Teletherapy and Radiopharmaceutical Therapy of Painful Bone Metastases

Edward B. Silberstein, MD

Bone pain from metastatic disease is most common in cancers of the breast, prostate, and lung. Despite the World Health organization algorithm for treating such pain, the outcomes are not often satisfactory. In 2005, there will be 3 radiopharmaceuticals available in the United States that can reduce or relieve bone pain caused by osteoblastic metastases with apparently equal efficacy. Phosphorus-32 as sodium phosphate, strontium-89 (^{89}Sr) as the chloride, and samarium-153 lexidronam may all be given intravenously (and ^{32}P also orally) in patients where bone scintigraphy demonstrates a metastatic lesion causing the patient's bone pain. Side effects are usually mild and include pancytopenia with leukocyte and platelet nadirs at approximately 50% of baseline, and a mild-to-moderate, but brief, increase in pain ("flare") in approximately 10% of patients. At least 1 of these radiotracers, ^{89}Sr, has the availability to reduce the incidence of new bone metastases as well, but, given alone, none prolong life. In a few studies in which ^{89}Sr has been combined with chemotherapy, prolongation of patient survival has been demonstrated. Many questions remain as to the optimization of use of this group of radiopharmaceuticals, including whether combinations of radiopharmaceuticals with each other, with bisphosphonates or with chemotherapy can improve the therapeutic outcomes even more.
Semin Nucl Med 35:152-158 © 2005 Elsevier Inc. All rights reserved.

Approximately 1 in 3 residents of the United States will be diagnosed with some form of cancer in his/her lifetime, with more than 1 million cases occurring per year. Approximately three-fourths of patients with advanced cancer will experience pain, much of this clinically significant, from osseous metastases.[1] The process by which tumor cells reach osseous tissue, enter the interstices of bone, survive, and grow is currently undergoing intensive investigation.[2] Metastases may reach bone by direct extension or, more commonly, through the hematogenous route, usually beginning in marrow. Of all patients with osseous metastatic disease, 70% will have disease in the vertebrae and ribs, 40% in the pelvis, 25% in the femur, and 15% in the skull, often concurrently, with 10% of osseous metastases causing fracture. Breast cancer causes more than half of all pathologic fractures.[3]

Treatment of the resultant pain so often following and caused by osseous metastatic disease is rarely satisfactory for the patient, despite the guidelines of the World Health Organization 3-step analgesic ladder or hierarchy of drugs to be used for analgesic pain management.[4] Most patients experiencing bone pain eventually require opiates, which can significantly alter the patient's quality of life as these drugs induce constipation, lethargy, and even confusion. Besides the pain, the clinical effects of bone metastases include pathologic fracture, immobility, hypercalcemia, loss of independence, anxiety, and depression.[1,5]

Of several nonnarcotic modalities available to treat the pain of osseous metastases, radiation therapy, both as teletherapy and unsealed sources (electron and β-emitting radiopharmaceuticals), has been effective over many years of clinical experience. The goal of radiation therapy in these patients is to reduce or relieve pain and thus improve functional status. To this, we may add the ability of electron or β-emitting radiopharmaceuticals to prevent or delay the onset of new painful metastatic disease[6] With the combination of radiopharmaceutical and chemotherapy, improvement in survival has recently been described.[7,8] Bisphosphonates are newer additions to the clinician's armamentarium of pain relieving agents, and this pharmacologic approach has become an important alternative to radiotherapy.

External Beam Radiotherapy

Teletherapy may be given to focal sites of painful disease or as hemibody radiation to wider fields when there are

Nuclear Medicine Division, Department of Radiology, University of Cincinnati Medical Center, Cincinnati, OH.
Address reprint requests to Edward B. Silberstein, MD, 234 Goodman Street, Nuclear Medicine Division, Department of Radiology, Mont Reid Pavilion, Room G026, Cincinnati, OH 45219. E-mail: silbererb@healthhall.com

multiple painful sites.[9,10] Common local radiotherapy fractionation schedules include 40 to 50 Gy in fractions of 180 to 200 cGy 5 days per week for 4 to 5 weeks, 20 to 40 Gy in doses of 250 to 400 cGy 5 days per week for 1 to 3 weeks, or a single dose of 8 to 10 Gy.[11] In a comparative study that stratified patients by initial primary site of painful metastasis, presence or absence of internal osseous fixation, and medical center, there was no difference in pain reduction from solitary lesions between a regimen of 20 Gy given over 1 week and one using 8 Gy in one dose. There appears to be little or no difference in pain reduction from multiple metastases between delivering a single fraction of 8 Gy to a painful site, 15 Gy in a week, and 30 Gy in 10 daily fractions during the course of 2 weeks, as measured by the time to onset of relief, incidence of relief, duration of response, or survival.[12,13] A meta-analysis suggested that for this purpose 20 Gy in 5 fractions, 30 Gy in 10 fractions or 35 Gy in 14 fractions were all acceptable.[14]

