Samarium-153-EDTMP: Pharmacokinetic, Toxicity and Pain Response Using an Escalating Dose Schedule in Treatment of Metastatic Bone Cancer

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Samarium-153 emits medium-energy beta particles and an imageable gamma photon with a physical half-life of 46.3 hr. When chelated to ethylenediaminetetramethylenephosphonic acid (EDTMP), it is remarkably stable in vitro and in vivo. In this study, we administered escalating amounts of ^{153}Sm-EDTMP, from 0.1 to 1.0 mCi/kg (3.7–37 MBq/kg), to 22 patients with painful metastatic bone cancer. A complete concordance was found when the scintigrams of ^{153}Sm-EDTMP were compared qualitatively to ^{99m}Tc-HDP bone images. Moreover, the skeletal uptake of the ^{153}Sm-EDTMP related to the number of metastatic sites ($r = 0.65$; $p = 0.001$) showed an inverse proportion to the plasma radioactivity at 30 min following injection ($r = -0.79$; $p = 0.0001$) and was unaffected by the administered (mCi/kg), ($r = 0.33$; $p = 0.13$). Myelotoxicity was observed in 10 of the 29 treatment courses and leukopenia occurred in two. Thrombocytopenia occurred in patients who had low pretreatment platelet counts, albeit within the normal range ($p = 0.001$), most suffered from prostate cancer ($p = 0.007$) and retained a higher percentage of the ^{153}Sm-EDTMP in their skeleton ($p = 0.057$). In four patients an exacerbation of the pre-existing pain ("flare reaction") was recorded. Pain palliation occurred in 65% of the treated patients (mean: 3.8 mo, range: 1–11 mo). Retreatment in first time responder patients was quite effective. Our preliminary results indicate that ^{153}Sm-EDTMP is a promising radiotherapeutic agent for palliative treatment of metastatic bone cancer pain, and further study is necessary to ascertain its optimal dose, efficacy and toxicity.

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In the last four decades, several radionuclides have been used to treat metastatic bone cancer. They have included ^{32}P (*3–11*), ^{89}Sr (*12–14*), ^{186}Re (*15*), ^{90}Y (*16*) and ^{131}I (*17, 18*). Except for ^{32}P and ^{89}Sr, these radionuclides have required chelation to ligands possessing the propensity to concentrate in malignant bone lesions.

Samarium-153 ethylenediaminetetramethylenephosphonic acid) (*2*) is a radiopharmaceutical developed at the University of Missouri that appears to have bone cancer localization and pain palliation properties after intravenous administration. It is produced by thermal neutron irradiation of enriched ^{152}Sm-oxide ($^{152}Sm_2O_3$) in the University of Missouri Research Reactor (MURR) (*19,20*) and is complexed with EDTMP in a single step by adding ^{153}Sm in 0.1 NHCl to a freeze-dried sterile, pyrogen-free preparation of EDTMP (*19,20*).

We have reported our results of a radiopharmacokinetic study using a 2.0-mCi (74 MBq) dose of ^{153}Sm-EDTMP in five patients with metastatic bone cancer (*1,2*). An excellent distributional correlation of the scintigraphic images compared to their ^{99m}Tc-hydroxyethylidene diphosphonate (HDP) bone images was observed. Values comparing the lesion to normal bone ratios of the two radiopharmaceuticals were almost identical (^{153}Sm-EDTMP = 4.04 ± 2.62; ^{99m}Tc-HDP = 4.01 ± 1.97). Samarium-153-EDTMP cleared rapidly from the blood with 5.2% ± 1.1% and 2.1% ± 0.5% remaining in plasma at 2 and 4 hr postinjection (*1*). The amount of ^{153}Sm-EDTMP excreted by the kidneys into the bladder at 24 hr was 56.1% ± 10.5%, with most of the excretion (53.4% ± 10.4%) occurring during the first 8 hr. No extra-skeletal uptake or secretion of ^{153}Sm-EDTMP was observed.

In this report, we have expanded the radiopharmacokinetic studies and describe the toxicity and therapeutic results using an escalating amount of ^{153}Sm-EDTMP in 22 patients with painful metastatic bone cancer.

