

Therapy of Metastatic Bone Pain*

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Bone metastasis is a common sequella of solid malignant tumors such as prostate, breast, lung, and renal cancers, which can lead to various complications, including fractures, hypercalcemia, and bone pain, as well as reduced performance status and quality of life. A multidisciplinary approach is usually required not only to address the etiology of the pain and its complicating factors but also to treat the patient appropriately. Currently, the treatment of bone pain remains palliative at best with systemic therapy (analgesics, hormones, chemotherapy, steroids, and bisphosphonates) as well as local treatments (such as surgery, nerve blocks, and external beam radiation). However, many of these treatments are limited in their efficacy or duration and have significant side effects that seriously limit the cancer patient's quality of life. Various radiopharmaceuticals have shown good efficacy in relieving bone pain secondary to bone metastasis. This systemic form of metabolic radiotherapy is simple to administer and complements other treatment options. This has been associated with improved mobility in many patients, reduced dependence on narcotic and non-narcotic analgesics, improved performance status and quality of life, and, in some studies, improved survival. Additional radiopharmaceuticals are under investigation and appear promising. All of these agents, although comprising different physical and chemical characteristics, offer certain advantages in that they are simple to administer, are well tolerated by the patient if used appropriately, and can be used alone or in combination with the other forms of treatment.

Key Words: cancer; bone metastasis; treatment; pain; radiopharmaceuticals; metabolic radiotherapy

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The cancer patient seeking treatment for acute or chronic pain requires a comprehensive evaluation to determine the etiology and site(s) of the specific pain syndrome (1-7). A multidisciplinary approach is often required not only to differentiate the specific cause of the pain but also for appropriate patient management.

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Bone metastasis, a major complication of several different cancers, may be the first indication that the disease has spread beyond the local area and that the prognosis may have worsened. Bone metastasis, a common sequella of solid malignant tumors, can lead to severe pain, reduced performance status and quality of life, fractures, and several other complications that contribute to morbidity.

Comprehensive evaluations must be made to determine the etiology of the pain and any possible complicating factors, such as cord compression, neuropathic conditions, and impending pathologic fractures (5-8). The use of conventional radiography and bone scanning helps confirm the presence of bone metastasis but can also assess the extent; classify the lesions into predominantly osteoblastic, osteolytic, or mixed type; and, finally, stratify those lesions that are at risk for fracture or cord compression.

TREATMENT OF BONE PAIN

The treatment of bone pain from metastases remains palliative at present (1,2) and can consist of systemic analgesics, antitumor agents, hormones, chemotherapy, steroids, local surgery, anesthesia, and external beam radiation. In general, no single method will keep the patient free of symptoms for an extended period of time, and usually a combination of systemic and local modalities may be required.

Analgesic Therapy

Analgesic medications are the first line of treatment for bone pain in cancer (3,4,6,8). The World Health Organization (3) recommends a progressive 3-step approach starting with nonsteroidal anti-inflammatory drugs such as aspirin, ibuprofen, and naproxen to relieve mild to moderate pain. If pain persists or increases, step 2 adds a weak opioid such as codeine or hydrocodone. For persistent or moderate to severe pain, step 3 calls for more potent or higher doses of opioids such as morphine, hydromorphone, or fentanyl on a continuous or as-needed basis. Their efficacy may be improved by the concurrent administration of tricyclic antidepressants or phenothiazine.

The use of many of these agents can be hindered by their substantial side effects, which often complicate the treatment of patients with cancer pain, including constipation, limitations in physical and mental status, and, rarely, addiction. Their prolonged use may require increased dosages or

more continuous forms of treatment that may significantly increase the cost of using these agents on a long-term basis.

Another approach to alleviate bone pain that results from the release of biochemical mediators is to use specific inhibitors. For example, osteoclast activity can be inhibited by using bisphosphonates, mithramycin, or calcitonin (9–16). Bisphosphonates, in addition to reducing bone pain, can decrease hypercalcemia and the subsequent risk of fractures (14–16). These agents require chronic administration over long periods to be effective. Contraindications include sensitivity to phosphates.

External Beam Radiation Therapy

Conventional palliative external beam radiation therapy (EBRT) for painful metastases includes several different local and wide-field methods (17–19). Local radiation therapy using a variety of dose-fractionating methods and dose schedules has been shown to be effective in relieving pain, especially when pain is limited to 1 site or region in 60%–90% of the patients in several studies (19–23). Single and multiple fractionated doses have been used with no significant difference in response. Pain relief may occur as early as 48 h after the start of radiotherapy, with a dose as small as 4 Gy. However, the number of patients requiring further treatment was more frequent in the single-dose group than in the multifractionation group (24,25).

Recurrent pain within a previously EBRT-treated field may prove difficult. The tolerance of normal tissues may limit the use of additional radiation therapy to the area. A suitable alternative is the use of systemic radioisotope therapy because this may be given in situations in which further treatment with EBRT is contraindicated.

The development of multifocal or diffuse metastatic bone pain sometimes necessitates more-extensive hemibody or magna field irradiation. Studies have shown that 73%–83% of patients may be successfully treated with 6–7 Gy given as a single fraction to either the upper or the lower part of the body (with the body divided above and below the umbilicus), followed by 6–8 Gy given 4–6 wk later to the remaining portion of the body (23,26). The response is rapid (within 24–48 h) but, in as many as 60% of patients, treatment is complicated by toxic effects, including nausea, vomiting, and diarrhea. Alopecia of the skull and radiation pneumonitis frequently complicate upper body radiation therapy. Myelosuppression occurs in approximately 10% of patients treated with hemibody radiation and in significantly more patients treated with whole-body radiation.

Hemibody plus local irradiation has been shown to delay the progression of disease. Additional treatment can be delayed up to 15% longer in patients treated with local plus hemibody irradiation than in those treated with only local external beam irradiation (26).

The cost of EBRT depends on the number of fractions required as well as the extent of disease involvement. The cost of hemibody radiotherapy can be higher because of the additional patient preparation required (prehydration com-

bined with antiemetics and steroids) and the subsequent toxic effects, which can necessitate more extensive care after treatment and hospitalization.

Hormonal Therapy and Chemotherapy

Up to 70% of patients with cancer report relief from bone pain after hormonal therapy or after single or multiagent chemotherapy (27–29). However, hormonal therapy appears to be effective only in patients with breast or prostate cancer. Tamoxifen and aminoglutethimide relieve metastatic bone pain in about 50% of those with breast cancer, and antiandrogens, estrogens, and orchiectomy (surgical or chemical) can dramatically decrease bone pain within 24 h in patients with prostate cancer (29). However, pain usually recurs in patients who are treated with hormonal therapy because patients become refractory to the treatment.

Chemotherapy, by reducing the tumor volume, usually reduces bone pain in most cancers, with pain reduction resulting in 20%–80% of patients. A positive response often occurs within 2 wk and can last for many months. Unfortunately, patients develop multidrug resistance, and recurrence of bone pain is common. Toxic effects, especially because of myelosuppression, are also common with chemotherapy for bone pain (28,29).

Surgical Intervention

In some cancers, patients may require various types of surgical intervention (30). For example, nearly 10% of patients with advanced prostate cancer develop spinal cord compression. Acute and severe cord compression can require surgical decompression, and an unstable spine may require support with a frame or surgical fusion. Patients with prostate cancer whose pain is so severe that they are confined to bed may do well with pituitary ablation, which is reportedly beneficial in 75%–80% of cases. Fractures can occur in body areas other than the spine. These pathologic fractures require stabilization and fixation to allow further therapy. Cord compression may need to be treated with hormonal therapy, chemotherapy, and radiation therapy as well as surgery depending on the degree of neurologic involvement, vertebral collapse, and instability. Areas at risk for fracture are best treated with surgical stabilization before they fracture and before external radiation therapy or systemic therapy.

SYSTEMIC RADIOISOTOPE THERAPY

Several radiopharmaceuticals for treating painful bone metastases have been developed (Table 1) (31–43). The physical characteristics of these radionuclides vary, and each confers certain benefits. Most of these agents are administered intravenously and target the painful bone metastases by accretion to the reactive bone sites with a high target-to-nontarget tissue ratio and a very low concentration in the surrounding normal bone, underlying bone marrow, or other structures. The nature of the emissions (β , internal conversion, or Auger electrons) determines the therapeutic

TABLE 1
Radiopharmaceuticals Used to Treat Bone Pain

Compound or complex	Half-life (d)	β -energy MeV (maximum)	γ -energy or keV (%)
^{117m}Sn -DTPA	14	None; emits conversion electrons	158 (86)
^{153}Sm phosphonate	1.93	0.81	103 (29)
^{186}Re phosphonate	3.7	1.07	137 (9)
^{32}P various compounds	14.3	1.71	—
^{89}Sr chloride	50.5	1.46	—

DTPA = diethylenetriaminepentaacetic acid.

suitability of the radionuclide because the range of penetration is related to the energy of the electrons.