Partial body radiation, involving 6 to 8 Gy to the upper hemibody, 8 Gy to the lower hemibody, or 6 to 8 Gy from neck to pubis, has been used successfully to ameliorate bone pain. From upper body hemiradiation not exceeding 8 Gy there has been grade three (out of four) gastrointestinal toxicity in one-sixth of cases, and similar hematologic toxicity in approximately one-third. One must assume that the stomach was in the radiation field in these cases. Radiation pneumonitis could be avoided with doses at or less than 8 Gy. Lower hemibody radiation caused lesser toxicity in both organ systems. These techniques yielded a complete response (pain-free) in 19%, 47% partial response; 34% of patients in this series with "some" or "no" response must all be classified as nonresponders until further information becomes available. In this group, a better performance scale score predicted a greater chance for pain reduction with hemibody radiation.[15]

Radiopharmaceuticals Used for Pain Relief

Bone-seeking radiopharmaceuticals play a significant role in the treatment of the pain of osteoblastic metastatic disease. These radiopharmaceuticals, called "unsealed sources" by the United States Nuclear Regulatory Commission, are beta or electron-emitters with a chemical affinity for sites of new bone formation by one of several mechanisms. These include direct substitution for stable analogs in hydroxyapatite (^{89}Sr for calcium and ^{32}P-orthophosphate for stable phosphate); chemisorption on the hydroxyapatite surface by the phosphate moiety of phosphonate chelates (^{186}Re, ^{188}Re, and possibly ^{153}Sm), and formation of insoluble salts with bone (trivalent ^{153}Sm and ^{117m}Sn). The uptake of these radiopharmaceuticals is greater where new reactive bone is being formed, due to increased blood flow to the site and increased surface area of calcium phosphate salts as they are secreted and become hydroxyapatite molecules.[14]

Table 1 lists 6 radiopharmaceuticals that have been examined by multiple investigators for the ability to reduce or relieve pain of osteoblastic metastatic disease, ordered

by physical half-lives. The range of physical properties of these radiopharmaceuticals is remarkable, with half-lives ranging from less than a day (^{188}Re) to 50.5 days (^{89}Sr) and mean particle energies as low as 0.13 MeV (the electrons of ^{117m}Sn) and as high as 0.79 MeV (the beta of ^{188}Re). The mean range in soft tissue is proportional to particle energy so that the ^{117m}Sn electron range is only 0.2 mm, whereas that of the beta of ^{188}Re exceeds 3 mm. Unfortunately the Re-186, Re-188, and Sn-117m chelates are unavailable in the United States.

Most of these emit gamma rays, which have been used to document the localization of the injected radiopharmaceutical at precisely the sites of osteoblastic metastases identified by a ^{99m}Tc-labeled bisphosphonate bone scan and also allow dosimetric calculations. This gamma-emitting property provides no advantage and can lead to some radiation being received by bedmates.

There could be differences in response to these radiopharmaceuticals because of the dramatically different dose rates. A longer mean path of the electron or β particle in the marrow might yield a greater tumoricidal effect, but also perhaps greater myelosuppression. There are several other variables that could affect tumor dose from these radiopharmaceuticals:

1. The intensity of uptake by reactive bone can vary dramatically. Although the usual ratio of abnormal to normal bone is 3 to 5:1, ratios as high as 13 to 15:1 have been noted.[16]
2. Widespread uptake from diffuse osseous metastases could dilute the effect of an injected radiopharmaceutical, with fewer radioactive atoms per volume of tumor.
3. The inhomogeneity in distribution of tumor, marrow, and trabecular bone within a given site of osteoblastic uptake seen scintigraphically is another variable determining the dose to individual lesions.
4. The greater the osteoblastic trabecular volume, the greater the deposition of these therapeutic agents, with a resultant increase in tumor dose. However, the thicker that the trabeculae become in a marked osteoblastic response, the more beta particles or electrons are locally absorbed, with a resultant reduction in tumor dose.[17,18]
5. Because the radiopharmaceuticals appearing in Table 1 all have significant renal excretion, altered renal function will increase body and lesion dose.

However, as will be discussed in greater detail below, we see no significant differences between all these radiopharmaceuticals in reducing the pain of osseous metastases. And for all of these radiotracers the dosage-response curve is flat above some threshold activity, ie, giving more activity does not increase the response rate. Nor does there appear to be a difference in response rates between cancers as long as the metastatic lesions are present on the bone scan.

