Pergamon

European Journal of Cancer Vol. 33, No. 10, pp. 1583–1591, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00155-X

Original Paper

A Dose-controlled Study of ^{153}Sm-Ethylenediaminetetramethylenephosphonate (EDTMP) in the Treatment of Patients with Painful Bone Metastases

I. Resche,[1] J.-F. Chatal,[1] A. Pecking,[2] P. Ell,[3] G. Duchesne,[3] R. Rubens,[4] I. Fogelman,[4] S. Houston,[4] A. Fauser,[5] M. Fischer[6] and D. Wilkins[7]

[1]Centre Rene Gauducheau, Nantes; [2]Centre Rene Huguenin, Paris, France; [3]University College Hospital, London; [4]Guy's Hospital, London, U.K.; [5]Klinik für Hämatologie/Onkologie, Idar-Oberstein; [6]Staedt Klinik, Kassel, Germany; and [7]Wilkins Biomedical, 19 Boulevard de l'Orangerie, 67000 Strasbourg, France

One hundred and fourteen patients with painful bone metastases participated in this randomised, dose-controlled study of the efficacy and safety of ^{153}Sm-ethylenediaminetetramethylenephosphonate (EDTMP), a systemically administered radiopharmaceutical. Fifty-five patients received single doses of 0.5 mCi/kg and 59 patients received single doses of 1.0 mCi/kg. Treatment with ^{153}Sm-EDTMP produced improvement from baseline in all patient-rated efficacy assessments, including degree of pain, level of daytime discomfort, quality of sleep and pain relief. During the first 4 weeks after dose administration, when the patients evaluated efficacy daily, there were statistically significant changes from baseline with the 1.0 mCi/kg dose but not with the 0.5 mCi/kg dose. The difference between doses in visual analogue pain scores was statistically significant at week 4 ($P = 0.0476$). Among subsets of patients examined, female patients with breast cancer receiving 1.0 mCi/kg had the most noticeable improvement. The physicians judged that approximately half of the patients in each dose group were experiencing some degree of pain relief by week 2. This value increased to 55% for the 0.5 mCi/kg group and 70% for the 1.0 mCi/kg group at week 4. More patients in the higher dose group (54%) than in the lower dose group (44%) completed the 16-week study. A predictable level of dose-related marrow suppression was the only toxicity associated with ^{153}Sm-EDTMP treatment. Values for platelets and WBCs reached nadirs at 3 or 4 weeks with both doses and recovered by 8 weeks. Even at their lowest point, the values were generally higher than those associated with infectious or haemorrhagic complications. Myelotoxicity was no greater in female patients than in male patients. 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. The results suggest that the 1.0 mCi/kg dose of ^{153}Sm-EDTMP is safe and effective for the treatment of painful bone metastases. © **1997 Elsevier Science Ltd.**

Key words: ^{153}Sm-EDTMP, pain relief, bone metastases, systemic treatment
Eur J Cancer, Vol. 33, No. 10, pp. 1583–1591, 1997

INTRODUCTION

A NUMBER of therapies specifically targeted to the treatment of bone metastases are currently available. External beam radiation therapy is a highly effective treatment for painful metastatic bone disease, often producing a fairly rapid onset of pain relief [1]. It can be administered on an outpatient basis and is well tolerated. The major drawback of this therapy is that it is local, i.e. only one area of painful metastatic bone disease can be treated at any one time. However, the majority of patients with bone metastases, have multiple areas of involvement. Frequently, after patients complete a course of local-field radiation therapy, different areas of bone become painful and the treatment must be repeated. Bone marrow suppression may become

Correspondence to D. Wilkins.
Received 23 Oct. 1996; revised 3 Mar. 1997; accepted 13 Mar. 1997.

apparent as larger volumes of disease are treated, limiting the scope of further external beam radiation therapy. Hemibody radiation therapy is potentially useful in patients with widespread bone pain, although it is associated with an unpredictable degree of toxicity, particularly involving the lung (if the upper body is treated) or the gastrointestinal tract (if the lower body is treated) [2].

Bisphosphonates have been shown to prevent certain complications of bone metastases, such as pathological fracture [3], and to be effective in the treatment of other complications, such as hypercalcaemia [4]. Placebo-controlled studies of intravenous bisphosphonates in combination with chemotherapy [5] have demonstrated a significant effect in slowing the progression of lytic bone metastases with a reduction in attendant morbidity.

Several systemically administered beta-emitters have been evaluated for the treatment of painful bone metastases and two (^{32}P and $^{89}SrCl_2$) have been studied extensively. Both of these agents are effective in relieving pain from osteoblastic metastases, but both have properties that limit their utility. The very high beta energy of ^{32}P coupled with a low lesion-to-normal bone ratio have inhibited widespread use of this radiopharmaceutical as a palliative agent for bone pain [6]. The long physical half-life of ^{89}Sr (50.5 days) results in a slow delivery of the dose of radiation. Consequently, the onset of pain relief may not occur for several weeks after administration [7]. The long half-life can also produce a prolonged and variable suppression of haematopoietic elements [8], limiting the availability or efficacy of concurrent myelosuppressive therapies (e.g. external radioation, surgery or chemotherapy) that these patients frequently require.

