

Original Article:**Role of samarium-153-ethylene diamine tetramethylene phosphonate radionuclide bone pain palliation in patients with metastatic bone disease**

Ravishwar Narayan,¹ Ranadheer Gupta Manthri,² Kannan Thiruvengadaswamy,³ Ayapati Tyagi,⁴ Pavan Gurraj Kale,⁵ Tekchand Kalawat²

Department of¹Nuclear Medicine, Mahavir Cancer Sansthan, Patna and Departments of²Nuclear Medicine, ³Medical Oncology, ⁴Urology, ⁵Radiodiagnosis, Sri Venkateswara Institute of Medical Sciences, Tirupati

ABSTRACT

Background: Bone pain is the most common symptom in advanced stages of malignancy and requires multidisciplinary approach for its treatment. Localized sites of involvement can be treated with surgery or external beam radiation, whereas radiopharmaceuticals, hormones, and chemotherapy are used to treat more diffuse bone involvement.

Methods: The present prospective study was undertaken to evaluate the efficacy of pain palliation achieved with samarium-153 (Sm-153) ethylene diamine tetra methylene phosphate (EDTMP) administration. During the period, June 2011 to June 2013, 30 patients with bone pain due to metastatic bone disease were treated with samarium-153 EDTMP. The patients were evaluated with visual analogue scale, Karnofsky performance score and analgesic score, before and after therapy, to assess extent of pain relief.

Results: Twenty out of 30 patients (67%) showed response to Sm-153 EDTMP therapy. In this group of patients, statistically significant decrease in pain intensity and drug intake was noted along with improvement of quality of life, which persisted till three months after therapy. Mild myelotoxicity was noted in most patients. Only two patients developed Grade 3 myelotoxicity.

Conclusions: Samarium-153 EDTMP is a safe, economical and well tolerated modality of treatment for patients with painful osteoblastic skeletal metastases and has a simple administration procedure. A single dose of Samarium-153 EDTMP provides good pain palliation lasting for several weeks.

Key words: *Samarium 153 lexidronam, Pain palliation, Metastatic bone disease*

Narayan R, Manthri RG, Thiruvengadaswamy K, Tyagi A, Kale PG, Kalawat T. Role of Samarium-153-ethylene diamine tetramethylene phosphonate radionuclide bone pain palliation in patients with metastatic bone disease. *J Clin Sci Res* 2017;6:89-94. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.16.07.001>

INTRODUCTION

Bone metastasis is common in prostate, breast, lung and renal cancers and can lead to complications like fractures, hypercalcaemia and bone pain, as well as reduced performance status and quality of life.¹ A multidisciplinary approach is required to treat bone pain and its complicating factors. Currently, the treatment of bone pain remains palliative with systemic treatment (analgesics, hormones, chemotherapy, steroids, and bisphosphonates) for diffuse bone metastases and local treatment

(surgery, nerve blocks, and external beam radiation) for focal bone metastasis.² Many of these treatments are limited in their efficacy or duration and have significant side effects that seriously limit the cancer patient's quality of life.

Various radiopharmaceuticals have been used for bone pain palliation and have shown good treatment efficacy. This systemic form of radiotherapy is easy to administer and complements other treatment modalities. Phosphorus-32 (³²P), strontium-89 (⁸⁹Sr),

Received: July 06, 2016; Revised manuscript received: September 14, 2016; Accepted: September 15, 2016

Corresponding author: Dr Tekchand Kalawat, Professor and Head, Department of Nuclear Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati, India.
e-mail: kalawat.svims@gmail.com

**Online access**

http://svimstpt.ap.nic.in/jcsr/apr-jun17_files/2oa.16.07.001.pdf

DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.16.07.001>

samarium-153 (^{153}Sm) and radium 223 (^{223}Ra) are the radio-nuclides currently approved for palliation of metastatic bone pain.³ P-32 is not regularly used because of its potential to cause greater degree of myelosuppression. Sr-89 and ^{223}Ra are not readily available in India.

