

*Efficacy and Toxicity of  
<sup>153</sup>Samarium Radiopharmaceuticals  
in the Palliative Treatment of  
Painful Skeletal Metastases  
in Thailand\**

.....

**Pusuwan P<sup>1</sup>, Chaudakshetrin P<sup>1</sup>, Virawat N<sup>2</sup>, Suntarapa S<sup>3</sup>, Pattaranutaporn P<sup>4</sup>, Chansilpa Y<sup>4</sup>,  
Srimuninnimit V<sup>5</sup>, Chakrapee-sirisuk S<sup>5</sup>, Chaudakshetrin P<sup>6</sup>, Buranapong P<sup>1</sup>, Chanachai R<sup>1</sup>,  
Pleehachinda R<sup>1</sup> and Na Songkhla S<sup>1</sup>**

*1. Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University*

*2. Isotope Production Division, Office of Atomic Energy for Peace*

*3. Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University*

*4. Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University*

*5. Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University*

*6. Department of Anaesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University*

**M**uch of the morbidity and mortality associated with cancer can be attributed to skeletal metastases which are the commonest cause of cancer pain and predispose to immobility, pathological fracture, bone marrow failure, neurological symptoms and hypercalcemia<sup>(1)</sup>. Any improvement in effective treatment for metastatic bone pain must represent a major advance in cancer management. At present, systemic radioisotopic therapy for patients with metastatic bone disease is used as palliative treatment. All patients have disseminated disease and are considered ultimately incurable. Even so, systemic bone seeking radioisotopes provide the opportunity for weeks, months, or years of improved quality of life for these patients<sup>(2)</sup>. Treatment is tumor specific, with relative sparing of the surrounding, healthy tissues. This should reduce toxicity, an important consideration in palliative care.

The success of treatment depends upon the choice of an appropriate radionuclide and carrier molecule to ensure that the radionuclide is delivered directly to the tumor target. Despite these theoretical advantages, the present use of therapeutic radionuclides is extremely limited. The cost of radionuclides remains a problem.

Although the effectiveness of strontium therapy has been demonstrated by a number of authors, it is unaffordable for us for routine treatment. At this time, <sup>153</sup>Sm can be supplied by the Office of Atomic Energy for Peace(OAEP) in Thailand and used to prepare <sup>153</sup>Sm EDTMP from a kit formulation<sup>(3)</sup>. By this condition, <sup>153</sup>Sm

---

\* IAEA Coordinated Research Programme E1.30.13

Presented at the First Research Coordination Meeting of the CRP on "Efficacy and toxicity of <sup>153</sup>samarium radiopharmaceuticals in the treatment of painful skeletal metastases" IAEA's Headquarters, Vienna, 17-19 November 1997.

EDTMP is initiate to be available in our country for the treatment of patients with painful bone metastases. The objective of our study is to determine the ability of a single intravenous dose of  $^{153}\text{Sm}$  EDTMP to alleviate the pain associated with metastatic bone disease and determine the occurrence of myelotoxicity with the treatment.

## MATERIALS AND METHODS

### *Patient Selection*

From April 15, 1996 to November 15, 1997 twenty-three patients had histologically proven primary cancer with painful bone metastases. The clinical features of the patients entered into the study were shown in Table 1. All patients required chronic analgesics for relief of bone pain. The number of metastatic bone lesions were determined by counting the abnormal skeletal foci characterized by increased radioactivity uptake of the  $^{99\text{m}}\text{Tc}$  MDP bone images.

The study was carried out with the approval of the Committee on Human Rights, Faculty of Medicine Siriraj Hospital, Mahidol University and written informed consent was obtained from each patient. Every patient received an instruction brochure.