Systemically administered radiopharmaceuticals offer the advantage of wide applicability in an outpatient setting. Injections of the radiopharmaceuticals are easily administered without the need for expensive high-technology equipment. Thus, these agents can be used not only in major medical centers but also in smaller institutions such as outpatient centers, community hospitals, and rural clinics that are licensed and have personnel trained to comply with Nuclear Regulatory Commission requirements.

Single injections of the systemic radioisotope, given over 2–3 min, reach all osteoblastic bone metastases, regardless of whether they are symptomatic or asymptomatic. In addition to targeting lesions that are predominantly osteoblastic, they also target lesions that are mixed and have both osteolytic and osteoblastic components. More than half of the patients who are treated obtain relief of pain, thus reducing their need for analgesics and improving the quality of life and mobility. Relief of pain may be achieved within 2–7 d depending on the agent and may last several months after a single injection. Serial injections may be given if response is partial or if symptoms return after appropriate recovery of the bone marrow.

The goals of systemic radioisotope therapy include alleviating pain; improving the quality of life; decreasing the amount of opioids, radiation, and chemotherapy used; and improving outcomes and survival. Systemic radioisotope therapy may reduce the overall long-term cost of pain palliation while improving the quality of life of cancer patients with bone pain.

Approved Radiopharmaceuticals for Systemic Radioisotope Therapy

The 3 approved radiopharmaceuticals used to treat metastatic bone pain are sodium phosphate (^{32}P), strontium chloride (^{89}Sr), and samarium (^{153}Sm) lexidronam.

Strontium-89. Significant clinical experience has been gained with ^{89}Sr over the last 3 decades. ^{89}Sr therapy for the treatment of painful bone metastasis was first reported in 1942 by Pecher (40). ^{89}Sr has a physical half-life of 50.5 d

and decays by β -emission with an energy of 1.46 MeV; it is typically used as the chloride salt (44–56). The maximum range of the β -particle in tissues is 8 mm.

^{89}Sr is chemically similar to calcium and is biodistributed to sites within the skeleton that normally metabolize calcium to form new bone. Biodistribution studies have shown rapid clearance from the vascular compartment and significant retention in the bone compartment. Approximately 70% is retained in the skeleton, with the remaining portion excreted in the urine and the gastrointestinal tract. The retention of the radioisotope varies with the degree of skeletal involvement of the metastasis—that is, the greater the involvement the greater the retention. At 90 d, the retention of ^{89}Sr ranged from a high of 88% (with significant metastatic involvement) to a low of 11% (with minimal involvement). Although ^{89}Sr is taken up by normal bone and by bone reacting to the bone metastasis, the biologic half-life differs at these sites. In normal bone, the biologic half-life is approximately 14 d, whereas that associated with reactive bone around metastasis measures >50 d. As such, the concentration of ^{89}Sr at sites of metastasis may be as high as 5–10 times that in normal bone, with the dose to the tumor averaging 20–24 Gy (46–49).

Studies performed as early as 1974 by Schmidt and Firusian (45) revealed that 8 of 10 patients treated with doses of 0.37–0.555 MBq/kg (0.01–0.015 mCi/kg) showed favorable clinical improvement. A European study by Buchali et al. (50) of 98 patients with painful bone metastasis from prostate cancer showed an 86% response rate. Most patients received 37 MBq (range, 37–75 MBq) ^{89}Sr . Twenty-six percent of patients developed leukopenia or thrombocytopenia.

Encouraged by these studies, several open-label studies were conducted. One of the first reported by Robinson et al. (51) in North America in 1987 was a study of 204 patients who had received 1 or more doses of ^{89}Sr . Doses were repeated at intervals of 12 wk or more in 56 patients. Virtually all patients had previously failed standard therapies for advanced disease. One hundred thirty-seven patients survived 3 mo or more and could be assessed. Most had carcinoma of the prostate; the others were categorized as having breast carcinomas and various other malignancies. The first 20 patients in this study received 1.11 MBq/kg (30 $\mu\text{Ci}/\text{kg}$), whereas all subsequent patients received 1.48 MBq/kg (40 $\mu\text{Ci}/\text{kg}$). Patients receiving 2 or more doses received 1.11 MBq/kg as the standard dose for all subsequent treatments. The overall response rate in terms of decreased pain or improvement in quality of life (or both) was 80% in the 137 patients who survived at least 3 mo. The best results were seen in patients with carcinoma of the prostate (80% response) and breast cancer (89%). A decrease in pain level was generally not observed until the second or third week after treatment. Eighty percent of patients for whom data were available showed a mild hematologic depression, generally occurring at the fifth week

with a 15%–20% decrease in total platelet and white blood cell (WBC) count from baseline.

An open-label multicenter study, conducted by Laing et al. (52) in the United Kingdom, included 119 patients with prostate cancer entered from 4 hospitals. Eighty-three patients were evaluable at 3 mo. Patients received a dose of 1.5–3.0 MBq/kg. Seventy-five percent had a meaningful response rate, and 22% of the patients became free of pain by 12 wk. Although pain relief began typically between 10 and 20 d, maximum relief occurred usually at 6 wk after ^{89}Sr administration. Occasionally a slower response rate occurred. Pain relief was maintained for 4–15 mo, with a mean of 6 mo. No advantage was found using higher doses within the range of 1.5–3.0 MBq/kg. A fall in platelet counts was seen in most patients with a nadir at 6 wk; however, no grade 3 hematologic toxicity was reported.

Lewington et al. (53) performed small prospective randomized double-blind, placebo-controlled studies that compared the effects of ^{89}Sr (150 MBq) with unlabeled strontium chloride in 33 patients, of whom only 26 were evaluable (active drug, $n = 13$; placebo, $n = 13$). Complete bone relief was seen in 4 patients, and a partial response was found in 4 of the patients treated with the radioactive drug (overall response, 8/13). The data showed a pain palliation effect of ^{89}Sr versus strontium chloride placebo with a confidence level of >99%.

The most important studies performed with ^{89}Sr were the randomized phase III trials that evaluated the efficacy and safety of ^{89}Sr adjuvant to local or hemibody EBRT therapy.

McEwan et al. (54) showed that the response rate in patients treated with 1.5 MBq/kg ^{89}Sr who were treated previously with wide-field irradiation was 83%, and the response rate of those treated previously with limited local-field irradiation was 71%. This variation was not statistically different between the 2 treated groups. No significant toxicity was seen in either group.

A preliminary study by Bolger et al. (55) reported on the results of the multicenter United Kingdom's Metastron Investigators Group trial. This was followed by the final report by Quilty et al. (56) that compared ^{89}Sr given at a dose of 200 MBq with EBRT (local or hemibody). Two hundred eighty-four patients with painful bone metastasis were evaluable according to the protocol with assessment at 4, 8, and 12 wk. No significant difference in survival of the 2 groups was found, and all treatments effectively reduced bone pain at existing sites of pain (range, 61%–66%). However, fewer patients reported new pain sites after ^{89}Sr therapy alone than after either local or hemibody EBRT ($P < 0.05$). Platelets and leukocytes fell 30%–50% after ^{89}Sr therapy, but no clinically significant untoward effects were seen.

Porter et al. (57) reported a randomized phase III study in the management of endocrine-resistant prostate cancer in a trans-Canadian study. In this trial, 54 patients who had been studied at 8 Canadian centers were analyzed, with patients randomized to receive either EBRT alone or combined

treatment (EBRT plus ^{89}Sr). Porter et al. used higher doses (400 MBq [10.8 mCi]) as a single injection and provided additional information on the role of ^{89}Sr as adjuvant therapy. The duration of symptom relief was longer in the group receiving combined EBRT and ^{89}Sr therapy. In addition, the need for additional EBRT subsequently to new sites of bone pain could be delayed much longer in the group that received combined therapy. A tumoricidal effect was suggested by the fact that a greater number of patients in the active treatment group showed a reduction in serum tumor markers (prostate-specific antigen [PSA] and prostatic acid phosphatase). However, at the high dose of ^{89}Sr administered (400 MBq [10.8 mCi]), a greater number of complications occurred. Whereas WBC and platelet counts dropped to a greater degree and remained depressed longer, grade 3 and grade 4 hematologic toxicity was seen in 28% and 10%, respectively, of patients receiving ^{89}Sr at this dose level.

A dose escalation study was conducted by Haesner et al. (58) in Europe on 200 patients with metastatic prostate cancer. Patients received 3 injections of ^{89}Sr , ranging from 0 (placebo) to 150 MBq. Fifty-nine percent of the ^{89}Sr -treated group had partial or complete pain relief compared with 34% in the placebo group. Eleven percent of the patients in the placebo-treated group deteriorated compared with 3% in the ^{89}Sr group.

Repeated injections were studied in 24 patients by Ben-Josef et al. (59). Fifteen patients received 2 doses, and 9 patients received 3 or more doses. The response rate was similar to that of those receiving 1 injection, with 58% having complete response, 29% showing dramatic improvement, and 12% with some improvement or no change. Grade I–II toxicity was seen in 13% and grade III–IV toxicity was seen in 4% of patients.