^{153}Sm-EDTMP (Quadramet^{TM}, CYTOGEN Corporation, Princeton, New Jersey, U.S.A.) is a radiopharmaceutical composed of the radioisotope samarium-153, which emits both beta particles and gamma photons, and the tetraphosphonate ligand ethylenediaminetetramethylenephosphonic acid (EDTMP). The resulting metal complex is highly stable. Like other phosphonic acid complexes, ^{153}Sm-EDTMP has an affinity for skeletal tissue and concentrates in areas of bone turnover in intimate association with hydroxyapatite [9]. Studies in animals have demonstrated that ^{153}Sm-EDTMP is cleared rapidly from the blood and localises to growing areas of bone matrix, specifically the layer of osteoid undergoing mineralisation [10]. Absolute lesion-to-normal bone ratios in animals were approximately 17 [11]. In clinical studies employing planar imaging techniques, ^{153}Sm-EDTMP accumulated with a lesion-to-normal bone ratio of approximately 5 and a lesion-to-soft tissue ratio of approximately 6 [9, 12]. Thus, areas of metastatic involvement can accumulate significantly greater amounts of ^{153}Sm-EDTMP than surrounding normal bone. The physical half-life of ^{153}Sm is 46.3 h, and its beta particle has a maximum range of 1.7 mm in bone and 3.1 mm in soft tissue [13]. The gamma emission at 103 keV (29% abundance) is of an appropriate energy for imaging using standard scintigraphic cameras, yet is low enough in abundance to result in minimal external exposure levels when administered at therapeutic levels [9].

The physical and biological characteristics of ^{153}Sm-EDTMP suggest that it may be an effective treatment for the pain of bone metastases. Several early clinical trails have shown that doses in the range of 0.28–3.0 mCi/kg provide rapid relief of pain in a majority of patients [14–16]. These trials, which generally involved small numbers of patients, have showed no difference in overall degree of pain palliation at doses ranging from 1.0 to 2.5 mCi/kg, and failed to demonstrate a dose response at lower doses. Therefore, we initiated a dose-contolled clinical investigation of 0.5 and 1.0 mCi/kg doses of ^{153}Sm-EDTMP in a larger group of patients to assess the comparative efficacy and safety of these doses in patients with bony metastases from a variety of primary tumours.

PATIENTS AND METHODS

Patient eligibility

All patients provided signed informed consent prior to study entry. The patients studied had confirmed disagnoses of malignancy and metastatic lesions in bone (blastic or mixed lytic/blastic). Each was requested to have a ^{99m}Tc bone scan before receiving ^{153}Sm-EDTMP. Pain at one or more sites overlying abnormal uptake on the bone scan was required for participation in the study, as were a performance status of 40 or greater on the Karnofsky scale [17] and an expected survival of at least 4 months. Patients were excluded if they had granulocyte counts below 2000/μL, platelet counts below 150000/μL or serum creatinine levels above 2.0 mg/dL. Other reasons for exclusion were previous treatment with maximum tolerated radiation to the spinal cord and/or hemi-body radiation, systemic chemotherapy or radiation therapy within 6 weeks of dosing, diphosphonate therapy within the preceding 6 months, $^{89}SrCl_2$ treatment within the preceding 9 months or initiation of hormonal therapy within 8 weeks of dosing.

Treatment with ^{153}Sm-EDTMP

$^{153}Sm_2O_3$ was produced by neutron bombardment of enriched $^{152}Sm_2O_3$ at either The Paul Scherrer Institute (Villingen, Switzerland), The European Commission Reactor (Petten, Holland), or Atomic Energy of Canada Limited (Chalk River, Ontario, Canada). $^{153}Sm_2O_3$ was dissolved in HCl to yield $^{153}SmCl_3$, which was then combined with Ca/Na EDTMP to produce ^{153}Sm-EDTMP. Individual doses, which were prepared by The Paul Scherrer Institute or Nordion International (Kanata, Ontario), were kept frozen until within 4 h of administration.

The patients were centrally randomised to receive either 0.5 or 1.0 mCi/kg of ^{153}Sm-EDTMP. The physicians knew which dose each patient received; the patients knew they were receiving active treatment but did not know the dose. Treatment was administered in single rooms with appropriate shielding. Each patient was given 1000 mL of fluid orally or intravenously before administration of the study agent and another 1000 mL in the subsequent 6 h period. ^{153}Sm-EDTMP was administered via an established i.v. catheter over 1 min, and the tubing was then flushed with normal saline.

Study procedures

The patients were followed for up to 16 weeks after they received ^{153}Sm-EDTMP. Efficacy, safety and excretion of the radionuclide were monitored during that time.

An earlier study had shown that urinary excretion of ^{153}Sm-EDTMP was essentially complete by 6 h [9].

Therefore, urine was collected for 6 h following dose administration for determination of the amount of ^{153}Sm-EDTMP excreted. Each patient had a ^{153}Sm-EDTMP bone scan 24–72 h after dose administration for comparison with the ^{99m}Tc bone scan that had been performed before dosing. Level of pain, sleep characteristics, and analgesic use were recorded in a diary that each patient completed once a day from the week before dose administration (baseline) until the end of week 4 and then once a week from week 5 to week 16. In the diary, the patient indicated the degree of pain in each of 13 body regions on a visual analogue scale of 0 (no pain at all) to 10 (worst pain possible). All of the pain medications taken each day were listed, along with the unit dose and number of doses. Sleep characteristics were rated as follows: slept without pain medication, slept with pain medication, woke with pain/relieved with medication, woke with pain/not relieved with medication, awake most or all of the night because of pain. The level of discomfort during the day was rated as follows: no pain, pain/normal routine, pain/some restrictions, pain most of the time, pain severe/all activities restricted. Finally, each patient made a weekly assessment of pain relief by answering the following question: "Did the study drug help lessen your pain this week?"

A Physician's Global Assessment (PGA) was completed by the physician when the patients returned for study visits, which occurred at weekly intervals for the first 4 weeks after the study agent administration and then at monthly intervals for the duration of the study. The patient's overall condition, including pain, discomfort and daily activity, was rated as much worse, worse, no change, better, much better or completely better.