METHOD

Patient Selection

All patients had histologically documented cancer with painful bone metastasis. Skeletal metastases were documented by one or

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TABLE 1
Clinical Characteristics of Treated Patients and Their Response to Treatment

Patient no.	Age	Sex	Tumor type	Previous treatment of bone metastasis	Number of metastatic bone lesions*	^{153}Sm-EDTMP treatment dose (mCi/kg)	Pain palliation (yes/no)	Duration of response (month)
1	22	M	Medulloblastoma	a,b	1	0.10	No	—
				a,b,d	5	1.00	Yes	2.0
2	63	M	Thyroid medullary carcinoma	b	30	0.10	No	—
3	62	F	Neuroendocrine tumor of unknown primary	—	7	0.20	Yes	8.0
				d	7	0.50	Yes	3.0
				d	7	0.75	Yes	3.0
				d	7	1.00	Yes	11.0†
4	69	M	Large cell lung cancer	b	3	0.20	NE	—
5	38	M	Transitional bladder carcinoma	a	21	0.20	No	—
6	64	M	Carcinoid unknown primary	b	31	0.20	Yes	4.0
				b,d	31	0.50	Yes	5.0
7	56	M	Small cell unknown primary	a	6	0.20	Yes	3.5
				a,b,d	6	0.50	Yes	3.5‡
8	61	M	Squamous cell carcinoma lung	—	3	0.35	NE	—
9	63	M	Adenocarcinoma prostate	c,a,b	3	0.35	Yes	3.5
				c,a,b,d	3	0.50	No	—
10	66	M	Adenocarcinoma prostate	—	53	0.35	NE	—
11	57	M	Adenocarcinoma lung	—	5	0.35	Yes	1.0
12	61	M	Adenocarcinoma prostate	c	35	0.35	No	—
13	79	M	Adenocarcinoma prostate	c,a,b	60	0.35	Yes	3.5‡
14	54	M	Large cell carcinoma lung	—	2	0.50	No	—
15	65	F	Adenocarcinoma breast	c,a,b	27	0.75	Yes	3.5§
16	58	M	Cystadenocarcinoma salivary gland	b	5	0.75	No	—
17	74	M	Adenocarcinoma prostate	c,b	13	0.75	Yes	2.0
18	58	M	Adenocarcinoma prostate	c	2	0.75	Yes	2.5
19	56	M	Adenocarcinoma prostate	c	40	1.0	Yes	4.0
20	72	M	Adenocarcinoma prostate	c	52	1.00	No	—
21	72	M	Adenocarcinoma lung	—	7	1.00	No	—
22	65	M	Adenocarcinoma prostate	c	33	1.00	Yes	2.0

* The number of metastatic bone lesions was counted from the ^{99m}Tc-MDP bone scan.
† Pain palliation continues.
‡ Patient died of cause unrelated to cancer while in pain remission status.
§ Pain remission status continued for an additional 8 mo following the onset of treatment with a progestational agent.
NE, not evaluable.
(a) Chemotherapy.
(b) Irradiation.
(c) Hormonal treatment.
(d) ^{153}Sm-EDTMP.

more of the following: x-ray, ^{99m}Tc-HDP bone image, CT scan, MRI and bone biopsy. The study was approved by the Institutional Review Board and written informed consent was obtained from each patient. All eligible patients must have had: discernable pain from bone metastasis, a performance status ≤3 (scale of 0–4) (*21*), hemoglobin >10 g/dl, WBC > 4.5×10^9/liter, platelet count >150×10^9/liter, serum creatinine <1.5 mg/dl and a serum bilirubin of <1.0 mg/dl. Previously untreated patients with therapeutic indication for hormonal treatment or chemotherapy were excluded. Alternatively, in treated patients, at least 8 wk must have passed since the cessation of prior therapy. No additional treatment intervention was introduced during the follow-up period. Retreatment with ^{153}Sm-EDTMP was allowed after 3 mo or longer in patients who exhibited pain relapse.

The clinical features of the 22 patients entered into the study are shown in Table 1. Seventeen had previously received hormones, chemotherapy or external beam irradiation. All patients were receiving analgesics. The number of metastatic bone lesions was determined by counting the abnormal skeletal foci characterized by increased radiopharmaceutical uptake of the ^{99m}Tc-HDP bone images. Twenty-nine courses of treatment with ^{153}Sm-EDTMP were administered to 22 patients. Four patients received two courses, while one patient received four courses of treatment.