Kasalicky and Krajska (60) studied 118 patients with painful skeletal metastasis from a variety of tumors over a 3-y period. Patients received from 2 to 5 injections provided they had a satisfactory response to the first injection. The degree of pain palliation after the repeated injection was slightly better than that after the first injection, and the duration of response increased after each subsequent dose. Response rates of 3–4.5 mo were seen after the third injection and 4.2–5 mo after 4 or 5 injections. Mild myelosuppressive effects were reported.

Kimura et al. (61), investigators in Asia, reported on 90 patients with bone metastasis who were treated with ^{89}Sr , of which 53 had prostate cancer. An overall response of 70% was reported. In Europe, Pons et al. (62) reported on 50 patients with metastatic prostate cancer and 26 patients with metastatic breast cancer who were treated with 148 MBq (4 mCi) ^{89}Sr . Evaluation of the patients with prostate cancer at 3 mo revealed a good response in 64%, a partial response in 25%, and no response in the remaining 11%. Overall toxicity in the above studies was reported as low, provided platelet levels were above 100,000 before therapy.

Less favorable responses and greater toxicity in end-stage

disease have been reported. A study by Rogers et al. (63) on 60 patients with widespread symptomatic disease using doses of ^{89}Sr varying from 66.6 to 173.9 MBq (median, 133.2 MBq) (1.8–4.7 mCi [median, 3.6 mCi]) showed an overall response rate of 67% at 7–11 wk. Three patients (6%) had severe thrombocytopenia and bleeding diathesis at the time of death at 10, 12, and 16 wk after injection. Lee et al. (64) further reported unfavorable results in 28 patients with end-stage disease who were treated with doses of 81.4–162.8 MBq (2.2–4.4 mCi). Only 29% of patients experienced moderate to dramatic pain relief, 32% had some relief, and 50% had no pain relief. This group of patients had only a 23-wk median survival, and 32% required additional palliative EBRT. These patients had a subsequent greater drop in their blood count.

Numerous other studies with ^{89}Sr have been reported since the initial preliminary studies. These have used a variety of protocols and doses, with response rates and toxicity varying according to the stage of the disease (65–69).

Painful flare responses were seen in approximately 10%–20% of patients treated with ^{89}Sr . These were usually transient and generally appeared subsequent to good responses to the administered ^{89}Sr . Other side effects are related mainly to the patient's underlying disease. The use of ^{89}Sr is probably not indicated in patients with end-stage disease with an expected survival of <3 mo and in patients with disseminated intravascular coagulation (64).

Phosphorous-32. Significant clinical experience has been gained with ^{32}P since its introduction >50 y ago for the treatment of metastatic bone pain (70–74). ^{32}P has a physical half-life of 14.3 d and decays by β -emission to ^{32}S . The maximum β -energy is 1.71 MeV, with a mean energy of 0.695 MeV. This agent may be imaged with moderate success using the low-energy bremsstrahlung emission.

Most reports on ^{32}P have been on the orthophosphate form, but other forms, such as polymetaphosphate, pyrophosphate, and hydroxyethylidene diphosphonate (HEDP), have also been used clinically and in animal models. The ratio of phosphorus uptake in tumorous bone relative to normal bone is approximately 2:1. Several authors have advocated the use of agents such as androgens and parathyroid hormone (PTH) to increase this ratio (72–75). However, androgens may exacerbate bone pain as well as cause nausea and vomiting. Patients should be screened before androgen is given to ensure that they have no spinal cord compression, which could worsen and require emergency therapeutic interventions.

Androgens may stimulate hematopoiesis and thus could result in less anemia or myelosuppression than therapy with radiopharmaceuticals alone (76). In addition, subjective improvements specifically related to androgen administration may be seen in patients with breast cancer, making it difficult to interpret the therapeutic effectiveness of the radiopharmaceutical. For this reason, some authors have

advocated the use of alternative methods for increasing the uptake.

The administration of PTH increases bone mineral absorption. It has been postulated that when PTH therapy is withdrawn, a transient rebound effect results in greater deposition of phosphate at metastatic sites associated with increased osteoblastic activity.

A review of the literature on ^{32}P (for the period 1950–1986) by Silberstein et al. (77) found that most of these studies were conducted with androgen stimulation. The percentage of patients who responded ranged from 58% to 100%, with the mean in breast cancer (84%) being slightly higher than that in prostate cancer (77%). Common belief is that ^{32}P has disadvantages because of its myelosuppressive effects; however, to my knowledge, there are only 2 reports in the literature of serious complications (1 death secondary to pancytopenia and 1 cerebral hemorrhage secondary to thrombocytopenia) (78). The frequency of pancytopenia with ^{32}P therapy may be related to the degree and extent of disease that involves the bone as well as the reduced marrow reserve related to prior treatment.

However, pancytopenia is rare with a single injection, or even multiple injections, of up to 444 MBq (12 mCi) ^{32}P . The response in patients who are retreated after recurrence is in many instances as good as the initial response, but in some it is not as great or is of shorter duration.

Samarium-153. ^{153}Sm is reactor-produced in high radio-nuclidic purity by neutron bombardment of enriched ^{152}Sm oxide (79). Complexed with the chelator of ethylenediaminetetramethylenephosphonate (EDTMP), it is supplied as ^{153}Sm -lexidronam. ^{153}Sm has a physical half-life of 46.3 h and decays with emissions of both β - and γ -particles. The maximum β -particle energies are 810 keV (20%), 710 keV (50%), and 640 keV (30%), and the γ -photon energy is 103 keV (29%). Goeckeler et al. (79) first described its localization and distribution in bone and its potential as a therapeutic agent. Singh et al. (80) and others (81–83) described its human pharmacokinetics and performed radiation absorbed-dose calculations. ^{153}Sm -lexidronam is rapidly taken up by the skeleton in osteoblastic bone metastases and cleared from the plasma. The clearance from the blood is biexponential with estimated half-lives of 5.5 and 65 min (81). That portion of the compound that does not accumulate in the skeleton is rapidly excreted, and excretion is almost complete within 6 h after administration. There is, however, a large interpatient variability in the urinary clearance and bone retention depending on the extent of metastases: the greater the number of metastases, the greater the retention in the bone.

Using the 103-keV photon, the biodistribution of ^{153}Sm -lexidronam can be imaged with a gamma camera. Images comparable in quality with those obtained with $^{99\text{m}}\text{Tc}$ -HEDP bone scans have been achieved, and a high lesion-to-normal bone uptake ratio has been reported by various investigators (84–86).

A trial conducted by Lattimer et al. (87) on 40 dogs with

spontaneous skeletal neoplasia that were treated with ^{153}Sm -lexidronam found various responses to the treatment. After treatment, 7 of the 40 dogs were judged to be free of disease on histologic examination of the tumor site and had a mean survival of 2 y. Small lesions with minimal lysis, metastatic lesions, and axial skeleton lesions generally responded well to the therapy, whereas primary lesions with substantial ossification usually had a transient response. Twenty-five dogs had initial functional and radiographic improvement that was followed by regrowth or expansion of bone lesions. In a study of a single dog by Moe et al. (88), treatment with ^{153}Sm -lexidronam was combined with surgery (partial maxillectomy) for osteosarcoma. After 21 mo, the dog was in excellent condition, without evidence of local recurrence or metastases.

The dose-limiting effect of radioactive ^{153}Sm -EDTMP in dogs was bone marrow depression. A dose-related fall in the WBC count and platelets was observed (over the range of 18.5–74 MBq/kg [0.5–2.0 mCi/kg]), reaching a nadir in 2–4 wk and returning to normal after 5–6 wk. It is noteworthy that spontaneous marrow recovery occurred in healthy dogs when a dose as high as 1,110 MBq/kg (30 mCi/kg) was administered. These data support the view that ^{153}Sm -EDTMP does not deliver equivalent radiation to all bone marrow sites; the midshaft of long bones is relatively protected.

In a model of orthotopic human osteosarcoma tibial tumor, rats were given 200 MBq/kg ^{153}Sm -lexidronam (89). The median disease-free latency in 13 of 16 animals was nearly 30 d. The median disease-free latency with 400 MBq/kg was 27 d in 6 or 12 animals, and 6 animals were free of tumor at 60 d. On the basis of these encouraging results, preliminary studies were also conducted in humans.

In an ascending dose study, 29 single intravenous doses (3.7–37 MBq/kg [0.1–1.0 mCi/kg]) ^{153}Sm -EDTMP were administered to patients with painful bony metastases by Podoloff et al. (84). Seventeen palliative responses occurred in 26 evaluable treatment courses (65.4%). The response was usually associated with diminished use of analgesics; 4 patients were able to discontinue all analgesics. Pain remission lasted from 1 to 11 mo (mean, 3.8 mo). Positive responses occurred at all dose levels of ^{153}Sm -EDTMP from 7.4 to 37 MBq/kg (0.2–1.0 mCi/kg). Six of 9 treatment courses given to patients with prostatic cancer and 1 of 3 treatment courses given to patients with lung cancer resulted in positive responses; a single patient with breast cancer experienced pain relief. Patients with small cell, neuroendocrine, and carcinoid tumors also responded to treatment.