Safety was evaluated by laboratory tests, vital sign measurements, physical evaluations and recording of adverse experiences. The laboratory tests included complete blood counts and platelet counts, which were performed at baseline, weekly until full haematological recovery and then monthly for the remainder of the study.

The dosing and evaluation phase of the study was carried out from June, 1991 to June, 1993. Survival was subsequently followed until February, 1996.

Statistical methods

The diary ratings of pain evaluated 13 predefined body sites: head, neck, ribs (left), collar/breast bone, ribs (right), upper spine, lower spine, left arm, right arm, left hip, right hip, left leg, right leg. To obtain a meaningful overall score, the scores for individual sites were asymptotically combined using a hyperbolic transformation of the pain scale [18]. For the baseline period and the first 4 weeks of the study, when the diaries were completed daily, area under the pain curve (AUPC) scores were computed from the transformed overall scores for each 7-day period. Analysis of variance methodology was used to analyse temporal change over the 4 weeks within each treatment group and between treatment groups.

All opioid analgesics were converted to oral morphine equivalent doses. Average daily oral morphine equivalent dose was then calculated for baseline and each of the first 4 weeks of the study. Statistical methodology for analysing opioid use was the same as that employed for the AUPC data.

Average daily sleep response and average daily daytime discomfort were analysed by analysis of variance. The study site and dose were included in the model as class variables. The weekly pain relief assessment and the PGA response categorical data were analysed using the Cochran–Mantel–Haenszel test, with study site as a stratification variable.

To provide the most conservative presentation of the survival data, patients in the 1.0 mCi/kg dose group with missing survival data ($n = 3$) were assumed to have died one day after their last day in the study. Patients in the 0.5 mCi/kg group with missing survival data ($n = 3$) were assumed to still be alive.

RESULTS

Patient population

One hundred and fourteen patients participated in this study; 55 patients received 0.5 mCi/kg and 59 received 1.0 mCi/kg. Table 1 summarises their baseline characteristics. The most common malignancies were prostate and breast cancer. A large percentage of the patients had histories of surgical, hormonal and radiation therapy for cancer. Approximately one-third had prior chemotherapy. The two treatment groups were comparable at baseline for all parameters except duration of disease, which was longer in the 1.0 mCi/kg group, and the percentage of patients using opiate analgesics, which was higher in the 0.5 mCi/kg group. These differences were not expected to affect the outcome of the study.

Thirty-two patients (54%) in the 1.0 mCi/kg group and 24 patients (44%) in the 0.5 mCi/kg group completed 16 weeks in the study. Among the patients who did not complete the study, the most common reasons for premature

Table 1. Patients characteristics

	0.5 mCi/kg ($n = 55$)	1.0 mCi/kg ($n = 59$)
Sex		
Male	38	37
Female	17	22
Age (years)		
Median	62	65
Range	38–79	20–83
Primary cancer type		
Prostate	32	35
Breast	16	20
Lung	2	0
Other	5	4
Duration of disease (months)		
Median	30.23	52.86
Range	8.7–350.7	2.3–243.1
Prior treatment*		
Surgery	43 (78%)	48 (81%)
Hormones	46 (84%)	51 (86%)
Radiation	46 (84%)	45 (76%)
Chemotherapy	20 (36%)	16 (27%)
Daily opiate use		
Number (%)	39 (71%)	35 (59%)
Mean (SE)†	89.1 (10.2)‡	99.9 (14.8)

*Patients could be counted in more than one category. †Opiate use is expressed as morphine equivalent units. ‡Excludes the value for one patient who had a baseline opiate intake (1640 morphine equivalent units) that was far greater than that of all other patients.

discontinuation from the study were increased pain requiring alternative therapy (13 in the 0.5 mCi/kg group versus 7 in the 1.0 mCi/kg group), death (10 in each group) and disease progression (5 versus 8).

Eleven patients (6 in the 0.5 mCi/kg group and 5 in the 1.0 mCi/kg group) received concomitant therapies (chemotherapy or external radiation therapy) during either the baseline period or in the first 4 weeks following administration of the study agent. Since such therapies can affect pain, these patients have been excluded from the evaluations of efficacy, but, they are included in all safety-related evaluations.

^{153}Sm-EDTMP bone scans

Imaging studies performed 24–72 h after administration of ^{153}Sm-EDTMP revealed excellent visualisation of bone metastases. All of the metastases that had been demonstrated on the pretreatment ^{99m}Tc scans were present on the ^{153}Sm-EDTMP scans (Figure 1).

Patient diaries

Table 2 summarises the data recorded by the patients in diaries at baseline and during the first 4 weeks following administration of ^{153}Sm-EDTMP. All the parameters were recorded daily during that period, except for the pain relief assessment, which was recorded once a week.

The mean changes from baseline in the AUPC suggested that patients in both groups were experiencing alleviation of their bone pain. The magnitude of the change was larger in the higher dose group at each post-therapy week, with statistically significant reductions from baseline at weeks 3 and 4 for that group ($P < 0.005$). None of the changes from baseline in the lower dose group were statistically significant. The difference between groups was statistically significant at week 4 ($P = 0.0476$).