Treatment Regimen

Sterile ^{153}Sm-EDTMP was prepared on the day of treatment (*2,22*) using pyrogen-free solutions. Each preparation of the radiopharmaceutical was tested for endotoxin and millipore filtered (0.22 μ) prior to administration. The radiopharmaceutical was administered slowly through a secured intravenous line in a 1–2-ml volume. Approximately 20 ml of physiologic saline were infused for 10 min following ^{153}Sm-EDTMP to facilitate its clearance into the circulation. The administered amount of ^{153}Sm-EDTMP was escalated from 0.1 to 1.0 mCi/kg (3.7–37 MBq/kg) in groups of patients. The treatments were administered in the short-stay treatment center in adherence with all radiation safety requirements. Blood pressure, pulse and respiration rates were monitored during the brief hospital stay according to the protocol. To lessen bladder wall irradiation, the patients were prehydrated with oral fluid, a catheter was inserted in all patients with a history of bladder outlet obstruction and frequent urination was encouraged. Hemogram, urinalysis, prothrombin time, partial thromboplastin time, serum creatinine, aspartate aminotransferase (SGOT), lactic dehydrogenase, alkaline and acid phosphatases and bilirubin were measured weekly. Total-body scintigrams were obtained 3 hr after ^{153}Sm-EDTMP was administered and compared to pretreatment ^{99m}Tc-HDP bone image. Whole-body ^{99m}Tc-HDP images were repeated 1–2 mo after the ^{153}Sm-EDTMP administration.

Radiopharmacokinetic Studies

Venous blood was obtained at 0.5, 1, 2, 4 and 24 hr after ^{153}Sm-EDTMP administration to quantitate the radioactivity remaining in the whole blood and plasma. As reported previously (*2*), the whole blood and plasma clearance of radioactivity were found to be identical. In this paper, the plasma radioactivity data will be reported. Blood volume was estimated using the method of Nadler et al. (*23*). The quantity of ^{153}Sm-EDTMP radioactivity excreted in the urine was measured at the end of 1, 2, 4, 8, 12, and 24 hr post-treatment. The skeletal uptake of ^{153}Sm-EDTMP, expressed as percent of the injected amount (% ± ID), was calculated by subtracting the percent of ^{153}Sm-EDTMP excreted during the first 24 hr from what was injected. This formula was justified in light of the fact that renal excretion was complete in 12–24 hr and no appreciable extraskeletal uptake was seen on the scintigraphic images. Moreover, our own previous animal experiments (*20*) and those of others (*22*) demonstrated minimal uptake of ^{153}Sm-EDTMP by extraskeletal tissues.

Statistics

Spearman correlation coefficients were used to examine the relationships between the variables of interest. To determine factors influencing myelotoxicity, the Wilcoxon rank sums nonparametric analysis of variance was applied.

Assessment of Therapeutic Response

Analgesic medications were adjusted during the 3–7 days prior to treatment to obtain optimum pain control. Each patient was asked to identify up to three most painful sites and was instructed on how to maintain a diary to record the dose and frequency of analgesic medications. Pain intensity was evaluated three times daily and was scored using an analog scale of 0–10, with 10 being excruciating. Data thus generated were entered into a programmed (Sigma Plot) computer that provided numerical and graphic representation of the pain scores and medication course (see Fig. 5).

A therapeutic response was defined as a 50% or greater decline in average pain intensity lasting more than 2 wk without increasing the pain medications. Remission duration was defined as the time from response to the time of relapse of symptoms at the original site. A relapse was defined in part as a rise in the pain intensity score to the pretreatment level lasting longer than 2 wk.

RESULTS

Radiopharmacokinetic Data

The actual amounts of ^{153}Sm-EDTMP given to patients were very close to the planned dosages (D = 3.5%). Scintigrams obtained 3 hr after ^{153}Sm-EDTMP administration were compared to the pretreatment ^{99m}Tc-HDP bone images. Complete concordance between the two scintigrams in delineating the metastatic sites were demonstrated (Fig. 1). No localization of ^{153}Sm-EDTMP was observed outside of the skeleton. Rapid plasma clearance of the radioactivity occurred in all patients (Fig. 2A), and at 30 min postinjection only 9.6% ± 2.8% of the administered amount remained in the plasma (α $t_{1/2}$ = 14 min). At the end of 4 and 24 hr, plasma radioactivity had dropped to 1.3% ± 0.7% and 0.05% ± 0.03%, respectively, (β $t_{1/2}$ = 11.5 hr).