Table 1 Radiopharmaceuticals for Painful Metastases

Radiopharmaceutical	$t_{1/2}$ (d.)	Maximum E_B (MeV)	Mean E_B (MeV)	Max Range (mm)	Mean Range (mm)	Gamma MeV (% abundance) Half-Life
^{188}Re(Sn)HEDP*	0.7	2.12	0.73	11.0	2.7	0.155 (10%)
			0.79		3.1	
^{153}Sm-EDTMP	1.9	0.81	0.23	2.5	0.6	0.103 (28%)
						0.070 (5%)
^{186}Re(Sn)HEDP*	3.8	1.07	0.33	4.5	1.1	0.137 (9%)
^{117m}Sn-DTPA*	13.6	0.127†	–	0.27	0.2	0.159 (86%)
		0.152†	–		0.3	
^{32}P-phosphate	14.3	1.71	0.70	7.9	3.0	–
^{89}Sr-chloride	50.5	1.46	0.58	7.0	2.4	0.909 (0.10%)

*Not available in the United States.
†Conversion electrons.

Mechanisms of Radiation-Induced Pain Relief

There are patients whose bone pain may diminish after only a few days of teletherapy treatment or within a week of radiopharmaceutical administration, even when the total dose to the site is less than 5 to 10 Gy. However, in such a short period of time the tumor cells within the marrow have not disappeared, and, in fact, peritumoral edema may be seen. The neurons are too radioresistant to be affected by these low doses. Therefore, although pressure, mechanical nerve entrapment, and mechanical stretch may be invoked as possible mechanisms of pain from osseous metastases, there must be other mechanisms to explain the efficacy of radiation.[19]

Both the metastatic tumor and also reactive lymphocytes may be responsible for producing cytokines modulating the pain response of the neuron.[20] Thus, the cytocidal effects of the beta-particles on radiation-sensitive cells such as lymphocytes could lead to a decrease in cytokine-induced pain. Sensitization of nocireceptor neurons in bone, resulting in excessive substance P release, could also occur as a result of the lower intracellular and extracellular pH of solid tumors.[21,22]

Intramedullary hypoxia has also been hypothesized as a source of pain. Finally, as osseous metastases spread, there is destruction of trabecular and cortical bone. At what point does this destruction become an occult but painful fracture?

Radiopharmaceuticals Currently Used for the Treatment of Bone Pain

^{32}P-Orthophosphate

For 5 decades ^{32}P (as the orthophosphate) has been used for pain relief, and there are more than 30 articles in the medical literature describing its efficacy in relieving pain from osseous metastases.[23] Eighty-five percent of an administered dose is incorporated into hydroxyapatite. However, the phosphate moiety also appears in molecules involved with energy storage, cell structure, and, importantly, in the backbone of DNA and RNA where, as a β-emitter, it may damage the structure

and function of these nucleic acids. Bone marrow will thus receive radiation from the ^{32}P in marrow cells, as well as from the β particle of ^{32}P incorporated into surrounding bone, unlike all the other radiopharmaceuticals under consideration.

Single injections of ^{32}P-orthophosphate have been administered in activities from 5 to 12 mCi, as well as in multiple doses up a period up to a month, with total activities up to 24 mCi.[16] The optimum activity for ^{32}P-orthophosphate administration is unknown, as is the issue of whether the activity should be given in single or multiple doses. The oral route may be as efficacious as intravenously administered ^{32}P-orthophosphate and is far less expensive, since the oral preparation does not have to conform to the same good manufacturing practices the FDA requires for intravenously administered drugs in terms of sterility and apyrogenicity.

In the 1950s and 1960s, ^{32}P-orthophosphate often was given with an androgen to stimulate bone uptake for patients with metastases from breast (and prostate) cancer. Parathyroid hormone was similarly used, but there are no studies to indicate that these hormonal manipulations provide any therapeutic advantage over administration of intravenous ^{32}P-orthophosphate with no hormonal injection.

There is no relationship between the total administered activity and the percent of patients responding in breast cancer, ie, no dose-response relationship. The overall response rate in the literature has totaled approximately 85% in breast cancer, although the criteria for responding patients were not always clear.[23] The response rate is similar to that from teletherapy. The mean reported duration of response to ^{32}P-orthophosphate is 5.1 ± 2.6 months, with the longest responses noted in multiple series as 16.8 ± 9.4 months. There may be some radiographic or scintigraphic improvement with ^{32}P-orthophosphate, as with the other radiopharmaceuticals employed, but this does not correlate with pain reduction.

Adverse effects from ^{32}P-orthophosphate were probably caused by the androgen given before ^{32}P-orthophosphate administration, eg, an increase in bone pain (the "flare phenomenon") described in as many as one-half of the patients receiving androgen followed by ^{32}P-orthophosphate, while this

number is generally lower, in the 10% range, with the other radiopharmaceuticals.