A daily diary about pain intensity and analgesic usage was recorded by every patient. All eligible patients must have had histologic diagnosis of cancer, active uptake of  $^{99\text{m}}\text{Tc}$  MDP and osseous pain. Twenty patients had normal hematological parameters (leukocyte count  $> 5,000/\text{mm}^3$ , platelet count  $> 150,000/\text{mm}^3$ , absolute granulocyte count  $> 2,000/\text{mm}^3$ ) with the exception that the platelet count of patient no.3 was  $130,000/\text{mm}^3$ , patient no.6 was  $87,000/\text{mm}^3$  and patient no.13 was  $132,000/\text{mm}^3$ .

Thirteen patients were followed for 16 weeks following  $^{153}\text{Sm}$  EDTMP injection. Four patients died from disseminated diseases within 1, 3, 4, 7 weeks after the injection. One patient had to have chemotherapy at 4 weeks after injection due to intestinal metastasis. Four patients lost follow-up. One patient has been in the follow-up course.

### *Treatment*

$^{99\text{m}}\text{Tc}$  MDP bone scan was performed in each patient within 1 - 2 weeks before the  $^{153}\text{Sm}$  EDTMP injection. Randomized patients were divided into group I receiving  $0.5 \text{ mCi } ^{153}\text{Sm EDTMP/kg}$  ( $n = 12$ ) and group II receiving  $1.0 \text{ mCi } ^{153}\text{Sm EDTMP/kg}$  ( $n = 11$ ). Whole body images were acquired with selected spot images of the abnormal uptake regions. This was done to identify the metastatic sites in the patients and generate scintigraphic images of the bony lesion in order to be compared to the  $^{153}\text{Sm}$  EDTMP images.

After  $^{153}\text{Sm}$  EDTMP intravenous injection, whole body planar scintigraphic images with the same spot images as the previous  $^{99\text{m}}\text{Tc}$  MDP bone scan and 6-hr urinary excretion of the radiopharmaceutical were obtained. The images using the 103 keV gamma photon emission of  $^{153}\text{Sm}$  were started 3 hours following the injection of the  $^{153}\text{Sm}$  EDTMP using a large field-of-view (LFOV) scintillation camera equipped with a low-energy all purpose (LEAP) parallel hole collimator. The quantified indices from the static images included lesion to normal bone ratios, lesion to soft tissue ratios and normal bone to soft tissue ratios. Areas of abnormal radioactivity uptake were outlined and the average regional counts were used for calculation. Thirty-five lesions were studied in the 23 patients.

**Table 1** Clinical characteristics of treated patients and their responses to treatment

Patient no.	Age (years)	Sex	Primary tumor	Previous treatment of bone metastases	Dose of $^{153}\text{Sm}$ EDTMP (mCi/kg)	Pain Palliation			Duration (weeks)*
						Complete	Partial	No	
1	70	F	Ca breast	Irradiation, chemotherapy	0.5	✓			13.5
2	54	F	Ca breast	Irradiation, chemotherapy	1	✓			14
3	38	F	Ca breast	Irradiation, chemotherapy	1		✓		7
4	48	M	Ca lung	Irradiation, chemotherapy	0.5				dead
5	42	F	Ca breast	Irradiation, chemotherapy	1		✓		6
6	57	F	Ca common bile duct	Chemotherapy	0.5		✓		12
7	37	F	Ca cervix	-	1				lost follow-up
8	42	F	Ca breast	Chemotherapy	1	✓			15
9	52	F	Squamous cell Ca scalp	Chemotherapy	0.5		✓		6
10	80	M	Ca prostate	Hormone therapy	1	✓			8
11	77	M	Ca prostate	Hormone therapy	0.5	✓			15
12	50	F	Ca breast	Chemotherapy	0.5				lost follow-up
13	88	M	Ca prostate	Hormone therapy	1		✓		8
14	35	M	Ca penis	chemotherapy	1			✓	
15	67	F	Ca breast	chemotherapy	0.5	✓			11
16	70	M	Ca liver	Irradiation	0.5				lost follow-up
17	52	F	Ca breast	chemotherapy	0.5				unevaluable
18	60	M	Ca prostate	Hormone therapy	0.5			✓	lost follow-up
19	84	M	Ca prostate	Hormone therapy	1		✓		4
20	67	M	Ca prostate	Hormone therapy	1	✓			14
21	25	M	Ca nasopharynx	Irradiation, Chemotherapy	0.5		✓		4
22	87	M	Ca prostate	Hormone therapy	0.5	✓			13
23	40	F	Ca breast	Irradiation, Chemotherapy	1				On the process of follow-up