A single ascending dose, tolerance/efficacy study in patients with painful bony metastasis from prostate cancer was completed at the University of Washington by Collins et al. (85). Five groups of patients were treated with 37, 55.5, 74, 92.5, or 111 MBq/kg (1.0, 1.5, 2.0, 2.5, or 3.0 mCi/kg), with 4 patients in each group. An additional 16 patients were treated with 37 and 92.5 MBq/kg (1.0 and 2.5 mCi/kg). Through the 111 MBq/kg (3.0 mCi/kg) dose, there was a

consistent fall in platelets and WBCs; the magnitude of the fall was dose dependent. A fall in circulating platelets was observed 1–2 wk after treatment with ^{153}Sm -EDTMP; the nadir value was reached at 4 wk and values began to return toward normal at week 5. A fall in circulating WBCs was evident by 1 wk, the trough value was reached at 2 wk, and a return toward normal was observed between 7 and 10 wk after drug administration. Relief of bone pain was observed at all dose levels but not in all patients. Between 70% and 80% of all patients experienced partial or complete relief of pain. In general, pain palliation was observed at 1 wk after administration of the agent and was independent of dose.

In all clinical studies, approximately 10% of patients exhibited a painful flare response within 48 h after receiving ^{153}Sm -EDTMP.

Turner and Claringbold (86) reported on 35 patients with skeletal metastases who were treated with doses of ^{153}Sm -EDTMP between 10.36 and 31.08 MBq/kg (0.28 and 0.84 mCi/kg). Pain was relieved in 22 of 34 evaluable patients (65%) for periods ranging from 4 to 35 wk. Fifteen of the 34 evaluable patients exhibited stabilization or regression of metastatic lesions on the basis of radiograph and bone scan findings. Reversible myelosuppression was the only significant toxic effect of ^{153}Sm -EDTMP therapy, with dose-limiting thrombocytopenia that reached a nadir 6 wk after administration.

On the basis of these studies, several prospective controlled studies have since been performed on a large group of patients. These pivotal studies have been conducted in North America, Europe, and Asia (42,90–94).

In the first double-blind, placebo-controlled study, Serafini et al. (42) and Serafini (90) randomized 118 patients with painful bone metastases from a variety of primary tumors to placebo ($n = 39$), 18.5 MBq/kg (0.5 mCi/kg) ^{153}Sm -lexidronam ($n = 40$), or 37 MBq/kg (1.0 mCi/kg) ^{153}Sm -lexidronam ($n = 39$). The efficacy variables included a visual analog scale (VAS), a physician's global assessment (PGA), and daily opioid analgesic use. In this study, the mean VAS score decreased from baseline in each of the 4 wk after administration with both active doses, with greater decreases in the higher dose group. The scores remained essentially unchanged from baseline in the placebo group. The change in the area under the pain curve VAS in the lower dose group was significantly different from that in the placebo group at week 1 ($P = 0.044$) but not at any other week ($P = 0.078$). In the higher dose group, the change was significantly different from that of the placebo group in each of the first 4 wk ($P < 0.034$). A mild, transient, dose-related myelosuppression was the only undesirable pharmacologic effect seen in this study.

Furthermore, Serafini et al. (42) and Serafini (90) reported that the pain relief data obtained in this trial showed that 37 MBq/kg (1.0 mCi/kg) ^{153}Sm -lexidronam provides a relatively rapid onset of pain relief because the VAS and PGA scores for patients who received this dose were significantly improved over the scores of those who were given

the placebo during the first week after drug administration. This early response is of benefit to the patient from the standpoint of prompt relief of pain and in allowing an early reduction in the use of opioid analgesics. In addition, the pain-relieving effects of 37 MBq/kg (1.0 mCi/kg) ^{153}Sm -lexidronam are durable because more than half of the patients who received this dose and who were responders at week 4 were still judged as having some pain relief 16 wk after drug administration according to the PGA. These findings are consistent with the short half-life and high dose rate of ^{153}Sm .

A second double-blind, placebo-controlled study was reported by Sartor et al. (91) on 152 patients with hormone-refractory prostate cancer and painful bone metastases. They were randomized in a 1:2 ratio of placebo ($n = 51$) to 37 MBq/kg (1.0 mCi/kg) ^{153}Sm -lexidronam ($n = 101$). The efficacy variables comprised a patient-rated VAS of pain intensity, a patient-rated pain descriptor scale (PDS) that used words to describe the levels of pain, and daily opioid analgesic use. ^{153}Sm -lexidronam had a positive effect on all measures of efficacy. The mean changes in the VAS scores were significant at weeks 2 through 4 ($P = 0.0232$), and the mean changes in the PDS scores were significant at all 4 wk ($P = 0.0030$). There was significant correlation between the VAS and the PDS scores from baseline through week 4 ($r = 0.780$, $P < 0.0001$). Not only did the VAS and PDS scores decrease progressively over time in the active-treatment group but also the use of opioid analgesics decreased in parallel, indicating that the pain relief afforded by active treatment made it possible to reduce the dose of analgesics. ^{153}Sm -lexidronam was associated with a generally mild and transient myelosuppression, with WBC and platelet count nadirs occurring at a median of 4 wk and recovery occurring after approximately 5–8 wk.

Resche et al. (92) performed a single-blind, dose-controlled study of ^{153}Sm -lexidronam on 114 patients with painful bone metastases from a variety of primary tumors. Patients were treated with either 18.5 MBq/kg (0.5 mCi/kg) ($n = 55$) or 37 MBq/kg (1.0 mCi/kg) ($n = 59$). The main efficacy variables were a patient-rated pain intensity VAS and a record of daily opioid analgesic use. The investigators also performed a PGA of the pain response. The mean changes from baseline in the VAS scores indicated that both dose levels alleviated the subjects' pain, but the magnitude of improvement was greater in the higher dose group at each week after initiation of therapy, with statistically significant decreases from baseline at weeks 3 and 4 ($P < 0.005$). None of the changes from baseline in the lower dose group were statistically significant. The difference between groups was statistically significant at week 4 ($P = 0.0476$). Long-term follow-up revealed longer survival among breast cancer patients who had received the higher dose than among those who had received the lower dose.

Myelotoxicity is the major safety concern with the administration of radiopharmaceuticals to patients with bone metastases. ^{153}Sm -lexidronam has been associated in all

large controlled studies currently performed (at doses of 37 MBq/kg [1 mCi/kg] or lower) with only a generally mild and transient myelosuppression. WBC and platelet counts are reduced by approximately 40%–50% from baseline, with the nadirs occurring at a median of 4 wk and recovery occurring after approximately 5–8 wk. Less than 10% of patients in the controlled studies had grade 3 or 4 myelotoxicity.

This has been confirmed subsequently by other large multicenter trials performed independently in China (93) and also by the International Atomic Energy Association (94).

The results of the International Atomic Energy Association Multicenter Study on the efficacy and toxicity of ^{153}Sm -EDTMP in the palliative treatment of painful skeletal metastasis was reported by Olea et al. (94). Four hundred seventeen patients were divided into 3 groups receiving 18.5 MBq/kg (0.5 mCi/kg), 37 MBq/kg (1.0 mCi/kg), or 55.5 MBq/kg (1.5 mCi/kg). Seventy-three percent had effective pain palliation, with most (82% of those responding) having analgesics reduced completely or significantly; 50% had responses lasting >8 wk with the response being independent of dose. No life-threatening toxicity was encountered, with only mild to moderate myelotoxicity, which recovered completely. In the multicenter trial in China (93), 105 patients with painful bone metastases from various primaries were treated with ^{153}Sm -EDTMP at a dose of 37 or 18.5 MBq/kg; 83.8% of patients experienced effective palliation, whereas major toxicity was only temporary myelosuppression.

Retreatment with ^{153}Sm -EDTMP has been described as safe, feasible, and efficacious. For example, Menda et al. (95) recently reported retreatment results in a patient with hormone-refractory prostate cancer and metastatic bone pain. This patient received 11 treatments with ^{153}Sm -lexidronam, 37 MBq/kg (1 mCi/kg) over 28 mo. With the first 5 doses, the patient clearly reduced his bone pain and improved his quality of life as determined by pain assessment scores and the impact of pain on daily living. With doses 6–11, the beneficial effects were maintained but were not as apparent because the pain scores were more difficult to assess; the scores were lower and the patient had also begun to increase his use of opioid analgesics. During the 28-mo treatment period, ^{153}Sm -lexidronam produced transient decreases in WBC and platelet counts, but these never fell low enough to cause clinical concern.

Bushnell et al. (96) gave multiple administrations to 18 patients with hormone-refractory prostate cancer. The median interval between doses was 133 d (range, 55–595 d), with doses ranging between 2 and 11 per patient. The mean administered dose was $2,997 \pm 629$ MBq (81 ± 17 mCi) (range, 1,924–4,181 MBq [52–113 mCi]). A treatment decrease in time to nadir of 4–5 wk was seen regardless of the number of administrations. Grade 3 or grade 4 toxicity of WBCs and platelets was uncommon ($<10\%$ of doses).