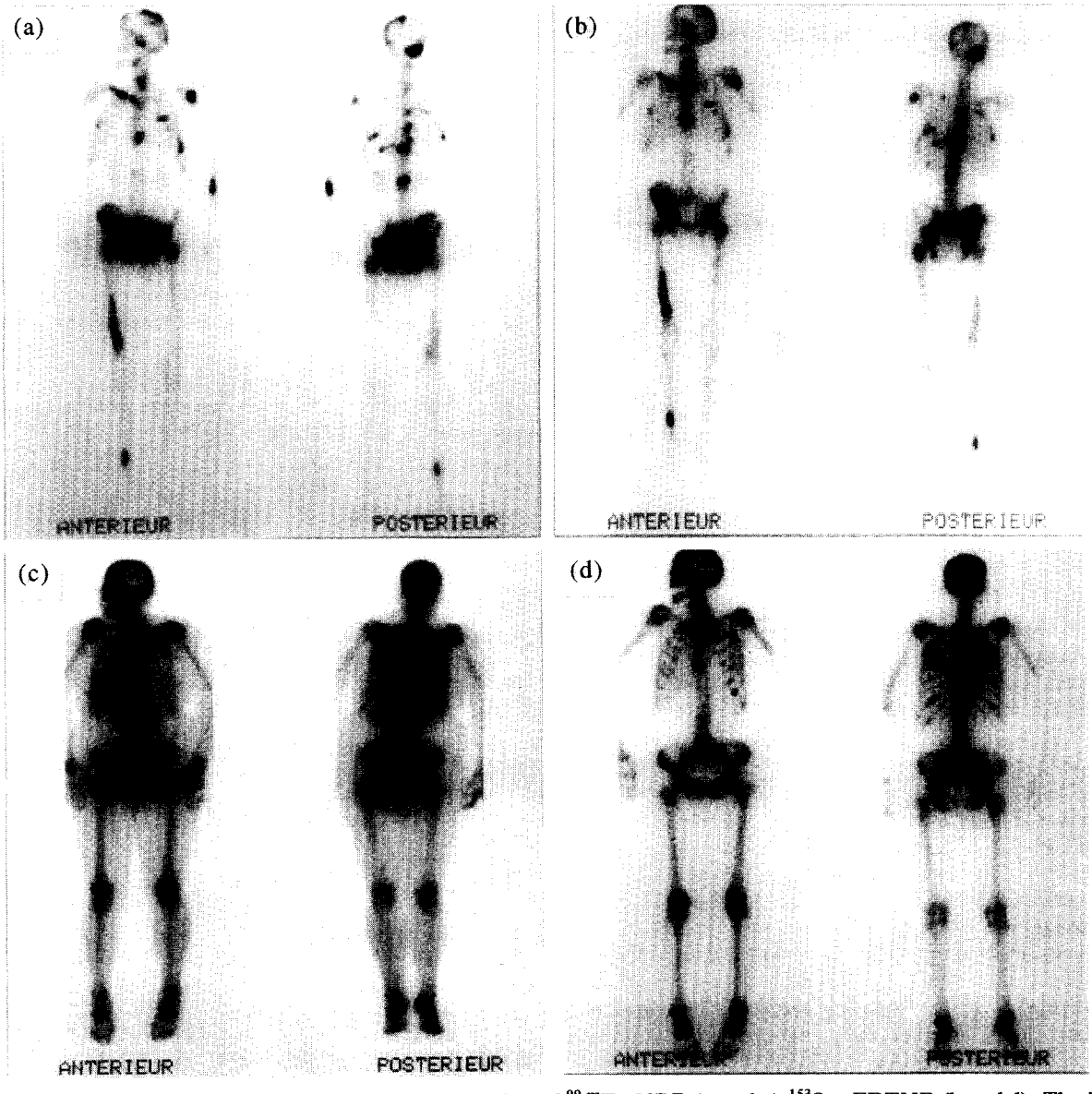

Figure 1. Scintigraphic images obtained after administration of ^{99m}Tc-MDP (a and c) ^{153}Sm-EDTMP (b and d). The images in panels (a) and (b) were obtained from a patient with metastatic prostate cancer and those in (c) and (d) were obtained from a patient with metastatic breast cancer.

Table 2. Summary of patient diaries

Assessment Group	N*	Baseline	Week 1	Week 2	Week 3	Week 4
AUPC (mean change from baseline and SE)						
0.5 mCi/kg	49	46.86 (2.20)†	−0.30 (1.07)	−3.28 (1.71)	−3.52 (1.85)	−3.86 (1.73)
1.0 mCi/kg	54	47.54 (1.89)†	−1.22 (1.47)	−3.71 (1.99)	−6.55 (1.92)‡	−6.59 (2.23)‡
Daytime discomfort (% of patients with no pain, pain/normal routine or pain/some restrictions)						
0.5 mCi/kg	49	43%	47%	61%	55%	53%
1.0 mCi/kg	54	41%	59%	61%	72%‡	65%‡
Sleep (% of patients who slept all night with or without medication)						
0.5 mCi/kg	49	33%	37%	47%	53%	45%
1.0 mCi/kg	54	33%	41%	54%	52%	59%‡
Pain relief (% of patients who thought ^{153}Sm-EDTMP treatment lessened their pain)						
0.5 mCi/kg	49	—	35%	57%	59%	67%
1.0 mCi/kg	54	—	46%	52%	72%	70%
Opioid analgesic use (mean daily oral morphine equivalent dose and SE)						
0.5 mCi/kg	48	60.0 (11.8)	65.6 (12.3)	58.7 (10.6)	58.8 (11.7)	64.0 (11.8)
1.0 mCi/kg	54	62.0 (14.1)	64.7 (14.6)	65.9 (14.9)	65.5 (15.6)	65.0 (16.1)

*One patient in the 0.5 mCi/kg group was excluded from the evaluation of analgesic use because his daily opiate use was much greater than that of all other patients in both groups at baseline (1640 morphine equivalent units) and throughout the study. †Mean (SE) value at baseline. ‡Indicates a statistically significant difference from the baseline value ($P < 0.05$)

The assessment of daytime discomfort revealed that, in both dose groups, the proportion of patients experiencing pain most of the time or severe pain that caused total restriction of activity decreased over the course of the first 4 weeks. Conversely, the proportion experiencing less pain increased. The changes from baseline in average daytime discomfort were statistically significant at weeks 3 and 4 in the 1.0 mCi/kg group ($P < 0.011$) but not in the 0.5 mCi/kg group.