With all of the electron or beta-emitters pancytopenia occurs. There has been only one death reported to be caused by myelosuppression from [32]P. However, an intracerebral hemorrhage in another patient in the literature is probably also related to ^{32}P-orthophosphate-induced marrow suppression.[16] ^{32}P-orthophosphate has been used as a myelosuppressive agent for polycythemia vera and essential thrombocythemia, and there is some evidence that the degree of myelosuppression from this radiopharmaceutical could be greater than that from the other agents in Table 1.[24,25] The leukocyte and platelet counts do return to normal by 8 weeks[26] after ^{32}P myelosuppression.

A small study comparing ^{32}P given orally with intravenous ^{89}Sr indicated that the 2 agents had equal efficacy of approximately 90% in pain reduction[24,] which a later publication, incorporating the data from this single site into a larger multi-institutional study sponsored by the IAEA confirmed. However in this larger study the efficacy of ^{89}Sr was reduced to 78%, that of ^{32}P to 60%, but the differences were again not statistically significant.[25] In the smaller study ^{32}P gave 2 of 16 patients grade 2 (of 4) leukocyte toxicity and 6 of 16 grade 2 (of 4) platelet toxicity, with none requiring hospitalization. The ^{89}Sr patients had only grade 1 toxicity, suggesting that although ^{32}P may be more myelotoxic, this has no clinical significance.[24] These data were upheld in the larger study.[25] [32]P has been associated with acute myelogenous leukemia when used to treat myeloproliferative diseases such as polycythemia vera, but the life-expectancy in these cancer patients with bone pain, as well as the lack of an underlying preleukemic state, makes this complication of little concern in these patients.

[89]Sr-Strontium Chloride

Because strontium and calcium are both in family 2 of the periodic table, ^{89}Sr, injected as the chloride, substitutes for calcium in the hydroxyapatite molecule. [89]Sr was the first radiopharmaceutical used for the palliation of bone pain from metastatic disease,[26] preceding the earliest reports of ^{32}P-orthophosphate for this purpose, although ^{32}P was widely used for the next 30 years and ^{89}Sr hardly at all. After intravenous injection, ^{89}Sr is excreted by both renal (80%) and fecal (20%) routes, with a biologic half-life of 4 to 5 days. However, approximately 30% to 35% of the radiopharmaceutical remains in normal bone for 10 to 14 days with 20% retention at 3 months. The biologic half-life of ^{89}Sr in the woven, reactive bone around osteoblastic metastases is very long, with retention of 80% to 90% of the injected dose in involved sites at 3 months following injection.[16] This phenomenon, not yet explained, has been observed for all the radiopharmaceuticals listed in Table 1.

The optimum ^{89}Sr activity to be administered to achieve a maximum response is unknown, but there is no convincing dose-response relationship. The usual dosage administered is either 148 MBq (4 mCi) or 1.48 MBq/kg (40 μCi/kg). With larger dosages of strontium, more myelosuppression will re-

sult.[27] Even in a patient with no previous chemotherapy, one cannot predict the degree of myelosuppression with a high degree of certainty, because metastatic tumor replacing marrow leaves fewer stem cells available to participate in recovery from the radiation-induced myelosuppression. Therefore one may see platelet and leukocyte nadirs as low as 25% to 30% of the initial counts. The more usual response is milder myelosuppression, with a decrease in these counts to approximately 60% to 70% of pretreatment levels, a nadir at 5 to 8 weeks, and recovery by 10 to 16 weeks.[24-29]

The response time to ^{89}Sr has been reported as early as 3 days, but is most commonly noted in the second or third week after administration. In analyzing data on ^{89}Sr efficacy, one should, therefore, exclude patients who were treated but did not survive for 1 month. The published data on strontium response show a range of 65% to 90%, with complete relief of pain in 5 to 20% of patients injected.[24-29] The mean duration of pain reduction is 3 to 6 months. Retreatment for responders is possible at approximately 3-month intervals. Most, but not all, of these also will respond to a second treatment. It is not likely that patients who do not respond to the first injection will respond to a second injection, but a few such anecdotal occurrences have been reported. In reviewing these data the reader must be careful to note series wherein patients who did not live 3 months were excluded, as this bias can change the results considerably.

In an important Canadian study patients were randomized to receive teletherapy to painful sites or teletherapy plus an adjuvant dosage of 10.8 mCi of ^{89}Sr, an amount well in excess of the 4 mCi dosage commonly used in the United States. In patients who received the ^{89}Sr there was a significant delay to time of recurrence of the painful site, and also a delay in appearance of painful new sites compared with patients who received teletherapy alone.[6] Confirming the Canadian data was a British study using only 5.4 mCi of ^{89}Sr, also indicating that new sites of pain occurred less frequently in the patients who received this radiotracer.[30] This effect may be related to the long physical and biologic half-life of the radiopharmaceutical and has not yet been reported with the other radiopharmaceuticals listed in Table One. There was no life prolongation with ^{89}Sr in this study. However patients who had a tumor marker fall after Sr-89 lived over twice as long as those with no chemical response.[31] In a contrasting study however, a drop in marker did not correlate with the clinical response,[32] suggesting that death of tumor cells is not the only mechanism for pain reduction. When ^{89}Sr has been used in conjunction with cisplatin an enhancing effect on pain relief has been described.[8,33] An actual prolongation of mean survival occurred with the use of ^{89}Sr plus doxorubicin versus doxorubicin alone in the therapy of hormone-independent prostate cancer.[7] Data on breast cancer combined therapy is sparse, however.