Similar to ^{89}Sr , ^{153}Sm -lexidronam had a low incidence of

flare response (approximately 10%) in all studies reported. These were short lived and self-limiting in most cases. The incidence of other adverse events does not appear to be significant, and in the placebo-controlled studies the incidence was similar in both groups, suggesting that these adverse events are attributed mainly to the patients' underlying disease. ^{153}Sm -lexidronam would be contraindicated in patients who are allergic to phosphates and should not be administered on the same day as other bisphosphonates that are being received intravenously because both agents compete for the same binding sites on the hydroxyapatite crystal associated with new bone formation.

Investigational Radiopharmaceuticals

Rhenium-186. ^{186}Re , which is produced by irradiating enriched ^{185}Re , is chemically similar to $^{99\text{m}}\text{Tc}$. It can be readily complexed with HEDP with a relatively high radionuclide and radiochemical purity. ^{186}Re -HEDP has a 3.7-d half-life and decays by the emission of a β -particle with an energy of 1.07 MeV and a γ -emission of 137 keV (9% abundance). In addition, ^{186}Re can be imaged, having a body distribution similar to that of $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) on bone scans. ^{186}Re is rapidly cleared from the blood, predominantly by renal excretion, with 70% eliminated within 72 h.

Dosimetric studies with an injected dose of 1,295 MBq (35 mCi) found a high dose rate, with a mean tumor lesion midpoint dose to the tumor lesions of 35.3 Gy and a mean midpoint marrow dose of 1.2 rad. The tumor-to-marrow dose ratios have a high therapeutic index, with a mean value of 34:1 and a median value of 20:1 (41).

A preliminary trial of ^{186}Re -HEDP was conducted in the United States by Maxon et al. (97) on 51 patients with a variety of cancers, the majority having prostate or breast cancer. Hormonal therapy, EBRT, and chemotherapy had failed in many of them, and they were being treated with long-term opioids. Thirty-three of 43 assessable patients (77%) responded to the treatment, with the onset of pain relief occurring within 2 wk. Twenty percent of the patients became free of symptoms. Fourteen patients in the group still exhibiting symptoms were given a second dose of the agent, and 7 of these patients had responses of magnitude and onset comparable with those of the patients who had received 1 dose (97).

A double-blind crossover study was conducted by Maxon et al. (98) on 13 patients, 6 of whom received ^{186}Re -HEDP (1,258 MBq [34 mCi]) and 7 of whom received the control, $^{99\text{m}}\text{Tc}$ -MDP (666 MBq [18 mCi]). Preliminary results found a response in 5 of the 6 patients given ^{186}Re -HEDP but in only 1 of the 7 given the control. A pain flare occurred in 1 patient at 2 or 3 d after the injection, but it resolved within 1 wk. Myelotoxicity with the ^{186}Re was minimal, with transient myelosuppression that resolved within 8 wk. Similar response rates have been observed in a study conducted in Europe by de Klerk et al. (99); however, a high flare rate (50%) was noted by Zonnenberg et al. (100).

Similarly, Han et al. (101), using ^{186}Re -HEDP etidronate, showed a 58% response in the palliative treatment of metastatic bone pain in breast cancer.

Tin-117m. A neutron inelastic scattering reaction has been used to produce $^{117\text{m}}\text{Sn}$ from an enriched $^{117\text{m}}\text{Sn}$ target in the Oak Ridge National Laboratory high-flux isotope reactor and the Brookhaven National Laboratory high-flux beam reactor. Once $^{117\text{m}}\text{Sn}$ is chelated to diethylenetriamine-pentacetic acid ($^{117\text{m}}\text{Sn}$ -DTPA), its distribution is similar to that of other bone-seeking radiopharmaceuticals. Its physical characteristics are interesting in that it emits conversion electrons of a limited range (0.2–0.3 mm), which should result in decreased marrow toxicity compared with β -emitters.

Preliminary studies have shown that $^{117\text{m}}\text{Sn}$ -DTPA is effective in alleviating bone pain in patients with breast and prostate cancer and has minimal toxicity. A phase I/II trial of $^{117\text{m}}\text{Sn}$ -DTPA conducted by Srivastava et al. (102) on 47 patients with painful bone metastases from various cancers found an overall response rate of 75% (range, 60%–83%) in 40 assessable patients. Patients were assigned to 5 different dose levels ranging from 2.63 to 10.58 MBq (71–286 μCi) per kilogram body weight. Twelve patients (30%) experienced complete relief. The time to onset of pain relief was 19 ± 15 d with doses of 5.29 MBq/kg or less and 5 ± 3 d with doses of 6.61 MBq/kg or greater. Myelotoxic effects were minimal with only 1 patient. Three patients received a second treatment, having a marginal grade 3 WBC toxicity.

$^{117\text{m}}\text{Sn}$ -DTPA has an imageable γ -photon (158.6 keV, 86.4% abundance) and an intermediate physical half-life (14 d) that provides a useful shelf life for distribution. This agent is still in the earliest stages of evaluation, and its efficacy profile and physical characteristics are encouraging. Further clinical trials are planned, with new and improved formulations of $^{117\text{m}}\text{Sn}$ -labeled stannic chelates (103).

ADDITIONAL CONSIDERATIONS

Systemic Radioisotopes and Radiosensitizers

The complementary role of radioisotopes and radiosensitizers appears promising. ^{89}Sr in a single dose and low-dose cisplatin chemotherapy were evaluated in a phase I/II study by Mertens et al. (104). Complete pain relief or a significant reduction of narcotic intake was seen in 55% of patients. No cases of grade 3 hematologic toxicity were seen with this regime, although the marrow was more sensitive to suppression with further injections of ^{89}Sr .

Other agents have been evaluated with encouraging results. This includes a study of 15 patients treated with ^{89}Sr alone (148 MBq) and 15 patients treated with ^{89}Sr (148 MBq) followed by carboplatin (100 mg/m²) given at 7 and 21 d. A response was seen in 20 of 27 evaluable patients, with the pain response being considered by Sciuto et al. (105,106) as being superior with combined therapy.

Tu et al. (107) treated 25 patients concurrently with ^{89}Sr (2.04 MBq/kg [55 $\mu\text{Ci}/\text{kg}$] every 3 mo) and doxorubicin at 15 mg/m² as a continuous infusion over 24 h once per week. Pain relief was achieved in 76% of patients, and 40% had improved performance status. This study was significant in that it showed an improved survival of patients with hormone-refractory prostate cancer. PSA values were seen to decrease >75% from baseline in 32% of patients, suggesting a tumoricidal effect. The median survival of patients was 15.4 mo, which appears to be improved. Wehbe et al. (108) evaluated ^{89}Sr , estramustine, and vinblastine in hormone-refractory prostate cancer as a phase II clinical trial of concurrent chemoradiation. Patients received 2.2 MBq/kg ^{89}Sr every 12 wk; estramustine, 600 mg/m² daily during weeks 1–4 and 6–10; and vinblastine 4 mg/m² weekly during weeks 1–4 and 6–10. Seventeen patients completed 1 treatment cycle and 8 patients completed 2 or more treatment cycles. No grade 3–4 toxicity was seen during 1 treatment cycle but was seen if patients received 2 or more treatments. PSA values decreased in 60% of patients >50% from baseline.

Dahut et al. (109) combined estramustine at different doses and ^{89}Sr in a group of patients with hormone-refractory prostate cancer. Forty-six percent (6/13) of evaluable patients showed PSA declines >50% from baseline. The treatment was well tolerated except for fluid retention at high doses of estramustine (14 mg/kg/d). The authors found this to be less of a problem if the dose was reduced to 8 mg/kg/d during days 1–15 and, if tolerated, then increased to 10 mg/kg/d.

Turner et al. (110) treated 15 patients using low-dose ^{153}Sm -EDTMP (740 MBq [20 mCi]) combined with intravenous bolus doxorubicin or mitomycin or with a 3-d bolus of fluoracil. A complete response to pain was seen in 4 patients (25%) and a partial response was seen in 8 (50%), for an overall response rate of 75%.

Although the results of most of the studies using radiopharmaceuticals combined with chemotherapy are encouraging, the optimal combination therapy dose and sequence have not been established.

Serum and Urinary Markers to Monitor Response to Radioisotopes

Quantitation of serum and urinary biochemical markers of bone resorption and bone formation has been used to predict the need for ^{89}Sr therapy and to monitor the response (111).

Serum procollagen type I C-terminal peptide (PICP) has been used by Papatheofanis (112) to evaluate the response to ^{89}Sr and EBRT. Clinical responders to ^{89}Sr showed a 4-fold decrease in PICP concentration, whereas nonresponders showed no change.

Similarly, urinary production of pyridinium collagen crosslinks pyridinoline and deoxypyridinoline was unchanged in patients who received ^{89}Sr , whereas those who did not receive ^{89}Sr were noted to have an increase, sug-

gesting that bone resorption in the latter group had not been stabilized.

Role of Systemic Metabolic Radiotherapy in Reducing Costs

Cost benefits with systemic radioisotopes have been shown directly and indirectly in various studies.