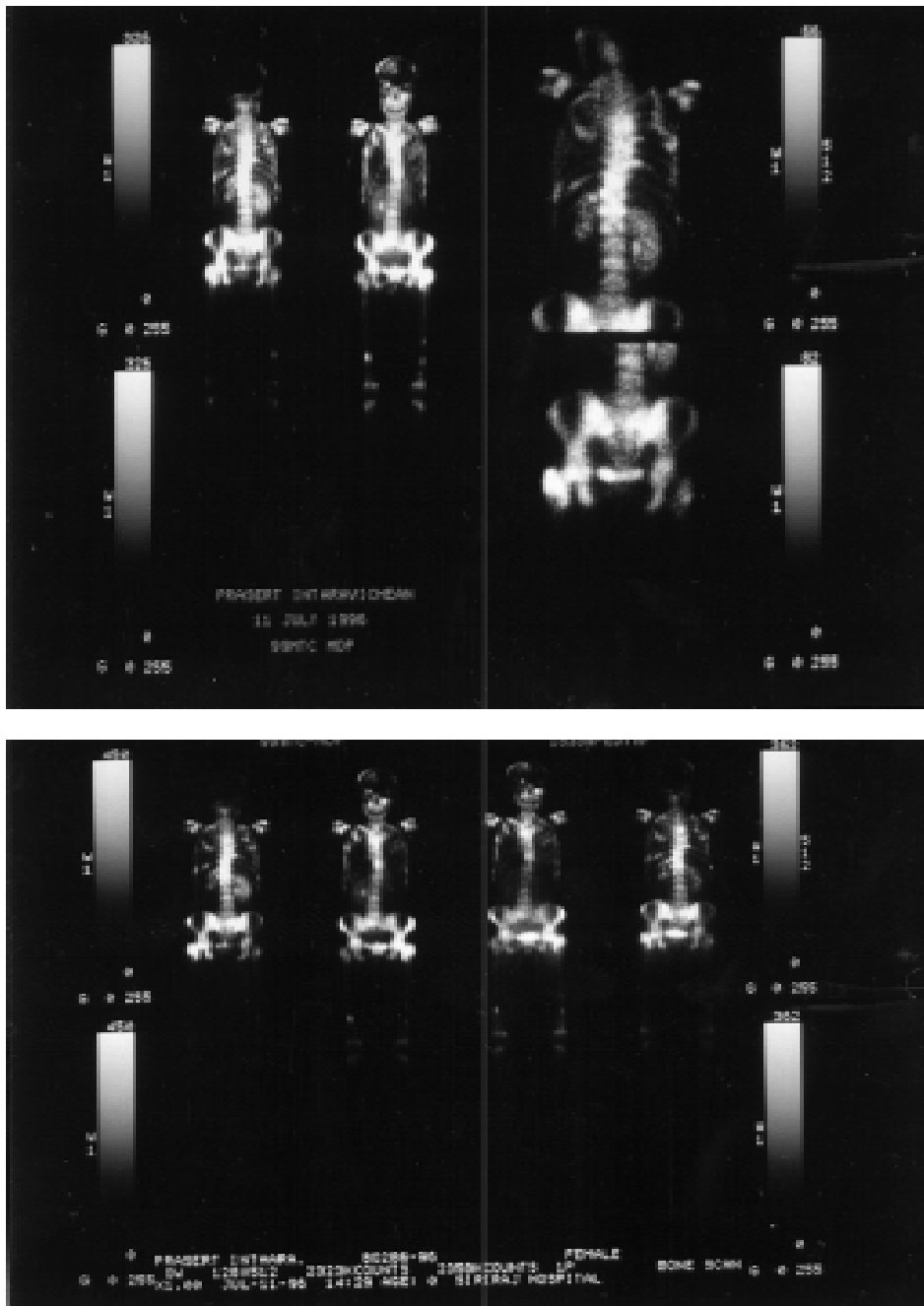
\*Total time of follow-up after  $^{153}\text{Sm}$  EDTMP was 16 weeks