Urinary excretion at 24 hr was 35.9% ± 13.5%, with a range of 9.7%–62.4% in the 22 patients. As shown in Figure 2B, most of the renal excretion occurred during the first 8 hr and was completed by 12 hr. The wide ranges in renal excretion cannot be attributed to variations in renal function, since all of the patients had normal serum creatinines. Low urinary excretions occurred in patients who had extensive bony metastasis, regardless of the amount of radiopharmaceutical administered. Significant correlation was found between skeletal uptake and the number of metastatic sites (r = 0.65; p = 0.001) (Fig. 3), while remaining inversely proportional to plasma radioactivity

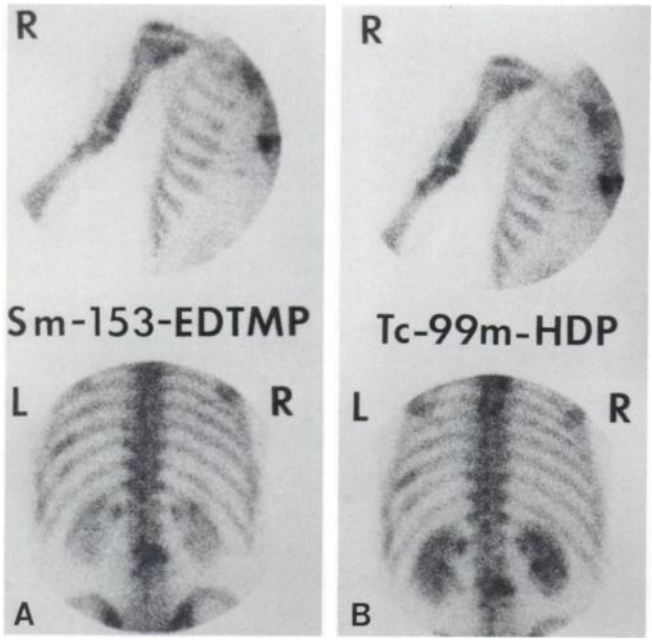

FIGURE 1. Scintigram 3 hr postinjection of ^{153}Sm-EDTMP (A) compared to a pretreatment ^{99m}Tc-HDP bone image of the same patient (B). Identical skeletal metastatic distributional pattern is observed in this patient who has a neuroendocrine cancer.

at 30 min after injection ($r = -0.79$; $p = 0.0001$) and unaffected by the amount of ^{153}Sm-EDTMP administered ($r = 0.33$; $p = 0.13$) (Table 2).

Toxicity

Toxicity, defined as bone marrow suppression, was mild and transient (Fig. 4). A post-treatment decline in platelet

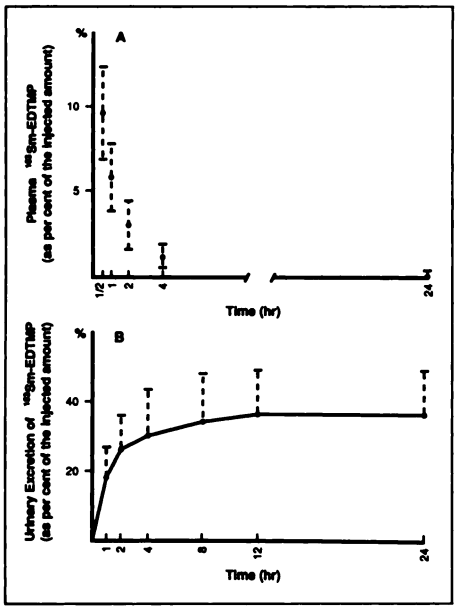

FIGURE 2. (A) Plasma clearance of ^{153}Sm-EDTMP. Shown on x-axis are total plasma radioactivity as % ± s.d. of the injected amounts at various time (y-axis). (B) Total urinary excretion of ^{153}Sm-EDTMP, as % ± s.d. of the administered amount during the first 24 hr.

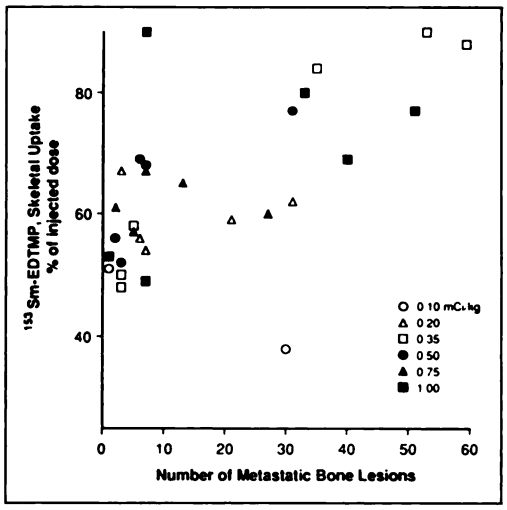

FIGURE 3. Skeletal uptake of ^{153}Sm-EDTMP (as percent of the amount injected) relative to the number of metastatic sites in 29 patient treatment courses.