Sm-153 is produced in India and is easily available at reasonable cost and supplied by Board of Radiation and Isotope Technology (BRIT) (Mumbai, India) every fortnight. ^{153}Sm also emits gamma (γ) radiation of 103 kilo electron volts (keV) which can be used for scanning purpose. ^{153}Sm is produced in a reactor by neutron bombardment of enriched Sm-152 oxide, has a physical half-life of 1.9 days and decays by beta (β)-emission. The β -particle has a maximum energy of 0.81 mega electron volts (MeV), a mean energy of 0.23 MeV, and an average soft-tissue range of 0.6 mm. Sm-153 is complexed with ethylene diamine tetramethylene phosphonic acid (EDTMP) to form ^{153}Sm EDTMP. Clearance is bi-exponential after intravenous administration, comprising rapid bone uptake (half-life: 5.5 min) and plasma renal clearance (half-life: 65 min).^{4,5} Fifty percent of injected activity is excreted through renal system within 8 hours of administration. Total skeletal uptake ranges between 15% and 95%, depending on the skeletal tumour burden.³ Sm-153 EDTMP targets hydroxyapatite at sites of increased osteoblastic activity, the tumour-to-normal bone ratio being 4:1-7:1.⁶ In approximately 10% patients, "flare response" has been documented. It is a short lived and self-limiting increase in pain intensity. This study was conducted to study the efficacy of Sm-153 EDTMP therapy for pain relief in patients with metastatic bone disease

MATERIAL AND METHODS

This prospective analytical study was conducted in the department of Nuclear Medicine, at Sri Venkateswara Institute of Medical Sciences, Tirupati, from June 2011 -

June 2013, after taking prior approval from institutional scientific and ethics committee. Thirty consecutive analgesic refractory skeletal metastatic cancer patients who presented with multiple bone pains not fitting into a single field of radiotherapy corresponding to foci of intense osteoblastic activity on $^{99\text{mTc}}$ MDP skeletal scintigraphy, good marrow reserve as evidenced by Hb greater than 9.0g/dL, total leucocyte count greater than 3500/mm³, platelet count greater than 1,00,000/mm³ and estimated glomerular filtration rate (GFR) greater than 50mL/min referred for pain palliation with radiopharmaceuticals were recruited into the study after obtaining informed consent. Patients presenting with features of spinal cord compression, poor marrow reserve, those with GFR<50mL/min, pregnant women and nursing mothers were excluded from the study.

For each patient, pain was evaluated using patient-rated pain intensity visual analogue scale (VAS),⁷ where the patient was asked to score pain on a 10-step scale, 0 being no pain and 10 the maximal pain. Their performance status was evaluated using the Karnofsky Performance Score (KPS).⁸ For each patient, an analgesic score⁹ was also computed as the product of analgesic type and administration frequency coded into integer form.

Patients were administered 37 MBq/kg body weight of Sm-153 EDTMP, slow i.v., on outpatient basis. The beta emission of Samarium was useful for therapy. All patients also underwent whole-body planar scintigraphy three hours post-injection for Sm-153 uptake at affected bones, in the anterior and posterior views. Scintigraphy was performed with a dual-head gamma camera, Symbia E (Siemens Ltd Berlin, Germany) equipped with a low-energy high resolution parallel-hole collimator, using a 20% window centred at 103 keV to document radiotracer concentration in the sites of $^{99\text{mTc}}$ MDP accumulation.

The follow-up protocol was explained to them and no other tumour-oriented therapy was

allowed up to 12 weeks post therapy. They were instructed to keep taking the prescribed analgesics and hormonal therapy, and to reduce the dose of analgesics as required.

Toxicity of Sm-153 EDTMP was evaluated by measuring changes in platelets, leucocytes and haemoglobin, every week for 4 weeks and graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 of U.S. Department of Health and Human Services.¹⁰ Patients were also evaluated for a possible pain flare (flare phenomenon), beginning at 48-72 hours after the therapy and lasting for two to three days.

The VAS, KPS and analgesic score were recorded every 4 weeks up to 12 weeks. All numeric data were expressed as mean \pm SD. Mean scores for VAS, analgesic scores and KPS, were calculated at four, eight and twelve weeks. Analysis of variance (ANOVA) for repeated measures was used to calculate the statistical significance of pre-therapy and periodic changes in post-therapy scores. Pearson chi-square test was also applied to find out significant difference in response to therapy, in different cancer groups. A p-value of <0.05 was considered as significant. SPSS for windows ver 20 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 30 patients (19 males) were included in this study, with a mean age of 61.3 years (range 31-80 years). The mean age of male patients was 69.8 ± 11.2 years (range 32-80 years) and that of female patients was 46.6 ± 07.6 years (range: 31-57 years). The most common primaries in these patients were prostate cancer (n = 18; 60%), breast cancer (n = 7; 23%), lung cancer (n = 2; 7%), cervix cancer (n = 2; 7%) and malignant peripheral nerve sheath tumour (n = 1; 3%).

The localization pattern of Tc-99m scan done before Sm-153 therapy is shown in Figure-1A.

Post therapy bone scintigraphy done to confirm the localization of Sm-153 EDTMP at the sites of increased bone turnover (Figure-1B) showed same pattern as that of pre-therapy Tc-99m MDP scan in all the patients studied.