Pain reduction from ^{89}Sr, or any of these tracers, cannot be predicted with great reliability. Specifically occurrence, and degree of cytopenia, the presence of narcotic tolerance, and the activity of ^{89}Sr administered have not been shown to be predictive of response. Some investigators have found a better response in patients with a higher performance level, and

a poorer response with very widespread metastatic disease, but not all agree.[27] No significant differences have been found in response rates to ^{89}Sr as compared with local teletherapy or hemibody radiation.[30]

[186]Re-Etidronate

[186]Re-hydroxyethylidene diphosphate (generic name of this chelator is etidronate), like the other bone-seeking radiopharmaceuticals, can only be used efficaciously in a patient whose ^{99m}Tc-diphosphonate bone scintigraph shows abnormal uptake. The phosphate moiety of the rhenium diphosphonate chemisorbs to calcium atoms in bone hydroxyapatite. Rhenium and technetium chemistry are predictably quite similar, as both are members of family VIIA of the periodic table, although rhenium is more easily oxidized than technetium.

As much as 70% of administered [186]Re-etidronate activity may be excreted in the urine by 72 h in patients with a relatively small mass of osteoblastic metastases, although extensive body retention can occur, analogous to a ^{99m}Tc-diphosphonate "superscan," attributed to widespread metastatic disease. This radiopharmaceutical is retained longer in the reactive bone around metastases than in normal bone, similar to the behavior of [89]Sr. With doses of approximately 30 to 70 mCi, a response (complete plus partial) has been seen in about 55% to 75% of cases.[34,35] The more carefully applied the pain reduction criteria are, with inclusion of effects of analgesics and changes in activities of daily living, the lower the response rate appears to be.[35] A "flare" response occurs from [186]Re-etidronate in approximately 10% of cases, similar to that noted with [89]Sr. Second (or additional) treatments have been performed in responders, with approximately 50% responding. Pain relief may occur within 1 to 3 weeks. Dose escalation studies have not shown an increase in response, although more myelosuppression results. No difference in response rates have been found in a small comparative study of ^{89}Sr, [186]Re-etidronate, and [188]Re-etidronate.[36] [186]Re-etidronate is widely used in Europe but is unavailable in the United States. [188]Re can be obtained from a [188]W/[188]Re generator. The efficacy of repeated doses of [188]Re-etidronate has been demonstrated in the bone pain of hormone-independent prostate cancer.[37]

[153]Sm-Lexidronam

[153]Sm, like rhenium, has been chelated with bone-seeking polyphosphonates. An optimum combination of high bone uptake, rapid blood clearance, and renal excretion was found to be with samarium chelated with ethylenediaminetetramethylenephosphonate, now called lexidronam.[30] [153]Sm-lexidronam clears more rapidly from the blood than the bone imaging agent ^{99m}Tc-MDP (methylene diphosphonate), while providing identical scintigraphic and bone marrow ratios. In patients with very small tumor burdens in bone, 50% to 65% of the injected [153]Sm-lexidronam will be chemisorbed, with higher levels of retention occurring in the presence of osteoblastic metastases. Renal excretion is complete within about 8 hours. [153]Sm-lexidronam, now given at 1.0

mCi/kg, leads to pain reduction in 55% to 70% of evaluable patients. A greater degree of myelosuppression is present from higher administered activities but no increase in pain relief. As with the other radiopharmaceuticals, pain reduction or relief begins in 1 to 4 weeks and has lasted as long as 11 months. Response to a second treatment parallels that of [186]Re-etidronate, with about 50% of patients noting pain reduction from a second injection.[38] Mild myelotoxicity predictably occurs, with a reduction in leukocyte and platelet counts of approximately 10% to 40% and full recovery in 6 to 8 weeks. No difference in response rates have been noted in a retrospective comparison of ^{89}Sr and [153]Sm-lexidronam.[39]

[117m]Sn-Pentetate

This radiopharmaceutical emits short range electrons and may produce less myelosuppression than the beta-emitters we have discussed, while probably retaining equal efficacy.[40] Economic factors have halted its development.