count was observed in patients receiving ≥0.35 mCi/kg (≥13 MBq/kg) dose of ^{153}Sm-EDTMP. The platelet count fell below 140×10^9/liter ($86–140 \times 10^9$/liter) in 10 of 29 (34.5%) treatment courses. The nadir platelet count occurred between post-treatment Days 16 and 45 (median Day 28). The platelet counts returned to the pretreatment range in all but one patient, who was shown to have extensive bone marrow replacement by prostatic cancer. A posttreatment decline in white cells was noted in patients receiving ≥0.75 mCi/kg (≥28 MBq/kg) of ^{153}Sm-EDTMP (Fig. 4). Leukopenia of less than 3500 occurred in only two instances and returned to pretreatment levels by 6–8 wk.

The profiles of patients exhibiting thrombocytopenia are shown in Table 3. These patients had significantly lower pretreatment platelet counts ($p = 0.001$), but all values were within the normal range. Most of these patients suffered from prostate cancer ($p = 0.007$) and retained a higher percentage of ^{153}Sm-EDTMP in the skeleton ($p = 0.057$). They received a slightly higher amount of ^{153}Sm-EDTMP (0.74 mCi/kg), however, this factor did not reach a level of statistical significance ($p = 0.088$).

Nonhematologic toxicity was limited to a transient exacerbation of preexisting pain (*flare reaction*), particularly in the cervical spine, beginning 2–3 days after therapy and lasting 3–4 days. Of the four patients demonstrating the flare reaction, two required a short (1–2 day) hospitalization for pain control. No arrhythmia or blood pressure, pulse or respiratory changes were observed during postinjection monitoring, and a review of the serum chemistry, urinalysis and urine microscopy revealed no changes.

Pain Palliation

Of the 29 courses of treatment administered, three could not be evaluated for response. Two patients died as a result of pneumonia and pulmonary embolization, and one patient did not maintain an adequate pain diary. Seventeen

TABLE 2
Correlation Between Skeletal Uptake and Number of Metastatic Sites

Patient no.	Metastatic bone lesions no.	^{153}Sm-EDTMP mCi/kg	^{153}Sm-EDTMP (total amount administered) mCi	30-min plasma radioactivity %*	Total skeletal uptake %*
1	1	0.10	5.28	N.D.	51.3
1	5	1.00	44.50	12.8	53.3
2	30	0.10	8.15	11.7	37.6
3	7	0.20	15.45	14.0	54.1
3	7	0.50	42.90	12.0	68.0
3	7	0.75	68.10	12.1	66.9
3	7	1.00	77.70	N.D.	90.2
4	3	0.20	14.35	10.4	66.7
5	21	0.20	14.21	11.5	58.8
6	31	0.20	15.56	7.7	62.3
6	31	0.50	37.92	8.4	77.3
7	6	0.20	12.32	9.6	56.1
7	6	0.50	30.98	10.5	69.3
8	3	0.35	18.96	12.1	49.6
9	3	0.35	23.70	11.3	47.7
9	3	0.50	37.60	10.4	52.1
10	53	0.35	28.35	4.4	90.3
11	5	0.35	25.50	10.9	57.6
12	35	0.35	23.80	3.9	84.4
13	60	0.35	23.87	4.8	87.6
14	2	0.50	41.71	8.0	56.2
15	27	0.75	47.30	10.1	59.6
16	5	0.75	51.20	9.2	56.2
17	13	0.75	67.90	7.2	64.6
18	2	0.75	66.04	N.D.	60.8
19	40	1.00	105.10	9.9	69.4
20	52	1.00	79.00	9.5	76.7
21	7	1.00	91.77	12.3	48.6
22	33	1.00	85.74	4.6	79.6

ND = not done.
* Percent of administered amount.
Total skeletal uptake versus ^{153}Sm-EDTMP mCi/kg: $r = 0.33$; $p = 0.13$.
Total skeletal uptake versus metastatic bone lesions: $r = 0.65$; $p = 0.001$.
Total skeletal uptake versus 30-min plasma radioactivity: $r = -0.79$; $p = 0.0001$.

