)
Absolute neutrophil >1,500/dL
PLT >100,000/dL (may consider in >60,000/dL)
Glomerular filtration rate (GFR) >50 mL/min—full dose
GFR >30 and <50 mL/min—half dose
Contraindication
Pregnancy: obtain pregnancy test the day of injection
Breastfeeding: stop permanently
GFR <30 mL/min or dialysis
Spinal cord compression and base of skull syndrome: needs XRT
Extensive bone marrow involvement: low blood counts ("superscan"—relative contraindication)

Adapted from Paes et al.[1]

tient selection criteria and contraindications are summarized in Table 3.

It is vital to inform the patient and the referring physician what they should expect after the radiopharmaceutical is given. Onset of pain relief may occur within days or weeks, and its duration may also vary according to the extent of metastatic bone disease. In general, radionuclide therapy is not recommended in patients with a life expectancy of less than four weeks, given that the onset of pain relief may be delayed in some patients. Flare painful response (FPR) has been observed in 10%–15% of patients and is described as an initial aggravation of pain within the first few weeks. The pathophysiology of FPR is thought to be related to the release of cytokines and inflammatory-related substances. This may be helped by temporary use of analgesics and steroids. FPR is a marker of good targeting and related to satisfactory clinical response to the therapy.[1]

Efficacy and Physical and Biological Characteristics of the Radiopharmaceuticals

The most common radiopharmaceuticals used for bone pain palliation in the United States are Sr-89 and Sm-153. Although they have a similar efficacy profile, they differ in their biological and physical characteristics and dose regimen.

STRONTIUM-89 CHLORIDE

Strontium is a divalent cation, similar to calcium, and is incorporated into hydroxyapatite in the bone after intravenous injection. Sr-89 chloride (Metastron®) was the first US Food and Drug Administration–approved radiopharmaceutical for bone pain palliation. The beta particles are responsible for its therapeutic effect and have an energetic penetration range within 6–7 mm in soft tissues and 3–4 mm in bone. It has a half-life of 50.5 days, decays to stable yttrium-89, emitting high-energy beta particles (E_{max} = 1.46 MeV) and 0.01% of gamma-rays (910 keV).[37] There is no radiation risk to others after Sr-89 administration; therefore, patients should be treated on an outpatient basis. Studies of Sr-89 pharmacokinetics have demonstrated a variable plasma clearance (1.6–11.6 L/day) with overall total-body retention of 20% in a healthy population 90 days after injection, particularly in the normal skeleton. Osteoblastic lesions show up to five times greater radiopharmaceutical uptake and prolonged retention time compared to areas of normal bone in the same patient (lesion/normal bone ratio 5:1).[2,38]

The standard recommended dose of Sr-89 chloride is 4 mCi (148–150 Mbq). No dose–response relationship for overall pain relief has been documented in the literature. There are extensive data on the efficacy of Sr-89 for bone pain palliation (Table 2) in different sets of patients with osseous metastasis, even though the majority of subjects in the clinical trials had breast or prostate cancer.

Some predictive factors for better response to Sr-89 have been described and included patients with limited skeletal involvement, those with higher performance status, and those with predominant osteoblastic lesions on bone scintigraphy. These subjects usually demonstrate greater pain relief with a longer duration of pain control.[39,40]

SAMARIUM-153 LEXIDRONAM

Sm-153 lexidronam (Quadramet®) is a commonly used radiopharmaceutical for bone pain palliation in cancer centers in the United States. Sm-153 is produced by neutron irradiation of Sm-152 oxide, which can then be complexed with the calcium salt of ethylenediaminetetramethylene phosphonic acid (EDTMP) to produce Sm-153-EDTMP. Sm-153 is a radionuclide that emits beta particles (E_{max} = 640, 710, and 810 keV) with maximum energy of 0.81 MeV; it has a physical half-life of 46.3 hours and an average penetration range of 0.83 mm in water.[34] Its purity is practically 100%. The beta decay is accompanied by 28% emission of 103.2 keV gamma-rays, which can be used for imaging. Sm-153-EDTMP forms a complex that selectively accumulates in skeletal tissue in association with hydroxyapatite, particularly in areas where the rate of bone turnover is high. The total skeletal dose of Sm-153 is unpredictable and ranges from 15% to 95% depending of the osteoblastic activity. Bone metastases accumulate 5 times more Sm-153 than healthy bone tissue, so adjacent malignant cells are selectively exposed to higher doses of radiation. Sm-153 is cleared rapidly from the blood with a half-life of 5.5 minutes and <1% of the dose remaining in the

circulation one hour after administration. Urinary excretion is the main route of elimination and is complete within six hours.

