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A Phase II Study of Treatment of Painful Multifocal Skeletal Metastases with Single and Repeated Dose Samarium-153 Ethylenediaminetetramethylene Phosphonate

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A phase II study of ^{153}Sm ethylenediaminetetramethylene phosphonate (^{153}Sm-EDTMP) palliative treatment was conducted on 23 patients with painful disseminated skeletal metastases. The administered activity of ^{153}Sm-EDTMP was determined by prospective dosimetry and the radiation absorbed dose to bone marrow was fixed at 2 Gy. Symptomatic relief of bone pain was experienced by 14 of 23 evaluable patients (61%) with a median duration of 8 weeks (range 0–40). Toxicity was limited to myelosuppression with median nadir counts of leucocytes 3.3 × 10^9/l (range 1.0–7.5) and platelets 133 × 10^9/l (range 24–176) occurring at 2 weeks and 4 weeks, respectively. Retreatment with ^{153}Sm-EDTMP was studied in 15 patients, including in 4 of the 23 patients treated with a single dose. The retreatment median radiation absorbed dose to red marrow was 1.9 Gy given at a median of 9 weeks (range 6–38) after initial treatment. Good control of pain was obtained in 13 of these patients (87%). Both the median duration of pain control (24 weeks) and survival (9 months) in the retreated group were substantially greater than for patients treated with a single dose, where duration was 8 weeks and survival 4 months. Additional toxicity in the retreated patients was confined to anaemia which required blood transfusion in 9 of the 15 patients (60%).
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INTRODUCTION

PATIENTS WITH advanced malignancy, particularly of the breast and prostate, often experience severe pain associated with multifocal bone metastases. Successful palliation may be achieved with conventional hormonal, chemotherapeutic and radiotherapeutic treatments [1], but often when tumour progression occurs there can be recurrence of bone pain. External beam radiotherapy has been the primary treatment modality for these patients, but application is limited by the widespread nature of the skeletal involvement.

However, recent application of internal radiotherapy using bone-seeking beta emitting radiopharmaceuticals has been reported to provide excellent palliation of painful skeletal metastases [2]. The favourable physical characteristics of samarium-153 (^{153}Sm), a beta emitter with a half-life of 46.27 hours and 103 keV gamma emission, permit optimum internal radiotherapy with prospective estimation of radiation dose to bone marrow in each patient [3].

In a phase I study of ^{153}-Sm-ethylenediamenetetramethylene phosphonate (^{153}Sm-EDTMP) we achieved pain control in 65% of patients with bone metastases from various tumours [4]. These results have subsequently been confirmed by other workers [5].

In the phase II study reported here we have sought to demonstrate that ^{153}Sm-EDTMP can be administered in a predetermined dose with predictable and manageable toxicity. Each patient treated for disseminated skeletal metastases received a radiation absorbed dose to bone marrow of 2 Gy, determined on an individual prospective basis according to the 6 hour urinary clearance of a tracer dose of ^{153}Sm-EDTMP. In addition patients from a similar group were retreated with the intent of prolonging the duration of control of pain.

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PATIENTS AND METHODS

Patient eligibility

The 34 patients studied had a variety of histologically confirmed malignancies, with multifocal bone metastases (Table 1). Each patient had normal haematological parameters, leucocyte count greater than 3.5 × 10^9/l and platelets greater than 100 × 10^9/l; however, anaemia was not an exclusion criterion for entry to the study. All patients had received maximum

Table 1. Patients' characteristics

	^{153}Sm-EDTMP			
	Single dose		Retreatment	
Patients	23	(100)	15	(100)
Median age (range)	72	(48–85)	70	(35–80)
Sex				
Male	13	(56)	10	(67)
Female	10	(44)	5	(33)
Performance status (ECOG)				
1	4	(17)	0	(0)
2	8	(35)	9	(60)
3	10	(44)	5	(33)
4	1	(4)	1	(7)
Tumour type				
Breast	9	(39)	5	(33)
Prostate	11	(48)	8	(54)
Other	3	(13)	2	(13)
Prior therapy				
Hormonal	20	(87)	14	(93)
Chemotherapy	10	(44)	7	(47)
Radiotherapy	15	(65)	11	(73)
None	3	(13)	1	(7)

No. (%).

conventional therapy appropriate for their tumour type, but any prior therapy was completed 4 weeks before admission to this study. No patient had received prior hemibody radiotherapy. All patients required regular chronic narcotic analgesia for relief of bone pain, and disseminated bone metastases were demonstrated on technetium-99m MDP bone scans, and conventional radiographs. Age and ECOG performance status were not exclusion criteria. Informed consent was obtained in accordance with National Health and Medical Research Council and Fremantle Hospital guidelines.