Twenty (67%) of these patients showed response to Samarium-153 EDTMP pain palliation therapy (responders), while 10 (33%) had no response to therapy (non-responders). The cancer wise distribution of responders and non-responders to therapy is shown in Figure 2.

Repeated measures ANOVA was applied to compare the pre therapy values with the post therapy values at 1st, 2nd and 3rd month respectively. The decrease in KPS, VAS and analgesic score were found to be statistically significant when compared to the respective baseline values (p value <0.01) (Table 1). None of the patients in this study developed flare in pain intensity following administration of Sm-153 EDTMP.

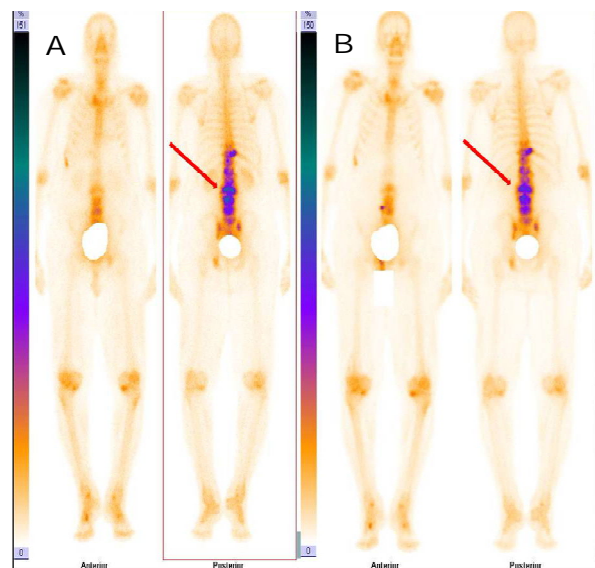


Figure 1a: Tc-99m MDP Bone scintigraphy, anterior & posterior whole body sweep views show multiple areas of osteoblastically active skeletal metastases, prominent at thoraco-lumbar region (solid arrows) (A). Sm-153 EDTMP bone scintigraphy, anterior and posterior whole body sweep views show localization of radio-pharmaceutical to the same areas as in A (B)

Table 1: KPS, VAS and analgesic scores pre-radionuclide therapy in comparison with post-therapy at 1 month, 2 months and 3 months follow-up

| Score | Pre Therapy | Post-therapy 1 st Month | Post-therapy 2 nd Month | Post-therapy 3 rd Month | p-value |
|-----------------|-------------|---------------------------------------|---------------------------------------|---------------------------------------|---------|
| KPS | 62.00±9.5 | 69.00±11.2 | 69.00±11.2 | 68.50±11.4 | <0.001 |
| VAS | 10.80±16.3 | 5.85±17.5 | 5.70±17.7 | 6.00±17.5 | <0.001 |
| Analgesic Score | 4.95±1.8 | 1.10±1.7 | 1.10±1.7 | 1.10±1.7 | <0.001 |

All data are presented as mean ± standard deviation

KPS = Karnofsky performance score; VAS = visual analogue score

Toxicity to samarium-153 EDTMP therapy was evaluated by assessing the change in haemoglobin levels, total leucocyte count and platelet count weekly for 4 weeks after therapy and comparing it to baseline. These changes were then graded according to CTCAE criteria for myelotoxicity. The haemoglobin level fell in patients after therapy and this fall was found to be statistically significant. Grading these changes in haemoglobin levels according to the CTCAE criteria ref for toxicity showed that 53% developed grade 1 toxicity, 40 % developed Grade 2 toxicity and 7% developed grade 3 toxicity. None of the patients developed grade 4 or 5 toxicity. The WBC count fell in patients after therapy and this fall was found to

be statistically significant. Grading these changes in total leucocyte counts for toxicity according to the CTCAE criteria showed that 93% developed grade 1 toxicity and 7 % developed grade 2 toxicity. The platelet count also fell in patients after therapy and this fall was found to be statistically significant. However, grading these changes in platelet counts for toxicity according to the CTCAE criteria showed that none of the patients developed toxicity of Grade 2 or worse (Figure 3).