Dose-escalation trials were performed in the early 1990s and demonstrated similar distribution of activity in doses ranging from 1 to 3 mCi/kg.[36,41] Nonskeletal sites received negligible doses. Total absorbed estimated marrow doses ranged from 1,277 to 2,250 rad in the 3 mCi/kg dose, with only mild hematological toxicity.[41] The current standard dose of Sm-153 lexidronam is 1 mCi/kg administered intravenously, which has been proven safe and effective, causing only mild reversible bone marrow suppression in patients with normal hematological parameters.

Prospective controlled trials were conducted in a large number of patients around the world, evaluating the efficacy of Sm-153 for the treatment of painful bone metastasis and are summarized in Table 2.

Administration, Precautions, Toxicity, and Follow-Up

The use of radiopharmaceuticals for metastatic bone pain is becoming more frequent. Thus, it is important to understand the appropriate management of these patients regarding administration, precautions, and toxicities. The administration of these agents is not dangerous for patients, administering personnel, and caretakers as long as standard radiation precautions are taken. The radiation safety measures vary according to the characteristics of the radioisotope used in the treatment. The radiation hazard is significantly minimized when the treating physician informs the patient of the basic precautions. The recommendations for patients undergoing treatment include the following: avoid pregnancy for at least 6–12 months, avoid contaminating shared toilets with radioactive urine and excrements, double toilet flushing for at least one week, bladder catheterization before injection if incontinent (Sr-89 for 4 days and Sm-153 for 24 hours), and avoid sexual contact for at least one week after injection. The administering physician must obtain an informed consent and use universal safety apparel during injection and handling of patients. The calculated dose of the radiopharmaceutical is administered on an outpatient basis with an injection over one to two minutes through a peripheral intravenous line, which is subsequently flushed with 10–20 mL of saline. After the drug is administered, patients should be observed for 4-6 hours to monitor possible site injection reaction and early side effects. The acquisition of a posttherapy total-body scan for Sm-153 to document adequate targeting is facultative (Figure 1).

The toxicity profiles of the radiopharmaceuticals are similar and can be used to implement a follow-up schedule. Regardless of the agent, approximately 10% of the patients will experience FPR. This reaction is typically transient, mild, and self-limiting, occurring within 72 hours of drug injection. When the osseous metastasis involves the cervical spine, a small chance of spinal cord compression posttherapy exists and prophylactic corticosteroids should be considered. Tran-
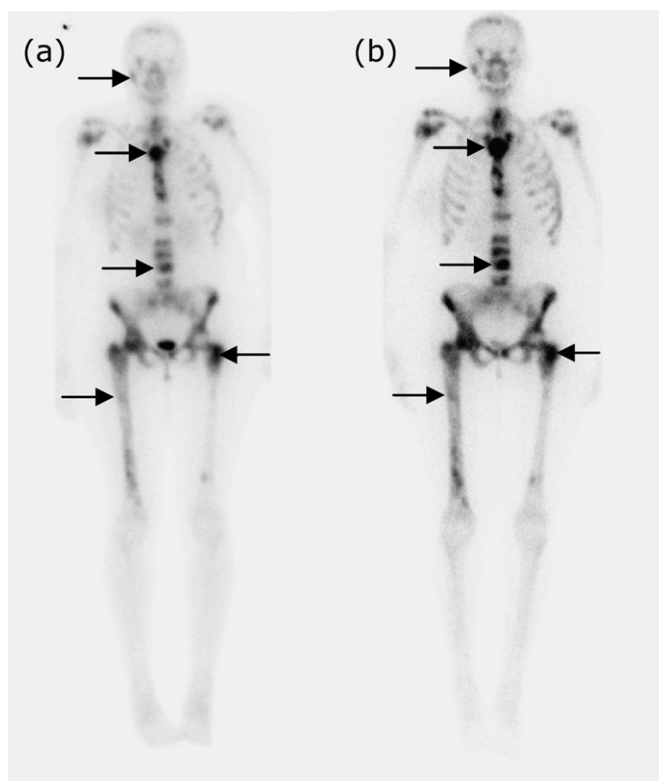
Figure 1 Targeting of Osteoblastic Metastases with Sm-153-EDTMP Posttherapy Scintigraphy