Treatment

^{153}Sm was supplied by the Australian Nuclear Science and Technology Organisation (ANSTO) and used to prepare ^{153}Sm-EDTMP from a freeze-dried kit formulation. Radiochemical purity, labelling efficiency, sterility and apyrogenicity were assured by standard methods [3].

Prospective beta radiation dosimetry was determined by gamma counting of a single 5 ml urine sample from the total 6 hour urinary excretion of an intravenous pretreatment tracer dose of 740 MBq ^{153}Sm-EDTMP as previously described [3]. The patient then received an additional dose of ^{153}Sm-EDTMP to achieve a total red marrow radiation absorbed dose of 2 Gy.

Another group of 11 patients received a second dose of ^{153}Sm-EDTMP at variable time intervals determined by recovery of blood counts and physician judgement. In addition 4 patients who failed to respond to a single dose, in the initial group of 23 patients, underwent retreatment. All patients were followed at intervals of 2 weeks for the first 8 weeks and then monthly. Pain response was scored on a visual-analogue pain scale (0–10); the quantity and type of analgesia (0–10), the number of pain sites (0–6) and the ECOG performance status (0–4) out of the possible total pain score of 30 points. Statistical analysis was performed using a simple two-tailed Student's *t* test.

RESULTS

Pain relief was assessed at fortnightly intervals after a single 2 Gy marrow radiation dose of ^{153}Sm-EDTMP in 23 evaluable patients (Table 2). 14 patients (61%) achieved relief of pain that in 1 patient was complete. There were 6 patients (26%) who experienced no pain relief. Pain relief was evident within 2 weeks of treatment and the median duration of benefit was 8 weeks (range 4–40 weeks). The median survival for the entire group was 4 months.

An additional group of 15 patients received a repeat dose of ^{153}Sm-EDTMP. The timing of the second dose was determined by factors such as blood counts, response to the initial therapy and physician judgement. The median time to repeat administration was 9 weeks. 1 patient was retreated at 38 weeks, another at 14 weeks and the remainder between 6 and 10 weeks after the initial dose. The median bone marrow radiation absorbed dose from the second treatment was 1.9 Gy (range 0.75–3.50 Gy). Of the 15 retreated patients, 4 were from the original single treatment arm of 23 patients. All these 4 patients had failed to respond to a single dose but 2 experienced pain relief on retreatment. 13 of the 15 retreated patients (87%) achieved pain control, which was complete in 6 patients (Table 2). The median duration of pain control was 24 weeks in the retreatment series, and survival was 9 months. Both median duration of pain relief and survival of patients in the retreated group were significantly better than that for patients treated with a single administration of ^{153}Sm-EDTMP.

Table 2. Response to bone pain

^{153}Sm-EDTMP Dose	Degree of pain relief*			Duration† (week)	Survival† (month)
	Excellent	Good	Poor		
Single 2 Gy	1	13	9	8 (4–40)	4 (1–18)
Retreatment 1.90 Gy	6	7	2	24 (4–52)	9 (2–17)
P	<0.05		<0.05	<0.05	<0.05

*Pain relief: excellent = complete disappearance of pain and no requirement for analgesia; good = greater than 50% improvement in pain score; poor = less than 50% improvement in pain score.
†Median (range).

Table 3. Haematological toxicity of ^{153}Sm-EDTMP

Parameter	Single dose 2 Gy (*n* = 23)*	Repeat dose 1.9 Gy (*n* = 15)*	*P*
Platelet count (×10^9/l)	133 (24–200)	150 (6–500)	NS
Leucocyte count (×10^9/l)	3.3 (1.0–7.0)	4.9 (1.7–8.6)	NS
Haemoglobin <9 g/l no. of patients (%)	0 (0)	9 (60)	<0.05

*Median (range).