A retroactive study performed by McEwan et al. (113) reported that lifetime management costs in patients treated with ^{89}Sr were significantly reduced. This was attributed to a reduction of direct treatment costs (need for additional external beam radiation) as well as tertiary inpatient requirements.

Similarly, Malmberg et al. (114) reported the total direct lifetime costs within the Swedish health care system for patients with hormone-refractory prostate cancer. Their conclusion was that ^{89}Sr therapy as an initial supplement to EBRT was beneficial to the patient and improved lifetime health service cost.

Analgesic costs can be quite significant in patients with pain caused by extensive bone metastasis. Clinical experience has shown that the majority of patients require significant dose escalations to manage pain related to progression of disease and that pharmacologic tolerance to the analgesic effects of opioids is not an uncommon problem.

Many studies with ^{89}Sr , ^{153}Sm -EDTMP, and other radiopharmaceuticals have shown that these agents can reduce the need for analgesic medications, which can be quite significant. It is estimated that the average monthly costs for opioid analgesics range between \$50 and \$400 per month of use and for palliative radiotherapy between \$850 and \$4,000 depending on duration and complexity per treatment (115).

Combining radiopharmaceuticals in the management of bone pain may be cost-effective if it succeeds in significantly reducing the level of narcotic analgesics used by patients and the cost of retreating patients with radiotherapy.

Quantification of Therapeutic Dose Administered by Systemic Radiopharmaceuticals

Quantitating the radiation dose to individual skeletal lesions or to the bone marrow has been reported by various groups using either direct measurements of the therapeutic agent (such as ^{153}Sm -EDTMP, $^{117\text{m}}\text{Sn}$, or ^{186}Re) that emit γ -particles or surrogate agents (such as the $^{99\text{m}}\text{Tc}$ bone-scanning agents) (116–122). These methods offer the potential of allowing individualized dosing and an improved therapeutic index relative to fixed dosing schema.

Use of Radiopharmaceuticals in Disseminated Intravascular Coagulation

Systemic radiopharmaceutical therapy for bone metastasis is theoretically contraindicated when disseminated intravascular coagulation occurs (123). When disseminated intravascular coagulation occurs in hormone-refractory prostate cancer, few treatments are available. Ruffion et al. (124) reported the successful use of ^{153}Sm -lexidronam for

relieving bone pain and controlling the disseminated intravascular coagulation. The patient subsequently received 4 additional treatments with ^{153}Sm -lexidronam over the following year without morbidity.

FUTURE APPLICATIONS

Metastatic bone pain can be alleviated with systemic metabolic radiotherapy. Selecting those patients who are most likely to benefit from this treatment requires a thorough assessment of the risks and benefits of the available therapies as well as of the patients' therapeutic history and clinical status. In the future we must develop strategies that enhance and advance the effectiveness of this form of therapy either alone or in combination with other currently accepted forms of pain therapy. Further improvement of the quality of life of patients with cancer is possible if we can apply these techniques more optimally.

Future consideration for systemic metabolic radiotherapy includes their use at an earlier stage in high-risk patients who are likely to develop bone metastasis to prevent this from occurring. This would include its use in asymptomatic patients with positive bone scans who may or may not as yet be refractory to chemotherapy or hormonal therapy or as adjuvant therapy in combination with EBRT to simplify the treatment dosing while enhancing the radiosensitivity of the treated tissue. Such a plan would include an up-front dose of metabolic radiotherapy followed by a single high dose of EBRT. Combination treatments with chemotherapy or bisphosphonates sequenced alternatively with radiopharmaceuticals may enhance efficacy while sparing the toxicity of chemotherapy or the cost of long-term therapy with bisphosphonates or chemotherapy (or both). Neoadjuvant therapy in malignant bone tumors combined with chemotherapy and radiation therapy are further opportunities to be explored. With some of the newer, short-lived agents (^{153}Sm , ^{186}Re , and $^{117\text{m}}\text{Sn}$), high dose levels can be administered over short periods of time with subsequent minimal residual radioactivity in the bone, allowing reinstitution of chemotherapy at an earlier stage. The increasing availability of radioprotectors and various salvage techniques such as colony-stimulating factor can now also be introduced in the management of these patients. These improvements would allow patients to be considered for systemic radioisotope therapy at an earlier stage rather than using this modality as a last resort for palliation of metastatic bone pain.

REFERENCES

1. Campa JA, Payne R. The management of intractable bone pain: a clinician's perspective. *Semin Nucl Med.* 1992;22:3-10.
2. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol.* 1991;9:509-524.
3. World Health Organization. *Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee.* Geneva, Switzerland: World Health Organization; 1990.
4. Agency for Health Care Policy and Research. *Management of Cancer Pain: Clinical Practice Guidelines.* AHCPR publication 94-0592. Rockville, MD: U.S. Department of Health and Human Services; 1994.
5. Garrett IR. Bone destruction in cancer. *Semin Oncol.* 1993;20:4-9.

6. Ventafridda V, Sbanotto A, DeConno F. Pain in prostate cancer. *Palliat Med.* 1990;4:173-184.
7. Coleman RE, Rubens RD. The clinical course of bone metastases in breast cancer. *Br J Cancer.* 1987;55:61-66.
8. Evans PJD. Experience with patients suffering cancer pain in hospital. In: Doyle D, ed. *Opioids in the Treatment of Cancer Pain: Royal Society of Medicine Services International Congress and Symposium Series No. 146.* London, U.K.: Royal Society of Medicine Services Ltd.; 1990:61-67.
9. Lipton A. Bisphosphonates in breast carcinoma. *Cancer.* 1997;80:1668-1673.
10. Carey PO, Lippert MC. Treatment of painful prostatic bone metastases with oral etidronate disodium. *J Urol.* 1988;32:402-407.
11. Gennari G, Francini G, Chierichetti SM, Nami R, Gonelli S, Poilini M. Salmon calcitonin treatment in bone metastases. *Curr Ther Res Clin Exp.* 1989;45:804-812.
12. Roth A, Kolaric K. Analgesic activity of calcitonin in patients with painful osteolytic metastases of breast cancer: results of a controlled randomized study. *Oncology.* 1986;43:283-287.
13. Adami S, Salvagno G, Guarrera G, Bianchi G, Dorizzi R, Rossini S. Dichloromethylene-diphosphonate in patients with prostatic carcinoma metastatic to the skeleton. *J Urol.* 1985;134:1152-1154.
14. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Eng J Med.* 1996;335:1785-1791.
15. Adami S. Bisphosphonates in prostate carcinoma. *Cancer.* 1997;80:1674-1679.
16. Rogers MJ, Watts DJ, Russell RCG. Overview of bisphosphonates. *Cancer.* 1997;80:1652-1660.
17. Price P, Hoskin PJ, Easton P, Austin D, Palmer SG, Yarnold JR. Prospective randomized trial of single and multifraction radiotherapy schedules in the treatment of painful bone metastases. *Radiother Oncol.* 1986;6:247-255.
18. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol.* 1989;1:59-62.
19. Friedland J. Local and systemic radiation for palliation of metastatic disease. *Urol Clin North Am.* 1999;26:391-402.
20. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastases. *Cancer.* 1985;55:1468-1472.
21. Epstein M, Stewart BH, Antunez AR, et al. Half and total body irradiation for carcinoma of the prostate. *J Urol.* 1979;122:330-332.
22. Hoskin PJ. Radiotherapy in the management of bone pain. *Clin Orthop.* 1995; 312:105-119.
23. Salazar OM, Rubin P, Hendrickson FR, et al. Single dose half body irradiation for palliation of multiple bone metastases from solid tumors. *Cancer.* 1986;58: 29-36.
24. Steenland E, Lee J, van Houwelingen H, et al. The effect of single fraction compared to multiple fractions in painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiat Oncol.* 1999;52:101-109.
25. Hoskin PJ, Ford HT, Harmer CL. Hemibody irradiation for metastatic bone pain in two histologically distinct groups of patients. *Clin Pathol.* 1991;1:67-69.
26. Poulter CA, Cosmatos D, Rubin P, et al. A report of RTOG 8206: a phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys.* 1992;23:207-214.
27. Lippman ME, Lichter AS, Danford DN. *Diagnosis and Management of Breast Cancer.* Philadelphia, PA: WB Saunders; 1988:569-574.
28. Marsoni S, Hurson S, Eisenberger M. Chemotherapy of bone metastases. In: Garrattini S, ed. *Bone Resorption, Metastasis and Diphosphonates.* New York, NY: Raven Press; 1985:181-195.
29. Tannock I. Is there evidence that chemotherapy is of benefit to patients with carcinoma of the prostate? *J Clin Oncol.* 1985;3:1013-1021.
30. Chisholm GD, Rana A, Howard GCW. Management options for painful carcinoma of the prostate. *Semin Oncol.* 1993;20:34-37.
31. McEwan AJB. Palliative therapy with bone-seeking radiopharmaceuticals. *Cancer Biother Radiopharm.* 1998;13:413-426.
32. DeNardo GL. Bone pain palliation. *Cancer Biother Radiopharm.* 1998;13:407-411.
33. Lewington VJ. Cancer therapy using bone-seeking isotopes. *Phys Med Biol.* 1996;41:2027-2042.
34. Eisenhut M, Berberich R, Kimming B, Oberhausen E. Iodine-131 labeled diphosphonates for palliative treatment of bone metastases. ii. Preliminary clinical results with iodine-131 BDP3. *J Nucl Med.* 1985;27:1255-1261.
35. Hoefnagel CA, Voute PA, de Kraker J, Marcuse HR. Radionuclide diagnosis and therapy of neuroectodermal tumors using I-131 metaiodobenzylguanidine. *J Nucl Med.* 1987;28:308-314.