At baseline, only 33% of the patients in each dose group were able to sleep through the night. These values increased to 45% and 59%, for the 0.5 and 1.0 mCi/kg groups, respectively, by week 4, when the change from baseline was statistically significant for the 1.0 mCi/kg group ($P = 0.026$).

The patients thought that treatment with ^{153}Sm-EDTMP lessened their pain, as evidenced by their responses to the weekly pain relief assessment. The rate of affirmative responses increased over time, reaching a maximum of 72% in the 1.0 mCi/kg group at week 3 and remaining at approximately that level at week 4.

Examination of mean daily opiate analgesic use revealed that the patients were not experiencing pain relief as a result of increasing use of analgesics. In both dose groups, the mean values increased slightly between baseline and week 1 and thereafter remained fairly constant. None of the mean changes from baseline were statistically significant.

The association between administered dose of ^{153}Sm-EDTMP, pain response and the use of opiate analgesics was investigated further by estimating the regression of change in AUPC and change in daily opiate dose. Linear slopes for those two parameters over the period from baseline through week 4 were estimated from the average weekly values for all patients with data included in Table 2. The more suggestive regression relationship between the reduction in opiate use and the reduction in pain was noted for the 1.0 mCi/kg dose group. The association between the slopes of AUPC and the slopes of opiate use had a corre-

Table 3. Summary of physician's global assessment

Group	Week	Better*	No change	Worse†	Not reported‡
0.5 mCi/kg	1	12 (24%)	25 (51%)	12 (24%)	0
($N = 49$)	2	24 (49%)	17 (35%)	8 (16%)	0
	3	27 (55%)	13 (27%)	9 (18%)	0
	4	27 (55%)	10 (20%)	12 (24%)	0
	8	22 (45%)	5 (10%)	5 (10%)	17 (35%)
	12	18 (37%)	5 (10%)	5 (10%)	21 (43%)
	16	15 (31%)	2 (4%)	6 (12%)	26 (53%)
1.0 mCi/kg	1	19 (35%)	18 (33%)	17 (31%)	0
($N = 54$)	2	26 (48%)	14 (26%)	13 (24%)	0
	3	36 (67%)	6 (11%)	12 (22%)	0
	4	38 (70%)	7 (13%)	9 (17%)	0
	8	28 (52%)	6 (11%)	9 (17%)	11 (20%)
	12	26 (48%)	2 (4%)	7 (13%)	19 (35%)
	16	21 (39%)	8 (15%)	3 (6%)	22 (41%)

*Possible responses of 'better', 'much better' and 'completely better' were combined in this column. †Possible responses of 'worse' and 'much worse' were combined in this column. ‡Includes patients who withdrew from the study.

Table 4. Change in AUPC at week 4 in subgroups of patients

Group	0.5 mCi/kg		1.0 mCi/kg		Difference
	N	Mean change (SE)	*N*	Mean change (SE)	
All patients	49	−3.86 (1.73)	54	−6.59 (2.23)	−2.73
All males	33	−3.84 (2.46)	32	−4.46 (2.66)	−0.62
Males with prostate cancer	28	−2.76 (2.47)	30	−5.00 (2.81)	−2.24
All females	16	−3.91 (1.59)	22	−9.67 (3.85)	−5.76
Females with breast cancer	15	−3.00 (1.39)	20	−12.09 (3.80)	−9.09

lation coefficient of $r = 0.258$ ($P = 0.059$) in that dose group, compared with $r = 0.041$ ($P = 0.776$) in the 0.5 mCi/kg dose group.

Physician evaluation

The PGA results at each evaluation time are summarised in Table 3. In the interpretation of the PGA results, the limitation should be noted that the physicians were not blinded as to the dose the patients had received. The data demonstrate an increase during the first 4 weeks in the percentage of patients who improved and a corresponding decrease in the percentage whose condition worsened, in both dose groups. The physicians judged that approximately half of the patients in each group were treatment responders at week 2, i.e., the patients were rated 'better', 'much better', or 'completely better'. At week 4, 55% of the patients in the 0.5 mCi/kg group and 70% of those in the 1.0 mCi/kg group had one of those ratings. Among the responders, 6% in the 0.5 mCi/kg group and 15% in the 1.0 mCi/kg group were either much better or completely better at week 2. At week 4, 22% and 33% of the patients, respectively, were either much better or completely better.

At all time points after week 4, the percentage of responders was larger for the 1.0 mCi/kg group than for the 0.5 mCi/kg group. At week 16, 39% of the total number of patients randomised to receive the higher dose were considered still to be experiencing some degree of pain relief, compared with 31% of those who received the lower dose. Likewise, at week 16 those rated either much better or completely better comprised 24% of the high-dose group compared to 14% of those randomised to receive the lower dose.

Factors affecting response to ^{153}Sm-EDTMP treatment

We examined factors that might have differed in treatment responders and non-responders, as measured by the PGA. There were no consistent differences between responders and non-responders in either dose group with respect to age, sex, baseline performance status on the Karnofsky scale, level of pain at baseline (baseline AUPC) or opiate analgesic use at baseline. The median duration of disease was longer among responders (64.3 months) than among non-responders (30.1 months) in the 1.0 mCi/kg group, but this difference was similar to that between groups at baseline.