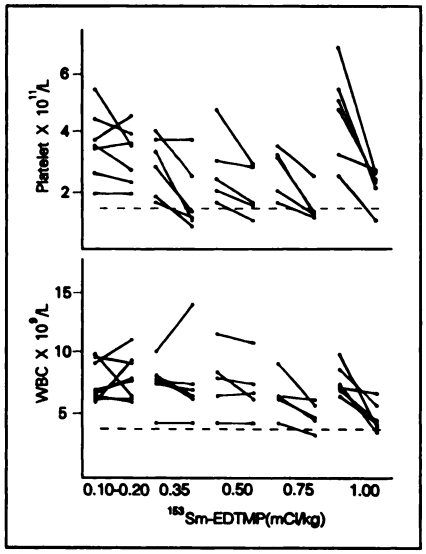

FIGURE 4. Pretreatment and the nadir post-treatment values for platelets and WBCs are shown for each of the five groups of patients receiving increasing amount of ^{153}Sm-EDTMP. A decline in platelets occurred with the ≥0.35 mCi/kg administration, while a drop in WBCs is evident at the ≥0.75 mCi/kg administration.

palliative responses occurred in 26 evaluable treatment courses (65.4%). An example of the course of pain palliation intensity score is shown in Figure 5. The response was usually associated with a diminished use of analgesics, however, only four patients were able to discontinue all analgesics. Pain remission lasted from 1 to 11 mo (mean: 3.8 mo). Two patients died of myocardial infarction while in pain remission status, and another patient with breast cancer exhibited a marked relief of symptoms that lasted 3.5 mo. The remission continued for another 8 mo while she was subsequently treated with a progestational agent.

Positive response occurred with all administered amounts of ^{153}Sm-EDTMP: from 0.2 to 1.0 mCi/kg (7.4–47 MBq/kg). Six of 10 (60%) patients injected with 0.1–0.35 mCi/kg (7.4–37 MBq/kg) and 11 of 16 (69%) patients receiving 0.5–1.0 mCi/kg (18.5–37 MBq/kg) showed pain palliation. This difference was not significant ($p = 0.692$). Six of nine treatment courses given to patients with pros-

TABLE 3
Characteristics of Patients with Thrombocytopenia Following Treatment with ^{153}Sm-EDTMP

	Nadir platelet count		p
	≤ 140^9 liter n = 9	> 140×10^9 liter n = 13	
Pre-treatment platelet count ($\times 10^9$/liter)	242 ± 68	415 ± 125	0.001
Prostate cancer	8	2	0.007
Skeletal uptake of ^{153}Sm-EDTMP (%Administered amount)	70.2 ± 15.4	57.4 ± 0.10	0.057
^{153}Sm-EDTMP (mCi/kg)	0.60 ± 0.25	0.42 ± 0.35	0.088
Number of metastatic lesions	25.6 ± 21.6	16.0 ± 16.9	
Previous treatment for cancer			
Chemotherapy	4	5	ns
Radiation therapy	7	10	ns
Hormonal therapy	8	2	0.007

ns = not significant.

tate cancer and one of three treatment courses given to patients with lung cancer resulted in a response to ^{153}Sm-EDTMP. Only one breast cancer patient was treated who responded to treatment. The best pain palliation was observed in three patients with small-cell, neuroendocrine and carcinoid tumors. Bone images obtained 1–3 months after treatment were compared with pretreatment images. No measurable change was observed in any of the responders, except in one patient who exhibited disappearance of two rib lesions. Serum acid phosphatase levels were elevated prior to treatment in six patients with prostate cancer. Four showed a maximum decline of 24%–47% after therapy. Three of these patients exhibited pain relief and the fourth was not evaluable for pain response due to his demise. Two nonresponders showed a continuous rise in their acid phosphatase levels following treatment.

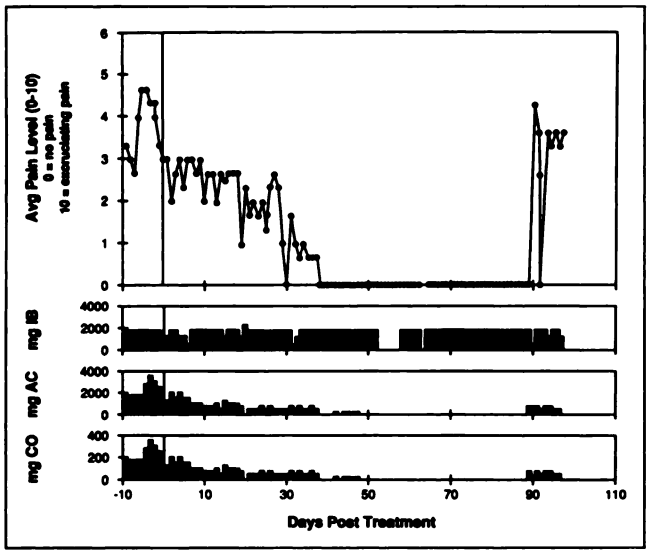

FIGURE 5. Computer-generated graphic representing the pain intensity scores before (Days −10 to 0) and post-treatment (Days 0–96) in Patient 3 who received 0.5 mCi/kg of ^{153}Sm-EDTMP. Daily doses and types of analgesics are also shown (IB = ibuprofen; Ac = acetaminophen; and CO = codeine).