36. Hosain F, Spencer RP. Radiopharmaceuticals for palliation of metastatic osseous lesions: biologic and physical background. *Semin Nucl Med.* 1992;22:11-16.
37. Blake GM, Zivanovic MA, Blaquiére RM, et al. Strontium-89 therapy: measurement of absorbed dose to skeletal metastases. *J Nucl Med.* 1988;29:549-557.
38. Brown AP, Greening WP, McCready VR, Shaw HJ, Harmer CL. Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. *Br J Radiol.* 1984;57:323-327.
39. Burnet NG, Williams G, Howard N. Phosphorous-32 for intractable bony pain from carcinoma of the prostate. *Clin Oncol.* 1990;2:220-223.
40. Pecher C. Biological investigations with radioactive calcium and strontium: preliminary report on the use of radioactive strontium in the treatment of metastatic bone cancer. *Univ Calif Publ Pharmacol.* 1942;2:1117-1149.
41. Maxon HR, Deutsch EA, Thomas SR, et al. Re-186 (Sn) HEDP for treatment of multiple metastatic foci in bone: human biodistribution and dosimetric studies. *Radiology.* 1988;166:501-507.
42. Serafini AN, Houston SJ, Resche I, et al. Palliation of bone pain associated with metastatic bone cancer using samarium-153 lexitronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* 1998;16:1574-1581.
43. Serafini AN. Current status of systemic intravenous radiopharmaceuticals for the treatment of painful metastatic bone disease. *Int J Radiat Oncol Biol Phys.* 1994;11:413-418.
44. Mertens WC. Radionuclide therapy of bone metastases: prospects for enhancement of therapeutic efficacy. *Semin Oncol.* 1993;20:49-55.
45. Schmidt CG, Firusian N. ⁸⁹Sr for the treatment of incurable pain in patients with neoplastic osseous infiltrations. *Int J Clin Pharmacol.* 1974;93:149-205.
46. Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med.* 1986;12:447-454.
47. Blake GM, Gray JM, Zivanovic A, McEwan AJ, Fleming JS, Ackery DM. Strontium-89 radionuclide therapy: a dosimetric study using impulse response function analysis. *Br J Radiol.* 1987;60:685-692.
48. Breen SL, Powe JE, Porter AT. Dose estimation strontium-89 radiotherapy of metastatic prostate cancer. *J Nucl Med.* 1992;33:1316-1323.
49. Blake GM, Zivanovic MA, McEwan AJ, Barty VB, Ackery DM. Sr-89 radionuclide therapy: dosimetry and hematological toxicity in two patients with metastasizing prostatic carcinoma. *Eur J Nucl Med.* 1987;13:41-46.
50. Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nucl Med.* 1988;14:349-351.
51. Robinson RG, Spicer JA, Preston DA, Wegst A, Martin NL. Treatment of metastatic bone pain with strontium-89. *Int J Rad Appl Instrum B.* 1987;14:219-222.
52. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol.* 1991;64:816-822.
53. Lewington VJ, McEwan AJ, Ackery DM, et al. A prospective randomized double blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer.* 1991;27:954-958.
54. McEwan AJB, Porter A, Venner P, Amyotte G. An evaluation of the safety and efficacy of treatment of Sr-89 in patients who previously received wide field radiotherapy. *Antibodies Immunocnj Radiopharmaceut.* 1990;3:91-98.
55. Bolger JJ, Dearnaley DP, Kirk D, et al. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial—UK Metastron Investigators Group. *Semin Oncol.* 1993;20(suppl 2):32-33.
56. 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.* 1996;31:33-40.
57. 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 Radiat Oncol Biol Phys.* 1993;25:805-813.
58. Haesner M, Buchali K, Pink V, et al. Efficacy of Sr-89 therapy in 200 patients with skeletal metastases from prostatic carcinoma. *Nuclarmedizin.* 1992;31:48-52.
59. Ben-Josef E, Lucas DR, Vasan S, et al. Selective accumulation of strontium-89 in metastatic bone deposits: radiohistological correlation. *Nucl Med Commun.* 1995;16:457-463.
60. Kasalicky J, Krajska V. The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases. *Eur J Nucl Med.* 1998;24:1362-1367.
61. Kimura Y, Hamamoto K, Furudate M, et al. Effectiveness of the radioactive strontium-89 (Sr-89) chloride agent, SMS 2P, for pain palliation in patients with metastatic bone tumor in phase III multicenter clinical trial. *Kahu Igaku.* 1996;33:1347-1358.
62. Pons F, Herranz R, Garcia A, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. *Eur J Nucl Med.* 1997;24:1210-1214.
63. Rogers CL, Speiser BL, Ram PC, et al. Efficacy and toxicity of intravenous strontium-89 for symptomatic osseous metastasis. *Brachyther Int.* 1998;4:133-142.
64. Lee CK, Aeppli DM, Unger J, et al. Strontium-89 (Metastron) for palliative treatment of bony metastases: the University of Minnesota experience. *Am J Clin Oncol.* 1996;19:102-107.
65. Nightingale B, Brune M, Blizzard SP, Ashley-Johnson M, Slan S. Strontium chloride Sr-89 for treating pain from metastatic bone disease. *Am J Health Syst Pharm.* 1995;52:2189-2195.
66. Altman GB, Lee CA. Strontium-89 for treatment of painful bone metastases from prostate cancer. *Oncol Nurs Forum.* 1996;23:523-527.
67. Uchiyama M, Narita H, Makino M, et al. Strontium-89 therapy and imaging with bremsstrahlung in bone metastases. *Clin Nucl Med.* 1997;22:605-609.
68. Baziotis N, Yakoumakis E, Zissimopoulos A, Gerinicola-Tripali X, Malamitsi J, Proukakis CH. Strontium-89 in the treatment of bone metastases from breast cancer. *Oncology.* 1998;55:377-381.
69. Pons F, Herranz R, Garcia A, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. *Eur J Nucl Med.* 1997;24:1210-1214.
70. Aziz H, Choi K, Sohn C, Yaes R, Rotman M. Comparison of P-32 and SHBI for bony metastases. *Am J Clin Oncol.* 1986;9:264-268.
71. Montebello JF, Hartson-Eaton M. The palliation of osseous metastases with P-32 or Sr-89 compared with external beam and hemibody irradiation: a historical perspective. *Cancer Invest.* 1989;7:139-160.
72. Maxfield JR, Maxfield JGS, Maxfield WS. The use of radioactive phosphorus and testosterone in metastatic bone lesions from breast and prostate. *South Med J.* 1958;51:320-327.
73. Hertz S. Modifying effect of steroid hormone therapy on human neoplastic disease as judged by radioactive phosphorous (P-32) [abstract]. *J Clin Invest.* 1950;29:821.
74. Silberstein EB. The treatment of painful osseous metastases with phosphorus-32 labeled phosphates. *Semin Oncol.* 1993;20:10-21.
75. Fowler JE, Whitmore WF. Consideration for the use of testosterone with systemic chemotherapy in prostatic cancer. *Cancer.* 1982;49:1373-1377.
76. Gardner FH, Pringle JC. Androgens and erythropoiesis. *Arch Intern Med.* 1961;107:846-862.
77. Silberstein EB, Elgazzar AH, Kapilivsky A. Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. *Semin Nucl Med.* 1992;22:17-27.
78. Tong ECK, Rubenfield S. The treatment of bone metastases with parathormone followed by radiophosphorus. *Am J Roentgenol Radium Ther Nucl Med.* 1967;99:422-434.
79. Goekeler WF, Edwards B, Volkert WA, Holmes RA, Simon J, Wilson D. Skeletal localization of samarium-153 chelates: potential therapeutic bone agents. *J Nucl Med.* 1987;28:495-504.
80. Singh A, Holmes RA, Farhangi M, et al. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *J Nucl Med.* 1989;30:1814-1818.
81. Bayouth JE, Macey DJ, Kasi LP, et al. Dosimetry and toxicity by samarium-153-EDTMP administered for bone pain due to skeletal metastases. *J Nucl Med.* 1994;35:63-69.
82. Heggie JCP. Radiation absorbed dose calculations for samarium-153-EDTMP localized in bone. *J Nucl Med.* 1991;32:840-844.
83. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *J Nucl Med.* 1993;34:1031-1036.
84. Podoloff DA, Kasi LP, Kim EE, Fosella F, Bhadkamar VA. Evaluation of Sm-153-EDTMP as a bone imaging agent during a therapeutic trial [abstract]. *J Nucl Med.* 1991;32(suppl):918P.
85. Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med.* 1993;34:1839-1844.
86. Turner JH, Claringbold PG. A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphonate. *Eur J Cancer.* 1991;27:1084-1086.
87. Lattimer JC, Corwin LA, Stapleton J, et al. Clinical and clinicopathologic response of canine bone tumor patients to treatment with samarium-153-EDTMP. *J Nucl Med.* 1990;31:1316-1325.
88. Moe L, Boyesen M, Aas M, Lonaas L, Gamlen H, Gruland OS. Maxillectomy