The only apparent difference between the dose groups in the characteristics of responders and non-responders related to primary disease. In the 0.5 mCi/kg group, 6 of 15 patients (40%) with breast cancer were responders, compared with 16 of 20 breast cancer patients (80%) in the 1.0 mCi/kg group. This difference was further substantiated by comparing the changes from baseline in AUPC at week 4 for all patients, all males, males with prostate cancer, all females and females with breast cancer. As shown in Table 4, the decrease from baseline was larger with 1.0 mCi/kg than with 0.5 mCi/kg for each of these subgroups. The difference between doses was greater for females, and particularly for females with breast cancer, than for males and males with prostate cancer.

Safety

Myelotoxicity is the major safety concern associated with the systemic administration of radionuclides to patients with bone metastases. In this study, a decrease in haematological parameters was the only toxicity noted. Table 5 displays the mean nadir values for platelets and WBCs, the change from baseline and the median time to nadir (TTN) for 107 patients who had haematology data available until at least week 4 after dose administration. The latter was considered the minimum amount of time required to assess the haematological effects of treatment.

The mean nadirs were lower and the changes from baseline were greater for the 1.0 mCi/kg group than for the 0.5 mCi/kg group for both platelets and WBCs. The median TTN was 3 or 4 weeks for each parameter in both dose groups. Platelet and WBC counts recovered by week 8 as shown in Figure 2.

Examination of these data for male and female subjects (data not shown) revealed similar changes from baseline in both subgroups. The baseline values were generally lower in female patients, reflecting the greater likelihood that they had previously received marrow-suppressive chemotherapy. The mean nadir values for WBCs and platelets for all patients and for male and female patients in both dose groups were above the levels that would be associated with infectious or haemorrhagic complications.

Table 5. Platelet and WBC nadirs

	0.5 mCi/kg ($n = 50$)	1.0 mCi/kg ($n = 57$)
Platelets		
Mean (SE) nadir (/μL)	154000 (12000)	119000 (9000)
Mean % of baseline	56%	43%
Median TTN (wk)	4	4
WBCs		
Mean (SE) nadir (/μL)	4400 (212)	3600 (172)
Mean % of baseline	60%	49%
Median TTN (wk)	4	3

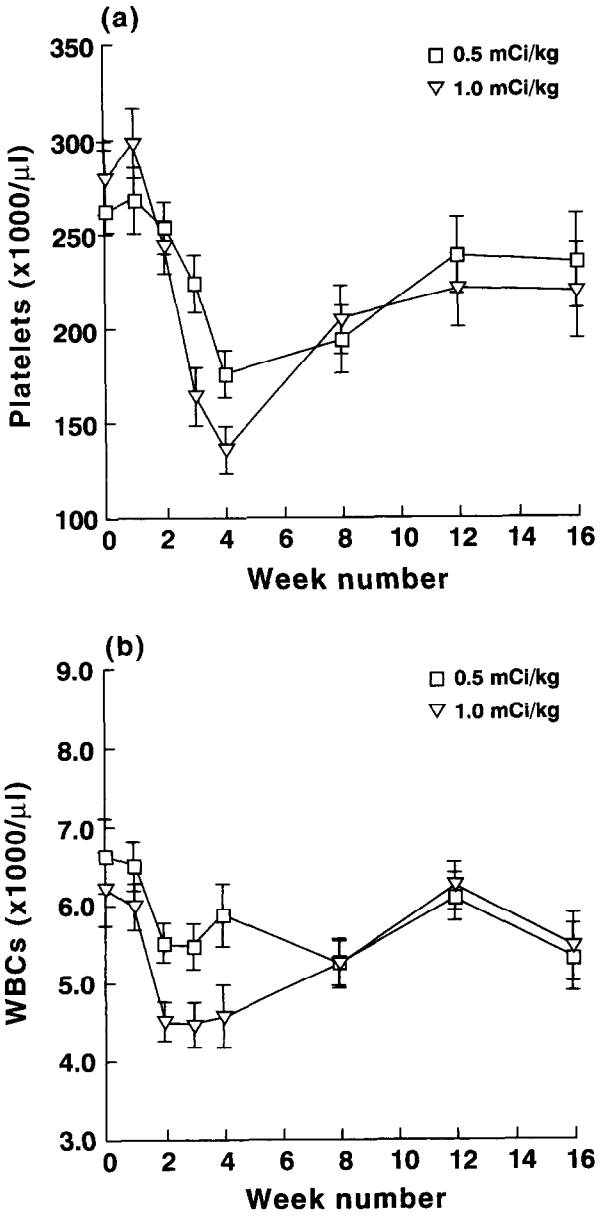

Figure 2. Mean (SE) counts for platelets (a) and WBCs (b) over time for patients in the 0.5 mCi/kg and 1.0 mCi/Kg groups.

The degree of haematological toxicity experienced by individual patients was determined by assigning each patient a toxicity grade, defined using the National Cancer Institute Common Toxicity Criteria and based on each patient's lowest WBC and platelet count (Table 6). The majority of the patients in each dose group had Grade 2 or lower WBC and platelet toxicity, i.e., their lowest values were 2000/μL or more for WBCs and 50000/μL or more for platelets. In spite of their generally lower baseline levels, the percentage of patients with higher grades of toxicity was lower among female patients than among male patients.

Three patients in the lower dose group and 1 in the higher dose group developed Grade 3 WBC toxicity only after receiving external radiation therapy subsequent to receiving the study drug. Three patients (6%) in the 0.5 mCi/kg group and 2 patients (4%) in the 1.0 mCi/kg group developed Grade 4 platelet toxicity (<25000/μL). Three of these 5 patients received external radiation therapy after receiving the study drug, the fourth patient had a low baseline platelet count (31000/μL) and the fifth patient received chemotherapy after receiving the study agent.