Five patients were re-treated using a higher amount of ^{153}Sm-EDTMP. Patient 1 (Table 1) who had metastatic medulloblastoma exhibited no pain relief with a 0.1 mCi/kg dose (3.7 MBq/kg), however, a decrease in bone pain occurred after treatment with 1.0 mCi/kg (37 MBq/kg). The other four patients had responded to the first dose of ^{153}Sm-EDTMP but subsequently relapsed. Pain palliation was re-established in three following a second treatment. Patient 3 (Table 1) who was diagnosed for neuroendocrine tumor of unknown primary site responded to each of four treatment courses (0.2, 0.5, 0.75 and 1.0 mCi/kg).

DISCUSSION

It has been estimated that half of the one million annual new cancer cases in the United States will develop metastatic bone cancer (*24*). Prostate, breast and lung cancer account for 80% of metastatic bone cancers. Following the diagnosis of bone metastases, patients with prostate and breast cancer have reasonably long survival, but increasing and protracted bone pain is a common complication. An effective and easy administered palliative treatment would be desirable. Radioactive bone-seeking drugs with the capability of delivering an effective radiation dose to all of the metastatic skeletal sites would be superior to external beam irradiation, since the latter has regional limitations. Unfortunately, due primarily to the undesirable myelotoxicity and in-vivo instability of agents, most of the radiopharmaceuticals used previously have not been widely accepted. Most of the clinical data have been derived from studies using ^{32}P as an orthophosphate (*3–10*) or diphosphonate (*11*). Significant myelotoxicity has limited its use, but ^{32}P was highly effective in treating bone cancer pain (*3–11*). Strontium-89 (*12–14*), with a physical half-life of 50 days, has been criticized for its unpredictable therapeutic results (*15*). Neither ^{32}P nor ^{89}Sr are gamma

emitters and are therefore unsuitable for scintigraphic imaging. Yttrium-90-EDTA concentrates in the liver as well as bone (*16*), a factor that limits its use. An ^{131}I-labeled diphosphonate compound (^{131}I BDP3) has been recently studied (*17,18*) and shown to produce pain palliation in half of the patients receiving an amount in the range of 6 to 48 mCi (222–1776 MBq). In-vivo instability of the compound, however, causes the release of ionic ^{131}I, thus making it a less than ideal therapeutic agent. Rhenium-186-HEDP, which is currently under investigation, requires several purification steps prior to administration (*15*). A kit preparation for ^{186}Re-HEDP is under development and should eliminate this apparent limitation.

Samarium-153 emits two medium-energy beta particles and has a physical half-life of 46.3 hr with an average penetration range of 0.83 mm in water (*25*). It also emits a 103-keV gamma photon (*2*). The high stability of ^{153}Sm-EDTMP has been documented in a number of in-vitro and in-vivo experiments (*19,20*). The biodistribution of ^{153}Sm-EDTMP after intravenous injection has been studied in rats, rabbits and dogs (*19,20,22*). Approximately half of the injected dose localizes in the skeleton, while the remainder is rapidly excreted into the urine with minimal uptake in nonosseous tissues. Radioactivity in the liver and kidney at 24 hr postinjection is slightly greater than 1% of the bone radioactivity (*22*). Transient myelotoxicity with complete bone marrow recovery was observed in a series of normal dogs given up to 2 mCi/kg (74 MBq/kg) (*26*). Appelbaum et al. (*22*) administered ^{153}Sm-EDTMP in increasing stepwise amounts of up to 30 mCi/kg (1.1 GBq/kg) to normal dogs. Marrow aplasia was observed in those animals receiving 6 mCi/kg or more. However, these animals unexpectedly demonstrated spontaneous bone marrow recovery, thought to be due to repopulation of the bone marrow by sublethally irradiated stem cells that survived because of the uneven distribution of the radiopharmaceutical in the skeleton.