- and targeted radionuclide therapy with ^{153}Sm -EDTMP in a recurrent canine osteosarcoma. *J Small Anim Pract.* 1996;37:241–246.
89. Winderen M, Kjonniksen I, Fodstad O. Pronounced therapeutic effect of samarium-153-ethylenediaminetetramethylene phosphonate in an orthotopic human osteosarcoma ibial tumor model. *J Natl Cancer Inst.* 1995;87:221–222.
 90. Serafini AN. Samarium Sm-153 lexidronam for the palliation of bone pain associated with metastasis. *Cancer.* 2000;88(suppl: Skeletal Complications of Malignancy):2034–2039.
 91. Sartor O, Quick R, Reid R, et al. A double blinded placebo controlled study of Sm-153-EDTMP for the palliation of bone pain in patients with hormone refractory prostate carcinoma [abstract]. *J Urol.* 1997;157:321.
 92. Resche I, Chatal JF, Pecking A, et al. A dose-controlled study of Sm-153-EDTMP in the treatment of patients with painful bone metastases. *Eur J Cancer.* 1997;33:1583–1591.
 93. Tian JH, Zhang JM, Hou QT, et al. Multicenter trial on the efficacy and toxicity of single dose samarium-153 ethylenediamine methylene phosphonate as a palliative treatment for painful skeletal metastases in China. *Eur J Nucl Med.* 1999;26:2–7.
 94. Olea E, Riccabona G, Tian J, et al. Efficacy and toxicity of 153-Sm-EDTMP in the palliative treatment of painful skeleton metastases: results of an IAEA international multicenter study [abstract]. *J Nucl Med.* 2000;41(suppl):146P.
 95. Menda Y, Bushnell DL, Williams RD. Efficacy and safety of repeated samarium-153 lexidronam treatment in a patient with prostate cancer and metastatic bone pain. *Clin Nucl Med.* 2000;25:698–700.
 96. Bushnell D, Quick D, Reid R, et al. Multiple administration of Sm-153-lexidronam in the treatment of painful bone metastases [abstract]. *J Nucl Med.* 1996;37(suppl):31P.
 97. Maxon HR III, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone resistant prostate cancer. *Radiology.* 1990;176:155–159.
 98. Maxon HR III, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double blind crossover comparison with placebo. *J Nucl Med.* 1991;32:1877–1881.
 99. de Klerk JMH, van Dijk A, van het Schip AD, Zonnenberg BA, van Rijk PP. Pharmacokinetics of rhenium-186 after administration of rhenium-186-HEDP to patients with bone metastases. *J Nucl Med.* 1992;33:646–651.
 100. Zonnenberg BA, de Klerk JMH, van Rijk PP, et al. Re-186-HEDP for treatment of painful bone metastases in patients with metastatic prostate or breast cancer: preliminary results [abstract]. *J Nucl Med.* 1991;32(suppl):1082P.
 101. Han SH, Zonnenberg BA, de Klerk JMH, et al. ^{186}Re -etidronate in breast cancer patients with metastatic bone pain. *J Nucl Med.* 1999;40:639–642.
 102. Srivastava SC, Atkins HL, Krishnamurthy GT, et al. Treatment of metastatic bone pain with tin-117m stannic diethylenetriaminepentaacetic acid: a phase I/II clinical study. *Clin Cancer Res.* 1998;4:61–68.
 103. Srivastava SC, Meinken GE, Atkins HL, et al. New formulations of tin-117 stannic chelate therapy of cancer in bone [abstract]. *Eur J Nucl Med.* 1999;26:1212.
 104. Mertens WC, Porter AT, Reid RH, et al. Strontium-89 and low dose infusion ablation for patients with hormone refractory prostate cancer metastatic to bone. *J Nucl Med.* 1992;33:1437–1443.
 105. Sciuto R, Festa A, Tofani A, et al. Platinum compounds as radiosensitizers in strontium-89 metabolic radiotherapy. *Clin Ther.* 1998;149:43–47.
 106. Sciuto R, Maini CL, Tofani A, Fiura C, Scelsa MG, Broccatelli M. Radiosensitization with low dose carboplatin enhances pain palliation in radioisotope therapy with strontium-89. *Nucl Med Commun.* 1996;17:799–804.
 107. Tu SM, Delpassand ES, Jones D, et al. Strontium-89 combined with doxorubicin in the treatment of patients with androgen independent prostate cancer. *Urol Oncol.* 1997;2:191–197.
 108. Wehbe T, Akerley W, Stein B, et al. Strontium-89 estramustine and vinblastine (SEV) in hormone refractory prostate cancer (HRPC): concurrent chemoradiotherapy labs [abstract]. *Proc Am Soc Clin Oncol.* 1997;16a:1110.
 109. Dahut W, Arcenas A, Feldman S, et al. Strontium-89 (Sr-89 Metastrone) and estramustine (EM) in hormone refractory prostate cancer (HRCP): a phase II study [abstract]. *Proc Am Soc Clin Oncol.* 1997;16a:1182.
 110. Turner JH, Claringbold PG, Martindale AA, et al. Samarium-153-EDTMP and radiosensitizing chemotherapy for treatment of disseminated skeletal metastasis [abstract]. *Eur J Nucl Med.* 1992;16(suppl):S125.
 111. Papatheofanis FJ. Quantitation of biochemical markers of bone resorption following strontium-89 chloride therapy for metastatic prostate carcinoma. *J Nucl Med.* 1997;38:1175–1179.
 112. Papatheofanis FJ. Serum PICP as a bone formation marker in ^{89}Sr and external beam radiotherapy of prostatic bony metastasis. *Br J Radiol.* 1997;70:594–598.
 113. McEwan AJ, Amyotte GA, McGowan DG, et al. A retrospective analysis of the cost effectiveness of treatment with Metastron in patients with prostate cancer metastatic in bone. *Eur Urol.* 1994;26(suppl 1):26–31.
 114. Malmberg I, Persson V, Ask A, et al. Painful bone metastasis in hormone refractory prostate cancer: economic costs of strontium-89 and/or external radiotherapy. *Urology.* 1997;50:747–753.
 115. Macklis R, Lasher J. Palliative radiotherapy for skeletal metastasis: cost substitution analysis and economic impact. *J Oncol Manag.* 1999;8:17–22.
 116. Van Rensburg AJ, Alberts AS, Lou WKA. Quantifying the radiation dosage to individual skeletal lesions treated with samarium-153-EDTMP. *J Nucl Med.* 1998;39:2110–2115.
 117. Israel O, Keidar Z, Rubinov R, et al. Quantitative bone single-photon emission computed tomography for prediction of pain relief in metastatic bone disease treated with rhenium-186 etidronate. *J Clin Oncol.* 2000;18:2747–2754.
 118. Swailem FM, Krishnamurthy GT, Srivastava SC, et al. In-vivo tissue uptake and retention of Sn-117m (4+) DTPA in a human subject with metastatic bone pain and in normal mice. *Nucl Med Biol.* 1998;25:279–287.
 119. Cameron PJ, Klemp PE, Martindale AA, et al. Prospective 153-Sm-EDTMP therapy dosimetry by whole body scintigraphy. *Nucl Med Commun.* 1999;20:609–615.
 120. McCullough SP, Wendt RE, Zarenyrizi F, et al. Tc-99m-MDP as a surrogate quantitative imaging agent for high dose Ho-166-DOTMP [abstract]. *J Nucl Med.* 2000;41(suppl):147P.
 121. Li L, Liang LZ, Deng FH, et al. ^{153}Sm -EDTMP therapy dosimetry by whole-body scintigraphy [abstract]. *J Nucl Med.* 2000;41(suppl):265P.
 122. Brenner W, Kampen WV, Kampen AM, et al. A new method to quantify total bone uptake of Re-186 HEDP and Sm-153 EDTMP [abstract]. *J Nucl Med.* 2000;41(suppl):95P.
 123. Leong C, McKenzie MR, Copland DB, et al. Disseminated intravascular coagulation in a patient with metastatic prostate cancer: total outcome following strontium-89 therapy. *J Nucl Med.* 1994;35:1662–1664.
 124. Ruffion A, Manel A, Valignant C, et al. Successful use of samarium-153 for emergency treatment of disseminated intravascular coagulation due to metastatic hormone refractory prostate cancer. *J Urol.* 2000;164:782.