Anterior whole-body bone scan images of a patient with metastatic prostate cancer demonstrating several osteoblastic lesions in the axial and appendicular skeleton (arrows). Image a was acquired 4 hours after injection of Tc-99m-MDP, whereas image b was acquired 2 hours after a therapeutic dose (70 mCi) of Sm-153-EDTMP. There is adequate match of the metastatic foci between the two images. Adapted with permission from Paes et al.[1]

sient myelosuppression, affecting mainly PLTs and WBCs, is expected and frequently observed. The nadir of myelosuppression is usually 4-8 weeks for Sr-89 and 3-5 weeks for Sm-153, which is delayed when compared to chemotherapeutic agents.[42] The severity of the bone marrow damage is dependent upon the patient's bone marrow reserve and previous chemoradiation therapies. In the majority of patients, blood cell counts will return to baseline levels within three months of therapy. This time frame may be shorter if patients were not previously treated with chemotherapy. After the radiopharmaceutical infusion is complete, patients should follow up with their medical oncologist, nuclear physician, or primary care doctor for management of flare phenomena, pain medications, and other symptoms as needed. It is also recommended to closely monitor myelosuppression with a weekly complete blood count between the third and eighth weeks after treatment or until return to baseline levels.

Radiopharmaceuticals and Chemotherapy

Patients and clinicians are greatly interested in the use of combined modalities in the treatment of metastatic bone pain. Among them, chemosensitization is a well-recognized

method of improving the efficacy of any radiation-based therapy. The cytotoxic effect of chemotherapy causes tumor cells to be more susceptible to radiation effects, enhancing the overall efficacy of the bone-seeking agents. Unfortunately, few studies have evaluated the effect of the concomitant use of radiopharmaceuticals and chemotherapy. The majority of the clinical trials used Sr-89 as the radioisotope of choice in combination with different chemotherapeutic agents as the radiosensitizer.

An Italian group in the late 1990s used low-dose carboplatin (100 mg/m^2 at 7 and 21 days) as a radiosensitizer in patients with osseous metastasis treated with Sr-89. The pain response was assessed 8 weeks postinjection, with continued follow-up for one year. They were able to demonstrate pain improvement in 74% of the patients, with a superior statistical significant response in the patients treated with Sr-89 and carboplatin compared to the control group (P = .025). However, survival was only slightly better in the combined treatment group (8.1 vs. 5.7 months, P = .19). Importantly, no clinically significant adverse effects or myelosuppression by carboplatin were observed. It was the first trial to report the feasibility of concomitant use of radiopharmaceuticals and chemotherapeutic agents.[43]

Another important randomized phase II clinical trial[44] evaluated patients after 2-3 cycles of induction chemotherapy (combination of ketoconazole and doxorubicin, alternating with estramustine and vinblastine) for hormone refractory prostate cancer. The patients who were stable or responsive after induction chemotherapy were randomly assigned to receive doxorubicin with or without Sr-89 every week for 6 weeks. Overall, 60% of patients had a 50% or greater reduction in serum prostate-specific antigen (PSA) that was maintained for at least 8 weeks, and 42% had an 80% or greater reduction. Almost 52% of the patients with bone pain at registration had complete resolution of pain. For the patients randomly assigned to receive Sr-89 and doxorubicin, the median survival time was 27.7 months (confidence interval [CI] 4.9–37.7), and for the 36 who received doxorubicin by itself the survival rate was 16.8 months (CI 4.4–34.2) (P = .0014). These results were the first to show possible improvement in overall survival with Sr-89 given as a consolidative therapy with doxorubicin after induction chemotherapy in patients with stable or responding metastatic prostate cancer.

Another group[45] published a small phase II study investigating the addition of Sr-89 to an alternating weekly regimen of doxorubicin, ketoconazole, paclitaxel, and estramustine in patients with metastatic prostate cancer. Interestingly, a ≥50% reduction in PSA level was maintained for at least 8 weeks in 77.7% of the patients at 16 weeks and in 66.6% at 32 weeks. The median progression-free survival was 11.27 months (CI 1.83–29.53), and the median overall survival was 22.67 months (CI 1.83–57.73). Overall, this study suggested that chemotherapy combined with Sr-89 also demonstrated a prolonged progression-free and overall survival with acceptable toxicity when compared to historical data.