DISCUSSION

Sm-153 EDTMP was approved for clinical use in 1997.¹¹ It has favourable pharmacokinetics

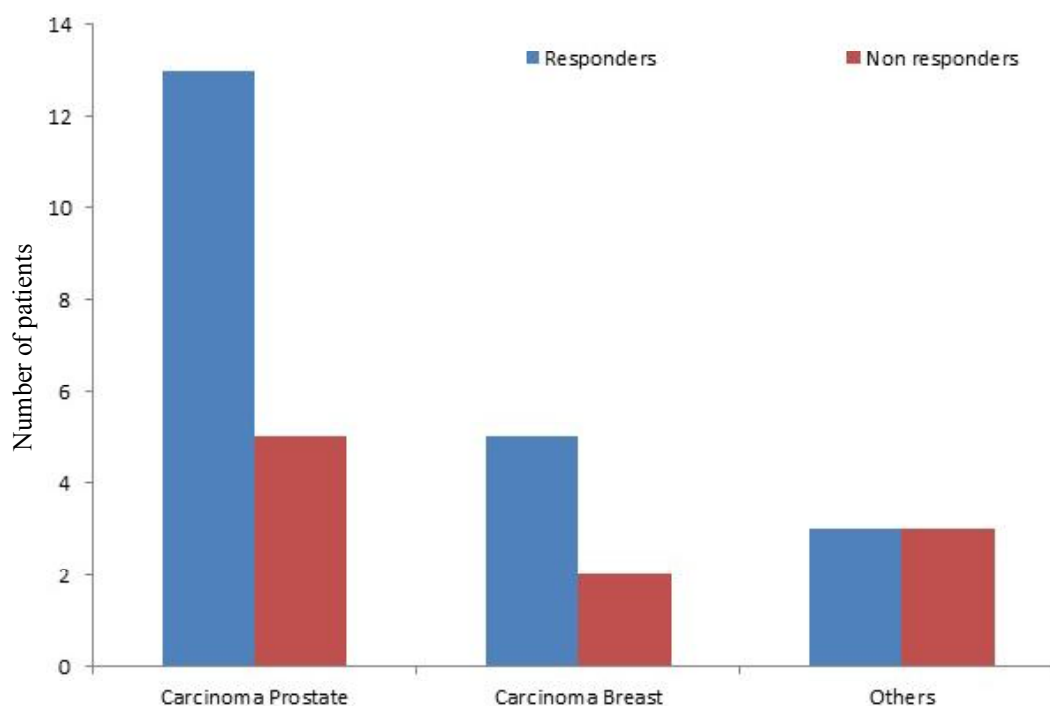


Figure 2: Cancer wise distribution of responders and non-responders to therapy

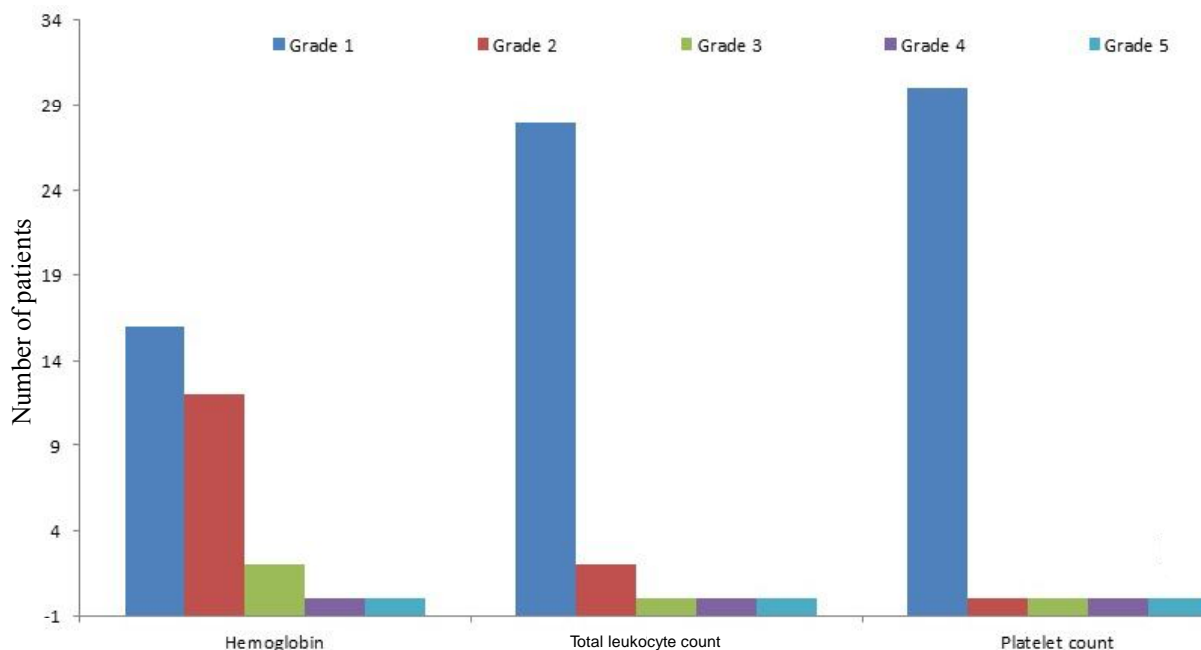


Figure 3: Severity of adverse effects according to CTCAE criteria in haematological parameters

with good target to background activity ratio and rapid clearance. It also emits 103 KeV gamma ray (20% abundance) which facilitates post-therapy bone scintigraphy to document its localization to osteoblastically active lesions.