Choice of Teletherapy Versus Internal β-Emitters

Both teletherapy and intravenous radiopharmaceuticals provide efficacious radiotherapy. Teletherapy is the treatment of choice if the bone scan is negative at the tumor site, since the radiopharmaceutical will not have adequate uptake to deliver a therapeutic dose. With impending pathologic fracture (more than 50% of the cortex destroyed), teletherapy is required for prophylaxis (or treatment) of this condition, since the radiopharmaceutical will not deliver a sufficient dose rapidly enough to be as effective. For treatment of cord compression, teletherapy is again the treatment of choice, since the extraosseous tumor will receive very little radiation from radiopharmaceuticals localizing in bone. Teletherapy to a single site of pain will affect only the adjacent bone marrow in a patient who may have had previous chemotherapy, while the radiopharmaceuticals we have reviewed will cause mild-to-moderate myelosuppression, which will not be observed with teletherapy. Pain relief may also be more prompt with teletherapy, although blinded comparative studies have not been performed to confirm this.

If there are multiple painful metastases in a patient whose diagnostic bone scan indicates that the painful sites correspond to osteoblastic lesions, one of the internal beta or electron-emitters should be used. Cord compression and soft tissue masses extending from bone to spinal cord must be excluded before radiopharmaceuticals are used for back pain. Single vertebral lesions may lead to spinal cord compression and should receive teletherapy first, but when the cord has received 40 to 45 Gy, a beta-emitting radiopharmaceutical is indicated for back pain caused by osteoblastic metastases. When it is impossible for the patient and his family to return daily for a fractionated course of radiotherapy, the intravenous radiopharmaceuticals provide a significant advantage, since only one injection is required.

The issue of which of these radiopharmaceuticals gives the highest response rate has not been resolved, since they all

reduce or eliminate pain approximately 60% to 80% of the time, and a study to determine differences of 5% to 10% efficacy between 2 or 3 radiopharmaceuticals would require hundreds of patients in each arm; there is no funding available for such a study. Comparisons between ^{32}P and ^{89}Sr,[24,25] [89]Sr and [153]Sm- lexidronam,[39] [89]Sr and [186]Re-etidronate,[41] and [188]Re-etidronate, [186]Re-etidronate, and ^{89}Sr,[36] have all shown no statistical differences in response rates.

Administration of Unsealed β-Emitters

Careful planning must precede the administration of these unsealed sources. The painful site must correspond to an area that is positive on a bone scan performed within the previous month or so. Radiographs of the site are necessary to exclude a lytic lesion large enough to cause pathologic fracture.

The patient's platelet and leukocyte counts must be adequate, probably more than 60,000 to 100,000/μL for the former and 3500 to 4500/μL for the latter, with an absolute neutrophil count in excess of 1500/μL. Significant disseminated intravascular coagulation has rarely been associated with very severe, or lethal, thrombocytopenia and should be excluded. Decreased renal function requires careful dose reduction. If the patient has received chemotherapy in the last 4 to 6 weeks, one must be certain that full recovery of the marrow has occurred. The patient must understand that the degree of myelosuppression is not entirely predictable, and that there is a remote chance of life-threatening cytopenia.

Patients receiving these radiopharmaceuticals have frequently had multiple injections of chemotherapy or other drugs, which may reduce the number of available veins. An intravenous line should be placed before the administration of the radiopharmaceutical, both to assure that there will be no infiltration of the injectate, which could deposit significant energy in a small volume, and also to reduce the radiation dose to the fingers of the physicians. A finger dosimeter is recommended for the injecting physician, and a plastic syringe shield should be employed since beta particles from these radiopharmaceuticals produce bremsstrahlung proportional to the atomic number of the material interacting with the particle. Therefore, a lead syringe shield is inappropriate.

These radiopharmaceuticals should be injected over at least one minute and then the tubing flushed with 5 to 10 mL of saline. [89]Sr, like its analog calcium, can cause vasodilatation and arrhythmia if injected rapidly, while the phosphonates chelating [153]Sm and [186]Re may also chelate calcium and cause hypocalcemic symptoms if injected too rapidly.

This author finds it impossible to withhold these radiopharmaceuticals based on estimated life expectancy, since physicians err not infrequently in this area. Obviously, a moribund patient is not a good candidate, but someone who may live 2 or more months deserves the opportunity to have cancer-related bone pain ameliorated.