Skeletal ratios of  $^{153}\text{Sm}$  EDTMP and  $^{99\text{m}}\text{Tc}$  MDP were analyzed to determine if a significant correlation existed between the lesion localization of the two agents. The same lesion in each patient served as control for the comparison.

## RESULTS

### *Skeletal uptake characteristics*

$^{153}\text{Sm}$  EDTMP doses were administered to 23 patients without problems. As was previously observed<sup>(4,5,6)</sup>, complete concordance between the two scintigrams in delineating the metastatic sites were demonstrated (Figure 1). The ratios of the lesion



**Fig. 1**  $^{99m}\text{Tc}$  MDP whole body imaging with spot image (above). Whole body images (below) compare visualization of bony metastases in the  $^{99m}\text{Tc}$  MDP baseline scan (left) and  $^{153}\text{Sm}$  EDTMP therapy dose (right).

quantification were tabulated in Table 2. Lesion to normal bone ratios for  $^{153}\text{Sm}$  EDTMP and  $^{99\text{m}}\text{Tc}$  MDP were  $7.1 \pm 4.6$  and  $9.7 \pm 8.9$ , respectively. Lesion to soft tissue ratios were  $15.8 \pm 10.2$  for  $^{153}\text{Sm}$ -EDTMP and  $18.8 \pm 12.7$  for  $^{99\text{m}}\text{Tc}$ -MDP. Normal bone to soft tissue ratios were  $2.9 \pm 1.6$  for  $^{153}\text{Sm}$ -EDTMP and  $2.9 \pm 1.4$  for  $^{99\text{m}}\text{Tc}$ -MDP. Significant correlation between the accumulation of these two agents in bone cancer lesions were observed ( $p < 0.001$ ). The data were similar to those of previous studies which indicated that  $^{153}\text{Sm}$  EDTMP was as sensitive as  $^{99\text{m}}\text{Tc}$  MDP for identifying bony lesions and the soft tissue localization was minimal<sup>(7)</sup>.

The complex cleared through the kidneys and the amount excreted into the urine at 6 hr was  $41.4 \pm 19.2$  % of the administered dose in group I and  $44 \pm 14.9$  % in group II.

The dependence of the  $^{153}\text{Sm}$  EDTMP on the administered activity was evaluated. The skeletal uptake of the group I and group II patients was  $58.6 \pm 19.2$  % and  $56 \pm 14.9$  % of the administered dose, respectively. Since the difference between these values was small, the percent administered dose localized in the skeleton was considered independent to the activity injected. This was similar to the results reported by Bayouth et al<sup>(8)</sup>.

### **Biological response characteristics**

The hematological toxicity for each patient was assessed from the decrease in platelet and white blood cell count observed in serial blood samples. Transient depression of both platelet and leukocyte counts was observed in 10 patients (4 cases in group I and 6 cases in group II). Transient depression of platelet count was shown in 3 patients (2 cases in group I and 1 case in group II) and one patient in group II showed only low leukocyte count (Table 3). The nadir of leukocyte count occurred in the 2nd to the 6th week and that for platelet was seen from the 2nd to the 8th week (Figure 2). No leukocyte count under normal limits was found in all patients but platelet count dropped below normal limits in 5 patients.

In the exceptional three cases whose the baseline platelet count was below  $150,000/\text{mm}^3$ , both the platelet and leukocyte counts decreased significantly. One of them got urinary tract infection and had to receive medical treatment to increase the number of both platelet and leukocyte.