However, in current clinical practice it is not yet recommended to combine these therapies. The acceptable situation where chemotherapy and radiopharmaceuticals can be administered simultaneously is within experimental clinical trials focusing on the antitumoral effects of combining modalities. Although promising, the existing recommendation is to discontinue any myelosuppressive chemotherapy at least 4 weeks before the administration of Sr-89 or Sm-153 and withheld for 6–12 weeks posttherapy to avoid concomitant bone marrow suppression.[13,46]

Radiopharmaceuticals and Bisphosphonates

Bone-seeking radiopharmaceuticals and bisphosphonates may be indicated in patients with cancer with painful osseous metastases to palliate pain symptoms or to prevent skeletally related events. Theoretically, both pharmaceuticals may have an additive or even synergistic palliative effect. The combined use is, however, currently controversial due to a hypothesis of possible competitive interaction between bisphosphonates and radiopharmaceuticals at the hydroxyapatite crystal surface in the skeleton, which could decrease the uptake and biological effect of both. Nevertheless, with the limited available data, there is no evidence of biological competition between these two modalities of treatment; therefore, they may be used concomitantly.

A pivotal trial divided patients with painful osseous metastasis from prostate and breast cancers in three therapeutic cohorts: group A included patients chronically treated with zoledronic acid, who received bone pain palliation with 4 mCi (150 MBq) of Sr-89 chloride, given at least 6 months after the bisphosphonate therapy began; group B included patients who received Sr-89 chloride alone; and group C patients were treated over a period of time and continued to receive only zoledronic acid therapy. Baseline characteristics were similar in all three groups, although the reduction of total discomfort and bone pain in group A was significantly greater compared to group B (P < .01) and group C (P < .01). During the monitored period, a significant improvement of clinical conditions was observed in group A compared to groups B and C.[47] These findings suggested that combined sequential therapy of Sr-89 chloride and zoledronic acid in patients with painful bone metastases is more effective at treating pain and improving clinical conditions than therapeutic modalities used separately.

Another group[48] recently evaluated the biodistribution and skeletal uptake of Sm-153 in patients with hormone-refractory prostate cancer treated with a combination regimen using zoledronic acid. After analyzing the urinary excretion, toxicity, and scintigraphic data, they concluded that zoledronic acid treatment did not influence Sm-153 skeletal uptake and suggested that combined treatment is both feasible and safe.

In a small study utilizing another biphosphonate,[49] skeletal uptake of Sm-153-EDTMP before and 1-4 days after pamidronate infusion was compared in patients with breast cancer metastatic to bone. Two of these patients continued to com-

pare Sm-153-EDTMP uptake at approximately 1, 2, 3 and 4 weeks after pamidronate infusion. There was no difference in skeletal uptake of Sm-153-EDTMP before or after pamidronate infusion.

These findings support the theory of no significant biological competition of these agents. The clinical experience using combined bisphosphonates and bone-seeking radiopharmaceutical therapy is increasing rapidly in academic referral centers.[50]

Conclusion

Bone pain palliation using the available radiopharmaceuticals is an effective systemic treatment for patients suffering with metastatic bone lesions and should always be considered in the earlier stages of osseous metastasis dissemination rather than as a last resort. This therapy decreases morbidity and improves patients' quality of life. The proper application of this modality will require continuous education of oncologists and pain specialists. At first, the task to propagate the proven efficacy of this therapy and advocate for the more widespread use of these agents lies with the nuclear medicine physician.

It is important to recognize that the radiopharmaceutical agent of choice has not yet been established, so therapy must be individualized. The agent should be selected taking into consideration the availability, toxicity, and goal of therapy. There are comprehensive review articles about the use of radiopharmaceuticals in the treatment of bone metastasis which support the above statements and are worthwhile reading.[1,51]

Many questions regarding bone-seeking agents still require definite answers: Is there a true beneficial effect of combining them with chemotherapy or bisphosphonates? What factors are predictive of good response? Is it safe to use radiopharmaceuticals in patients with extensive bone marrow substitution? Further clinical trials are necessary not only to clarify these questions but also to evaluate a potential role of bone-seeking radiopharmaceuticals beyond palliation, toward improvement in survival.

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