Medical Economics

There are data from several sources documenting that ^{89}Sr as an adjuvant to external radiotherapy can reduce patient management costs. by reducing the need for radiotherapy, narcotics, and hospitalization.[42,43]

The Role of Bisphosphonates

Although this review article is directed at the use of radiation to palliate the pain of osteoblastic metastases, several bisphosphonates (formerly referred to as diphosphonates) are also used for this purpose.[44,45] A phosphonate is formed by a nonionic bond between a carbon and a phosphorus atom. No human enzyme can cleave a phosphonate bond, so these compounds are quite stable in the body. They inhibit osteoclast-induced resorption by binding to bone mineral through the phosphate moiety, interfere with osteoclast activation and also induce osteoclast apoptosis. Meanwhile, these bisphosphonates have been shown also to stimulate osteoblast differentiation and hence new bone formation. Clinically bisphosphonates reduce the risk of developing skeletal complications of metastatic disease including hypercalcemia and pathologic fracture. They delay the progression of existing bone metastases and reduce the development of new lesions.[46] Some bisphosphonates also appear to have a beneficial effect on bone pain.[47]

Conclusions and Questions

Although the efficacy of these radiopharmaceuticals in ameliorating bone pain caused by osteoblastic metastases is clear, many questions remain. In breast cancer, there will often have been multiple courses of myelotoxic chemotherapy given, and the marrow may not be as resilient to the beta radiation it receives as one sees in prostate cancer where less effective chemotherapy is available. More published data come from patients with prostate than breast cancer.

There has been no study of the effect of treating painless osteoblastic metastases with one or more of these agents to determine if the onset of pain can be delayed. Also, since these agents all appear equally effective, while ^{32}P has only slightly more myelotoxicity than radiopharmaceuticals costing two or three times as much,[24,25] should not less expensive ^{32}P be used more widely, especially in developing countries? Do other agents besides ^{89}Sr delay the onset of new or recurrent painful osseous metastases? And, most crucially, what are the best combinations of radiopharmaceuticals, hormones, bisphosphonates, and chemotherapy to treat painful bone metastases, not only to reduce pain, but also to prolong life?

References

1. Foley KM: The treatment of cancer pain. N Engl J Med 313:84-95, 1985
2. Reddi AH, Roodman D, Freeman C, et al: Mechanisms of tumor metastasis to bone: Challenges and opportunities. J Bone Miner Res 18: 190-194, 2003
3. Abrams HL, Spiro R, Goldstein N: Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer 23:74-85, 1950

4. World Health Organization. Cancer pain relief and palliative care. Report of a WHO expert committee. World Health Organ Tech Rep Ser, 804: World Health Organization; Geneva, Switzerland, 1990, pp. 1-75

5. Nielsen OS, Munro AJ, Tannock IF: Bone metastases: Pathophysiology and management policy. J Clin Oncol 9:509-524, 1991

6. Porter AT, McEwan AJB, Powe JE, et al: Results of a randomized phase III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Rad Oncol Biol Phys 25:805-813, 1993

7. Tu SM, Millikan RE, Megistu B, et al: Bone-targeted therapy for androgen-independent carcinoma of the prostate: A randomized Phase II trial. Lancet 357:336-341, 2001

8. Sciuto R, Festa A, Rea S, et al: Effects of low-dose cisplatin on ^{89}Sr therapy for painful bone metastases from prostate cancer: A randomized clinical trial. J Nucl Med 43:79-86, 2002

9. Greenwald HP, Bonica JJ, Bergner M: The prevalence of pain in four cancers. Cancer 60:2563-2569, 1987

10. Poulson HS, Neilsen OS, Klee M, et al: Palliative irradiation of bone metastases. Cancer Treat Rev 16:41-48, 1989

11. Hoskin PJ: Palliation of bone metastases. Eur J Cancer 27:950-951, 1991

12. Tong D, Gillick L, Hendrickson FR: The palliation of symptomatic osseous metastases. Final results of the study by the Radiation Therapy Oncology Group. Cancer 50:893-899, 1982

13. Price P, Hoskin PJ, Easton D, et al: Prospective randomized trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother Oncol 6:247-255, 1986

14. Rose CM, Kagen AR: The final report of the expert panel for the radiation oncology bone metastases working group of the ACR. Int J Radiat Oncol Biol Phys 40:117-120, 1998

15. Salazar OM, Rubin P, Hendrickson FR, et al: Single dose half-body irradiation for palliation of multiple bone metastases from solid tumors. Final Radiation Therapy Oncology Group Report. Cancer 58:29-36, 1986

16. Blake GM, Zivanovic MA, McEwan AJB, et al: Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate. Eur J Nuc Med 12:447-454, 1986

17. Volkert WA, Keutsch EA: Bone-seeking radiopharmaceuticals in cancer therapy. Advances Metals Med 1:115-153, 1991

18. Samaratunga RC, Thomas SR, Hinnefeld JD, et al: A Monte Carlo simulation model for radiation dose to metastatic skeletal tumor from rhenium-186 (Sn)-HEDP. J Nucl Med 36:336-350, 1995

19. Urch C: The pathophysiology of cancer-induced bone pain: current understanding. Palliat Med 18:267-274, 2004

20. Pandit-Taskar N, Batraki M, Divgi CR: Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. J Nucl Med 45: 1358-1365, 2004