### **Clinical response to $^{153}\text{Sm}$ EDTMP therapy**

Pain relief was assessed every 2 weeks after treatment for 16 weeks. Of the 16 evaluable patients, complete pain palliation was reported in 8 cases (5 cases in group

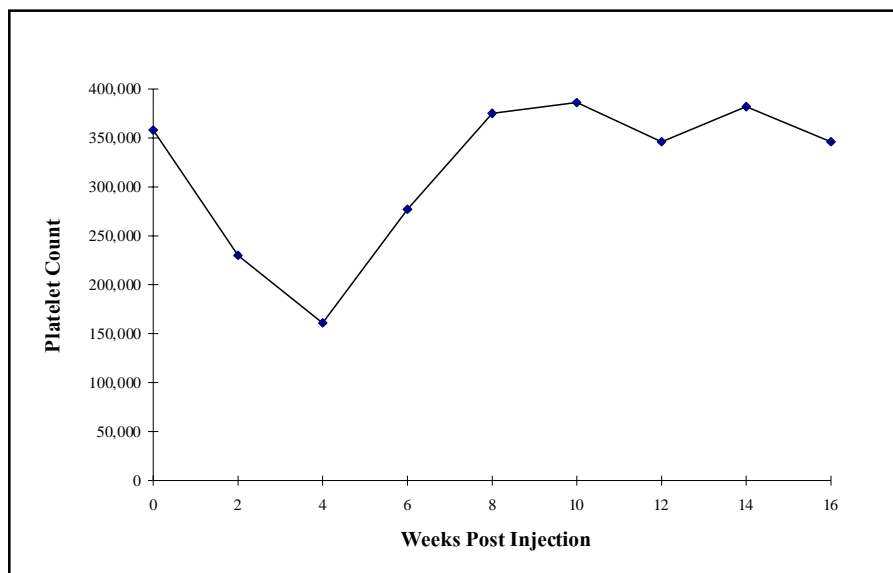
**Table 2** Correlation between skeletal localization of  $^{153}\text{Sm}$  EDTMP and  $^{99\text{m}}\text{Tc}$  MDP

Ratio	$^{153}\text{Sm}$ EDTMP	$^{99\text{m}}\text{Tc}$ MDP	Correlation coefficient (r)	P
Lesion to normal bone (n = 35)	$7.1 \pm 4.6$	$9.7 \pm 8.9$	0.86	<0.001
Lesion to soft tissue (n = 32)	$15.8 \pm 10.2$	$18.8 \pm 12.7$	0.86	<0.001
Normal bone to soft tissue (n = 27)	$2.9 \pm 1.6$	$2.9 \pm 1.4$	0.9	<0.001

All data is mean  $\pm$  1s.d.

**Table 3** Biological response characteristics

	$^{153}\text{Sm}$ EDTMP	
	Gr I	Gr II
Transient depression of plt & WBC	4	6
Transient depression of plt	2	1
Transient depression of WBC	-	1



**Fig. 2** Response of myelotoxicity from  $^{153}\text{Sm}$  EDTMP expressed as platelet counts in serial blood samples. This patient (no. 9) achieved platelet nadir at 4 weeks postinjection and recovered 6 weeks postinjection.

I and 3 cases in group II) and partial response was reported in 6 patients (2 cases in group I and 4 cases in group II). No response was found in one patient from each group (Table 4). Pain relief occurred within two weeks after administration of  $^{153}\text{Sm}$  EDTMP.

The duration of pain relief could not be completely concluded in this report because 1 patient had not yet completed her 16-week follow-up course. In 16 evaluable cases, duration of pain relief ranged from 4 - 14 weeks. Four patients died from disseminated disease after the treatment. Five

cases had short duration of pain palliation as shown in Table 1. Their symptoms recurred after 6 - 8 weeks of remission. Narcotics had to be administered by the Pain Clinic before the 16-week follow-up course could be finished.