Table 6. Platelet and WBC toxicity grades

	0.5 mCi/kg (N = 50)	1.0 mCi/kg (N = 57)
	N (%)	N (%)
Platelets		
Toxicity grade		
0–2	44 (88%)	49 (86%)
3	3 (6%)	6 (11%)
4	3 (6%)	2 (4%)
WBCs		
Toxicity grade		
0–2	46 (92%)	52 (91%)
3	4 (8%)	5 (9%)
4	0	0

Transient pain flares occurred in 6 patients (11%) in the 0.5 mCi/kg group and five patients (8%) in the 1.0 mCi/kg group. Other adverse events that occurred during the study were attributable to the patients' ages or underlying conditions. Spinal cord compressions secondary to skeletal metastasis occurred in 4 (7%) and 2 (3%) patients, respectively, while pathological fractures occurred in 3 patients (5%) in each group. Infections occurred in more patients who received 0.5 mCi/kg (9; 16%) than 1.0 mCi/kg (4; 7%). Only one of the infections occurred in a setting of leucopenia, that in a patient who received 0.5 mCi/kg and then received 3000 rad of external radiation over a 3-week period beginning 1 month later. His WBC count decreased to 1600/μL and he developed a mild urinary tract infection. The only haemorrhagic adverse event that occurred in a setting of thrombocytopenia was in a patient who entered the study with a platelet count of 149000/μL which fell to 41000/μL 4 weeks after receiving a 1.0 mCi/kg dose. During the next 3 weeks, she received 2600 rad external radiation in 13 fractions to her left femur and right humerus to stabilise impending pathological fractures. Subsequently, her platelet counts decreased to 18000/μL and she experienced 2 episodes of moderate to severe gingival bleeding. Her platelet counts recovered thereafter and she completed the study without further signs of toxicity. ^{153}Sm-EDTMP had no effects on non-haematological laboratory tests or vital signs.

Twenty patients—10 in each dose group—died during the 16-week study period or shortly thereafter. This rate of death was not unexpected in a population of patients with advanced metastatic cancer. Eight deaths were related to progressive malignancy with metastasis, 3 were due to cardiovascular causes, 2 were due to progressive disease and disseminated intravascular coagulation, 1 each was due to suicide and aspiration of stomach contents and 4 were due to unknown causes. The other death was due to cerebrovascular accident (CVA) in a patient with rapidly progressive metastatic prostate carcinoma. This patient's platelet count was 141000/μL at baseline, fell to 91000/μL 1 week after receiving 1.0 mCi/kg ^{153}Sm-EDTMP and recovered to 157000/μL 2 weeks later. During the ensuing 8 weeks his platelets count declined gradually to 66000/μL while his prostate-specific antigen increased dramatically from 2870 ng/mL to 10900 ng/mL. Thirteen weeks after receiving the

study drug this patient suffered a mild CVA from which he recovered and 4 days later a second CVA from which he expired.

Overall, there was no apparent difference in survival between the 0.5 and 1.0 mCi/kg groups. Because the majority of the patients in this study had either prostate cancer or breast cancer, survival for patients with these primary tumour types was plotted separately. The results are shown in Figure 3.

There was no apparent difference between the dose groups in the survival of patients who had prostate cancer. In contrast, the survival of breast cancer patients who had received 1.0 mCi/kg of ^{153}Sm-EDTMP was longer than that of breast cancer patients who had received 0.5 mCi/kg.

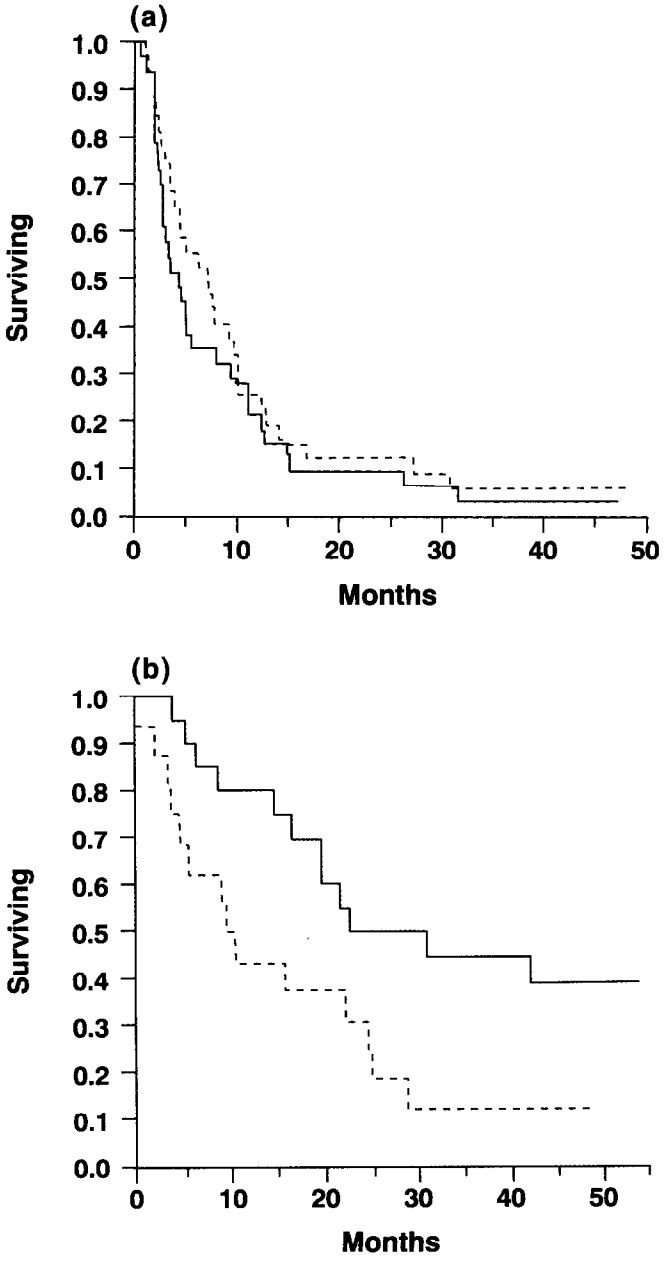

Figure 3. Survival curves for patients with prostate cancer (a) and patients with breast cancer (b). Solid line = 1.0 mCi/kg, broken line = 0.5 mCi/kg.