Evaluation of anti-tumour effect of ^{153}Sm-EDTMP, by analysis of serial radiographs and ^{99m}Tc-MDP bone scans, and by measurement of serum alkaline phosphatase and tumour markers such as prostate specific antigen, showed no correlation with clinical response to pain. Although occasional recalcification of lytic metastases on serial radiographs and improvement of bone scans was seen, this was not a consistent finding.

Toxicity

The only observed toxicity after single dose treatment with ^{153}Sm-EDTMP was reversible myelosuppression (Table 3). Mild granulocytopenia was observed in all patients with the median nadir white cell count of 3.3 × 10^9/l occurring approximately 2 weeks following ^{153}Sm-EDTMP administration. Recovery of leucocyte count was complete, usually within 4 weeks from the day of treatment. Delayed thrombocytopenia was the major toxicity with the median nadir platelet count of 133 × 10^9/l occurring approximately 4 weeks post-treatment. 3 patients (13%) developed platelet counts less than 50 × 10^9/l; however, there were no bleeding episodes or requirement for platelet transfusions. Platelet recovery was slow and often incomplete, with 25% of patients failing to achieve 65% of their pretreatment platelet count within 6 weeks of treatment.

In the 15 patients retreated with ^{153}Sm-EDTMP, similar myelosuppressive effects were observed. Transient granulocytopenia and delayed thrombocytopenia occurred at 2 and 4 weeks, respectively. However, in this group of 15 retreated patients therapy-related anaemia (haemoglobin less than 10g/l) was observed in 9 patients (60%). In 4 patients the anaemia occurred before administration of the second dose of ^{153}Sm-EDTMP and in the other 5 patients developed within 6 weeks of retreatment. More than one blood transfusion was required in only 3 of these 9 patients with treatment-related anaemia.

DISCUSSION

We have previously demonstrated in a phase I study of ^{153}Sm-EDTMP therapy that red marrow radiation absorbed doses of

up to 2 Gy caused only mild reversible toxicity which was limited to transient myelosuppression [4]. This clinical study has shown that a fixed dose of 2 Gy was associated with relief of pain in 14 of 23 patients (61%) with disseminated skeletal metastases from a variety of tumour types. Whilst amelioration of pain was consistently achieved within 2 weeks of treatment with ^{153}Sm-EDTMP, the duration of response was quite variable and ranged from 4 to 40 weeks with a median of 8 weeks.

The short duration of pain relief prompted the use of repeated doses of ^{153}Sm-EDTMP in an attempt to improve both the number of responders and the durability of response. In 15 patients with pain from advanced skeletal metastases a repeat treatment was administered upon recovery of haematological parameters and generally not before 6 weeks had elapsed since the initial therapy. This small, select group of patients, despite comparability of poor prognostic features with the other patients in the clinical study, achieved a significantly better outcome. The median duration of pain control in the retreatment group was 24 weeks compared with 8 weeks in those patients treated with a single dose of ^{153}Sm-EDTMP. There was also an increase in survival time from a median of 4 months to 9 months.

The mechanisms of relief of pain of skeletal metastasis after radiation therapy with bone-seeking, beta-emitting radionuclides remain to be determined. Objective evidence of tumour response such as recalcification of lytic lesions seen on radiographs has not been consistently seen [4] and local effects of beta radiation on bone metabolism and osteoblastic activity are conjectural. However, it is possible that pain relief may be attributed to irradiation of the interface of invading tumour with reactive bone [6], which may occur without substantially affecting tumour mass.

Strontium-89 was the first radionuclide applied to palliative treatment of painful skeletal metastases [7] but unpredictable dosimetry and the danger of myelotoxicity has militated against routine clinical use. Beta-emitting radionuclides which also have gamma emission, such as ^{153}Sm and rhenium-186, have recently been introduced in the form of bone-seeking chelates to permit definition of the variable and unpredictable skeletal uptake by quantitative gamma counting [3] [8]. We have developed a simple, accurate method [3] for prospective calculation of radiation absorbed dose to red marrow for each patient based on gamma counting of a single urine sample which represents the excretion of a tracer dose of ^{153}Sm-EDTMP. Accurate individualised dosimetry is particularly important to avoid toxic myelosuppression, since many patients with advanced bone metastases have low haemopoietic reserves in marrow already compromised by tumour infiltration, prior chemotherapy and external irradiation.