## DISCUSSION

In the field of nuclear medicine, several beta-emitting radionuclides are being tested clinically. A number of reports have now appeared indicating that  $^{153}\text{Sm}$  EDTMP can be used successfully to palliate pain from bone metastases<sup>(4,5,6,7)</sup>.

**Table 4** Clinical response to  $^{153}\text{Sm}$  EDTMP therapy

	$^{153}\text{Sm}$ EDTMP	
	Gr I	Gr II
Complete response (n = 8)	5	3
Partial response (n = 6)	2	4
No response (n = 2)	1	1

In this study we found that the chelates cleared from the plasma through the kidneys into the urine. Urinary clearance was essentially completed within 6 hours and accounted for 17.3 % to 62.3 % of the administered dose. The remaining activity represented skeletal uptake was 37.7 % to 82.7 % of the administered dose. The biodistribution of  $^{153}\text{Sm}$  EDTMP and  $^{99\text{m}}\text{Tc}$  MDP were very similar in metastatic and normal bone and the activity deposited in the soft tissue was very little. High lesion to normal bone ratios of  $7.1 \pm 4.6$  and lesion to soft tissue ratios of  $15.8 \pm 10.2$  were demonstrated.

In both groups of patients with normal baseline hematological studies, transient depression of both platelet and leukocyte count was observed in 10 patients. Transient depression of platelet count was shown in 3 patients and one patient showed only low leukocyte count. Myelotoxicity was more evident and prolonged in the exceptional group with abnormal baseline hematological studies (patient no. 3, 6 and 12).

A single administration of  $^{153}\text{Sm}$  EDTMP was effective in palliating pain due to multiple bone metastases. In both groups of patients, 50 % experienced complete pain relief, 37.5 % experienced partial pain relief and 12.5 % experienced no pain relief. Improvement of pain relief occurred within 1 - 2 weeks and maximal pain control was reported by 2 - 5 weeks. The duration of pain relief ranged from 6 - 14 weeks. Recurrence of pain was noted in five cases after 6 - 8 weeks of remission. We believed that repeated  $^{153}\text{Sm}$  EDTMP treatment should be beneficial to these patients. Our studied group was small and more cases should be collected to clearly determine the safely effective dose of  $^{153}\text{Sm}$  EDTMP.

#### **Acknowledgement**

The support of the IAEA (CRP E1.30.13) and the radiopharmaceutical supported by the Office of Atomic Energy for Peace, Thailand are gratefully acknowledged. The authors wish to thank Mrs. Nucharee Putrasreni for preparing all illustrations.

## REFERENCES

1. Lewington VJ. Targeted radionuclide therapy for bone metastases. *Eur J Nucl Med* 1993;20:66-74.
2. Robinson RG, Preston DF, Spicer JA, et al. Radionuclide therapy of intractable bone pain emphasis on strontium-89. *Sem Nucl Med* 1992;22:28-32.
3. Kullaprawithaya U, Virawat N, Chingjit S, et al. Optimization of the production and quality control of samarium-153 and  $^{153}\text{Sm}$ -EDTMP. 32<sup>nd</sup> Annual Scientific Meeting of the Radiological Society of Thailand, Bangkok, 26-28 January 1995 pp 120.
4. Turner JH, Claringbold PG, Hetherington EJ, et al. A phase I study of samarium-153 ethylenediaminetetramethylene phosphonate therapy for disseminated skeletal metastases. *J Clin Oncol* 1989;7:1926-31.
5. Singh A, Holmes RA, Farhangi M, et al. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *J Nucl Med* 1989;30:1814-8.
6. Farhanghi M, Holmes RA, Volkert WA, et al. Samarium-153-EDTMP: pharmacokinetic, toxicity and pain response using an escalating dose schedule in treatment of metastatic bone cancer. *J Nucl Med* 1992;33:1451-8.
7. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *J Nucl Med* 1993;34:1031-6.
8. Bayouth JE, Macey DJ, Kasi LP, et al. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. *J Nucl Med* 1994;35:63-9.