Excretion of ^{153}Sm-EDTMP

Urinary excretion data were obtained for 52 patients in each dose group. The mean (SE) percentage of the injected dose excreted in the urine during the first 6 h was 33.2% ± 2.33% in the 0.5 mCi/kg group and 35.5% ± 2.37% in the 1.0 mCi/kg group. Thus, dose had no effect on the per cent of ^{153}Sm-EDTMP excreted in the urine.

DISCUSSION

The results of this dose-controlled study revealed that single doses of either 0.5 or 1.0 mCi/kg of ^{153}Sm-EDTMP were effective in alleviating the pain of bone metastases in the majority of patients. Based on the PGA, 55% of those who received 0.5 mCi/kg and 70% of those who received 1.0 mCi/kg obtained pain relief during the first 4 weeks after study drug administration. At the same time, 67% of the patients in the lower dose group and 70% of those in the higher dose group considered their pain to have been lessened by ^{153}Sm-EDTMP. This improvement was not related to concurrent increases in the amount of opiate analgesics the patients were using.

At week 4, the primary endpoint for this study, there was a significant reduction in AUPC for patients who received the 1.0 mCi/kg dose of ^{153}Sm-EDTMP compared to those who received the 0.5 mCi/kg dose. Statistically significant changes from baseline were also associated with the higher dose but not the lower dose for, daytime discomfort and improvement in sleep. The onset of pain relief occurred during the first week after treatment for the majority of responders in the 1.0 mCi/kg group in both patient and physician based assessments.

Myelotoxicity was the only important adverse effect of ^{153}Sm-EDTMP treatment. Values for platelets and WBCs reached nadir levels at 3 or 4 weeks with both doses and recovered by 8 weeks after treatment. The nadirs attained were dose related, but with neither dose did the values reach a level that would be associated with infectious or haemorrhagic complications. This was further substantiated by the fact that there was only one mild infection (urinary tract) associated with leucopenia and one haemorrhagic episode (gingival bleeding) associated with thrombocytopenia. The patients who exhibited the greatest marrow toxicity were those who received external radiation therapy or chemotherapy within several weeks subsequent to receiving the study drug and those who had marrow involvement with disease.

Women with breast cancer generally receive more marrow-suppressive therapy during the course of their illness than do patients with other types of cancer that metastasise to bone. Because of this, we examined efficacy and safety for subgroups of patients based on sex and primary cancer. The difference between dose groups in changes in AUPC at 4 weeks was greater for female patients and particularly those with breast cancer, then for all patients, all male patients and men with prostate cancer. This suggests that the 1.0 mCi/kg dose would be expected to work well in this group of highly pretreated patients. In addition, myelotoxicity was no greater in the female patients than in the male patients, despite the fact that the female patients tended to enter the study with lower WBC and platelet counts because of their prior treatment. Long-term follow-up revealed that the group of patients with breast cancer who

had received the higher dose had longer survival than the group who had received the lower dose, however, although patients were randomly assigned to the dose groups no attempt was made to stratify the groups for primary tumour site or risk factors which could impact survival.

The amount of ^{153}Sm-EDTMP excreted in the urine was nearly identical in the two dose groups. Earlier studies had shown that excretion of ^{153}Sm-EDTMP is complete by 4–6 h after dose administration and that the amount of drug retained is related to the extent of metastases, not the dose [9, 15].

These findings suggest that the 1.0 mCi/kg dose of ^{153}Sm-EDTMP is safe and effective for the treatment of painful bone metastases. The physical half-life of ^{153}Sm (1.9 days) offers the benefit of delivering its dose of radiation in a relatively short period of time. This is advantageous because high initial dose rates of linear energy transfer radiation (such as that produced by beta particles) result in greater biological effect than equivalent total doses delivered at lower initial dose rates [19]. Therefore, the onset of pain relief is rapid and the duration of haematological toxicity is limited with ^{153}Sm-EDTMP. From a practical standpoint, the short half-life reduces problems associated with patient accommodation, potential radioactive contamination and waste handling and storage.

Unlike ^{89}Sr and ^{32}P, ^{153}Sm possesses a gamma emission of appropriate energy for scintigraphic imaging, thus allowing the physician to follow the fate of the radionuclide and to estimate dosimetry in individual patients. However, the gamma emission is low enough in abundance to present no exposure hazard when administered in therapeutic levels. Due to this low rate of exposure and the rapid clearance and excretion of ^{153}Sm-EDTMP, patients may be treated on an outpatient basis.

The well-defined toxicity of ^{153}Sm-EDTMP treatment and its excellent efficacy may make this radionuclide appropriate for use in earlier stages of treatment of metastases. The potential application warrants investigation in double-blind, placebo-controlled clinical trials.

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Acknowledgements—Supported by The Dow Chemical Company, Midland, Michigan, U.S.A. and CYTOGEN Corporation, Princeton, New Jersey, U.S.A.