In patients with baseline haematological parameters within the normal range, we have previously shown that a single radiation absorbed dose to red marrow of 2 Gy is a safe initial exposure [4]. Transient neutropenia is mild, nadir counts occurring within 2 weeks of administration of ^{153}Sm-EDTMP and recovery by 4 weeks. Delayed thrombocytopenia occurs in most patients around 4 weeks and recovery may be delayed up to 8 weeks. In an attempt to maximise antitumour activity Eary *et al.* [5] performed a simple dose-escalating study and found a maximum tolerated administered activity of 92.5 MBq (2.5 mCi) ^{153}Sm-EDTMP per kg. However myelotoxicity was unpredictable; 2 patients failed to recover bone marrow function and several underwent multiple platelet tranfusions. Our phase 1 pharmacokinetic study [4] demonstrated a marked variability in skeletal uptake of ^{153}Sm-EDTMP from patient to patient which emphasised the requirement for individual dosimetry based on measurement of total radiation exposure of red marrow for accurate prediction of myelotoxicity. Myelosuppression invariably occurred at marrow doses greater than 2.5 Gy which were delivered by administered activities of between 22 and 36 MBq/kg. We attempted to improve overall response and duration of pain relief by repeat treatment rather than by escalating a single dose of ^{153}Sm-EDTMP. Retreatment of 15 patients at least 6 weeks after initial therapy was, however, accompanied by further myelosuppression. Chronic anaemia was commonly seen, occurring in 60% of patients, and often required recurrent blood transfusion. Both leucocytes and platelet counts recovered spontaneously. Thus our small study would indicate that retreatment with ^{153}Sm-EDTMP is safe provided that the radiation dose to red marrow is limited to between 1.5 and 2 Gy and that retreatment is deferred until full haematological recovery from the initial treatment has occurred.

Despite the small number of patients studied, the increase in the duration of pain response and in the survival of retreated patients when compared with that observed in the single dose ^{153}Sm-EDTMP treated group is statistically significant. The explanation of this improvement in pain response and survival after additional follow-up beta-radiation therapy is speculative, but may be a consequence in some patients of direct antitumour effects of ^{153}Sm. However, the achievement of better control of pain with consequent reduction in requirement of narcotic analgesia, and improvement in mobility, strength and appetite undoubtedly had a major positive effect on outcome.

Definition of the place of ^{153}Sm-EDTMP radiotherapy in oncology practice awaits evaluation in large scale randomised clinicial trials comparing pain response with that obtained by the best available conventional palliative treatment for disseminated skeletal metastases. However, our early phase II study has demonstrated that ^{153}Sm-EDTMP therapy can be administered in a predetermined dose with predictable and manageable toxicity, and that repeat treatment appears to be beneficial with respect to both duration of response and survival.

1. Henderson IC, Hayes DF, Come S, *et al.* New agents and new medical treatments for advanced breast cancer. *Semin Oncol* 1987, **1**, 34–64.
2. Robinson RG. Systemic radioisotopic therapy of primary and metastatic bone cancer. *J Nucl Med* 1990, **31**, 1326–1327.
3. Turner JH, Martindale AA, Sorby P, *et al.* Samarium-153 EDTMP therapy of disseminated skeletal metastasis. *Eur J Nucl Med* 1989, **15**, 784–795.
4. Turner JH, Claringbold PG, Hetherington EL, Sorby P, Martindale AA. A phase I study of samarium-153 ethylenediametetramethylene phosphonate therapy for disseminated skeletal metastases. *J Clin Oncol* 1989, **7**, 1926–1931.
5. Eary JF, Collins C, Nemiroff C, *et al.* Single dose Samarium-153 EDTMP treatment in prostate carcinoma. *J Nucl Med* (in press).
6. 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.
7. Pecher C. Biological investigations with radioactive calcium and strontium: preliminary report on the use of radioactive strontium in treatment of metastatic bone cancer. *University of California Publications in Pharmacology* 1942, **11**, 117–149.
8. Maxon HR, Schroder LE, Thomas SR, *et al.* Re-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.

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