Lattimer et al. (*27*) treated 40 dogs with bone tumor, most with primary bone sarcomas, with ^{153}Sm-EDTMP. Single or two intravenous doses of ^{153}Sm-EDTMP (1.0 mCi/kg) were administered 1 wk apart. The majority of the animals (78%) exhibited pain palliation, as judged by improved locomotion or deglutition when the tumor was located in the jaw. In seven animals, a disease-free status was achieved with ^{153}Sm-EDTMP alone (five dogs) or with amputation (two dogs). Partial tumor regression was documented in 25 dogs, while eight showed no response. Tumor mass was usually greater in the nonresponding animals. The mean survival of the responding dogs was 27 mo, while the partial responders (5 mo) and the nonresponders (0.7 mo) survived for much shorter periods.

Samarium-153-EDTMP has several favorable features as a radiotherapeutic agent. It possesses a 103-keV gamma emission for scintigraphic imaging of its biological distribution. Due to ^{153}Sm-EDTMP's intermediate beta energy and low tissue penetration, the bone marrow, for the most part, is spared throughout the skeleton. The short physical half-life ($t_{½}$ = 1.8 days) of ^{153}Sm-EDTMP reduces the need for long patient isolation and facilitates the disposal of urine and other body fluid. Most important is the high affinity of ^{153}Sm-EDTMP for metastatic bone lesions that allows the simultaneous delivery of radiation to all targeted sites. From rat, rabbit, dog and our human data, ^{153}Sm-EDTMP does not undergo measurable in-vivo degradation and this lack of complex disassociation is evident since no liver or other soft-tissue uptake was seen on the scintigrams taken after treatment. This is in marked contrast to earlier rat experiments that showed high liver uptake (71%) when unchelated ^{153}Sm-EDTMP was injected (*20*).

Our radiopharmacokinetic studies using escalating amounts of ^{153}Sm-EDTMP demonstrated rapid blood clearance that was directly proportional to skeletal uptake ($p = 0.0001$). Similarly, the percent of skeletal uptake was strongly influenced by the extent and degree of bony metastasis ($p = 0.001$) (Table 2 and Fig. 3).

Grade 1 myelotoxicity (platelet count: 75–150 × 10^9/liter, WBC: 3–3.9 × 10^9/liter) occurred in all groups of patients treated with ^{153}Sm-EDTMP in doses from 0.35 to 1.0 mCi/kg. Surprisingly, four of six patients treated with 0.35 mCi/kg developed a posttreatment nadir platelet count of ≤140 × 10^9/liter, while only one of six patients receiving 1.0 mCi/kg exhibited similar toxicity. It is conceivable that factors, other than the amount of radiopharmaceutical administered, influenced the development of ,myelotoxicity. Our analysis of the data (Table 3) indicates that underlying conditions, such as pretreatment low platelet count (albeit within normal range), tumor type (prostate cancer) and the percent of ^{153}Sm-EDTMP skeletal uptake, exert more of an impact than the amount given (i.e., mCi/kg). A significant correlation was found between previous hormonal treatment and the development of myelotoxicity. This phenomenon can be explained by the fact that most patients in this group (seven of eight) suffered from an advanced stage of prostate cancer and appeared to have a more fragile bone marrow.

We observed pain palliation in 65% of the patients. A slightly higher response rate was seen in patients receiving 0.5–1.0 mCi/kg (18.5–37 MBq/kg). However, because of the small number of patients and the diversity of their neoplasms in each dose group, an absolute dose response relationship could not be clearly established. In responders who relapsed, subsequent treatment was nearly always effective.

It remains to be seen whether further dose escalation with its anticipated increased myelotoxicity will result in a greater percentage of responses and longer remissions. Our data indicate that ^{153}Sm-EDTMP doses of 0.5–1.0 mCi/kg are quite safe and will cause pain palliation in the majority of patients. Turner et al. (*27*), using a dose range of 0.28 to 0.84 mCi/kg for ^{153}Sm-EDTMP, reported similar myelotoxicity and pain palliation in patients with a variety of metastatic bone cancers.

CONCLUSION

Samarium-153-EDTMP, a radiopharmaceutical with beta particle emission, exhibits a strong proclivity for concentrating at metastatic bone sites after intravenous administration. Pain palliation is produced in the majority of patients receiving 0.2 to 1.0 mCi/kg. Complications include a slight and spontaneously reversible myelotoxicity. To better define its efficacy and the length of its response, a large cohort of patients with diverse tumor types must be studied. Dose escalations above 1.0 mCi should be attempted, but the benefit of such dose escalations must be weighed against the anticipated marrow toxicity.

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