21. Honore P, Rogers SD, Schwei MJ, et al: Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 98:585-598, 2000

22. Mantyh PW, Clohisy DR, Koltzenburg M, et al: Molecular mechanisms of cancer pain. Nat Rev Cancer 2:201-209, 2002

23. Silberstein EB: The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. Semin Oncol 20:10-21, 1993 (suppl 2)

24. Nair N: Relative efficacy of ^{32}P and ^{89}Sr in palliation in skeletal metastases. J Nucl Med 40:256-261, 1999

25. Fettich J, Padhy A, Nair N, et al: Comparative clinical efficacy and safety of phosphorus-32 and strontium-89 in the palliative treatment of metastatic bone pain: Results of an IAEA coordinated research project. World J Nucl Med 2:226-231, 2003

26. Pecher C: Biological investigations with radioactive calcium and strontium: Preliminary report on the use of radioactive strontium in treatment of metastatic bone cancer. U Cal Public Pharmacol 11:117-149, 1942

27. Silberstein EB, Williams C: Strontium-89 therapy for the pain of osseous metastases. J Nucl Med 26:345-348, 1985

28. Robinson RG, Preston DF, Spicer JA, et al: Radionuclide therapy of intractable bone pain: Emphasis on strontium-89. Semin Nucl Med 22:28-32, 1992

29. McEwan AJB, Porter AT, Vennes DM, et al: An evaluation of the safety and efficacy of treatment with strontium-89 in patients who have previously received wide field radiotherapy. Antibody Immunoconjugates Radiopharm 3:91-98, 1990

30. Quilty PM, Kirk D, Bolger JJ, et al: A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol 31:33-40, 1994

31. Zyskowski A, Lamb D, Morum P, et al: Strontium-89 treatment for prostate cancer bone metastases: Does a prostate-specific antigen response predict for improved survival? Australas Radiol 45:39-42, 2001

32. Turner SL, Gruenewald S, Spry N, et al: Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. Br J Cancer 84:297-302, 2001

33. Sciuto R, Maini CL, Tofani A, et al: Radiosensitization with low-dose cisplatin enhances pain palliation in radioisotope therapy with strontium-89. Nucl Med Commun 17:799-804, 1996

34. Maxon HR, Thomas SR, Hertzberg VS, et al: Rhenium-186 hydroxyethylidene diphosphonate for the treatment of painful osseous metastases. Semin Nucl Med 22:33-40, 1992

35. Quirijnen N, JMSP, Han SH, Zonnenberg BA, et al: Efficacy of rhenium-186 etidronate in prostate cancer patients with metastatic bone pain. J Nucl Med 37:1511-1515, 1996

36. Liepe K, Franke WG, Kropp J, et al: Comparison of rhenium-188, rhenium-186-HEDP, and strontium-89 in palliation of painful bone metastases. Nuklearmedizin 39:146-151, 2000

37. Palmedo H, Manka-Waluch A, Albers P, et al: Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: Randomized phase II trial; with the new, high energy radiopharmaceutical ^{188}Re hydroxyethylidenediphosphonate. J Clin Oncol 21:2869-2875, 2003

38. Holmes RA: [153Sm] EDTMP: A potential therapy for bone cancer pain. Semin Nucl Med 22:41-45, 1992

39. Dickie GJ, Macfarlane D: Strontium and samarium therapy for bone metastases from prostate carcinoma. Australas Radiol 43:476-479, 1999

40. Srivastava SC, Atkins HL, Krishnamurthy GT, et al: Treatment of metastatic bone pain with tin-117m stannic diethyltriaminepentaacetic acid: A phase I/II clinical study. Clin Cancer Res 4:61-68, 1998

41. Dafermon A, Colamussi P, Giganti M, et al: A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer. Eur J Nucl Med 28:788-798, 2001

42. McEwan AJB, Amyotte GA, McGowan DG, et al: A retrospective analysis of the cost effectiveness of treatment with Metastron in patients with prostate cancer metastatic to bone. Eur Urol 26:26-31, 1994 (suppl)

43. Malmberg I, Persson U, Ask A, et al: Painful bone metastases in hormone-refractory prostate cancer: economic costs of strontium-89 and/or external radiotherapy. Urol 50:747-753, 1997

44. Viney RP, Hayne D, Ayra M, et al: Pharmacological management of metastatic boney pain. Expert Opin Pharmacother 5:1555-1563, 2004

45. Browne JE, Neville-Webbe H, Coleman RE: The role of bisphosphonates in breast and prostate cancers. Endocr Relat Cancer 11:207-224, 2004

46. Powles TS, Paterson S, Kanis JA, et al: Randomized placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 20:3219-3224, 2002

47. Roemer-Becuwe C, Krakowski I, Conroy T: Bisphosphonates, pain and quality of life in metastatic breast cancer patients: A literature review. Bull Cancer 90:1097-1105, 2003