There are reports from other parts of the world to determine the efficacy of Sm-153 in bone pain palliation in patients with metastatic bone diseases. However, so far only one report has been published from India, reporting the efficacy of Sm-153 EDTMP pain palliation therapy in Indian population. In the first double-blind placebo controlled study, conducted in 1998, Serafini et al¹² randomized 118 patients with painful bone metastases from a variety of primary tumours to placebo, 18.5 MBq/kg and 37 MBq/kg of Sm-153. They concluded that the dose of 37 MBq/kg of Sm-153 provides a relatively rapid onset of pain relief compared to placebo during the first week after drug administration. They also reported that in addition to the pain relieving effects, the dose of 37 MBq/kg of Sm-153 was found to be durable, with >50% responders at 4 weeks and still having some pain relief at 16 weeks after

therapy. Another multicenter trial, involving 105 patients, performed by Tian et al,¹³ showed the efficacy and toxicity of single-dose of 37MBq/kg of Sm-153 as a palliative treatment for painful skeletal metastases in 83.8% of patients. A phase III randomized trial performed enrolling 152 patients, to assess the effectiveness of Sm-153 for palliation of bone pain in patients with prostate cancer, showed statistically significant improvement in analgesic consumption and pain.¹⁴

In India, Tripathi et al⁹ conducted a study, in 2006 to determine the efficacy and toxicity of single dose Sm-153 EDTMP as a palliative treatment for painful skeletal metastases and reported effective palliation in 73% patients. Most of the patients tolerated this treatment without any untoward event and major toxicity was temporary myelosuppression.

In the current study, 20 (67%) patients showed significant pain palliation after Sm-153 EDTMP therapy, while 10 (33%) had no relief. Pain relief was observed in all responders by 7th day of therapy. The shortest duration of pain palliation achieved was 6 weeks while the

longest pain free period observed was 9 months. In the non responders, the mean KPS was lower while both VAS and analgesic score were higher, compared to the responders. This suggests that radionuclide therapy may be more effective in pain palliation if administered at an earlier stage of the bone disease. All patients experienced post-therapy myelotoxicity. Most patients developed grade 1 and 2 myelotoxicity but recovered spontaneously. Two patients developed grade 3 myelotoxicity. One patient was transfused with 2 units of whole blood while the haemoglobin level of other patients improved spontaneously on follow-up. None of the patients developed grade 4/5 toxicity.

Samarium-153 EDTMP is a safe, simple, economical, easily available and well tolerated modality of treatment for pain palliation of osteoblastically active disseminated skeletal metastases. A single dose of Samarium-153 EDTMP provides good pain palliation lasting several weeks. It also improves quality of life in patients of advanced stages of cancer with painful osteoblastic skeletal metastases.

REFERENCES

1. Serafini AN. Therapy of metastatic bone pain. *J Nucl Med* 2001;42:895-906.
2. Ayse H, Ozlem NK, Meltem NA, Yildiz G, Erkan I. Role of radionuclide therapy as adjuvant to external beam radiotherapy for painful multiple skeletal metastasis. *World J Oncol* 2010;1:158-66.
3. Paes FM, Serafini AN. Systemic Metabolic Radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; 40:89-104.
4. Singh A, Holmes RA, Farhangi M, Volkert WA, Williams A, Stringham LM, et al. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *J Nucl Med* 1989;30:1814-8.
5. John EB, Daniel JM, Leela PK, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. *J Nucl Med* 1994;35:63-9.
6. Ahonen A, Joensuu H, Hiltunen J, Hannelin M, Heikkilä J, Jakobsson M, et al. Samarium-153-EDTMP in bone metastases. *J Nucl Biol Med* 1994;34:123-7.
7. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-84.
8. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale. An examination of its reliability and validity in a research setting. *Cancer* 1984;53:2002-7.
9. Tripathi M, Singhal T, Chandrasekhar N, Kumar P, Bal C, Jhulka PK, et al. Samarium-153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. *Indian J Cancer* 2006;43:86-92.
10. Common Terminology criteria for adverse events (CTCAE) version 4.0 V4.03. USA. U.S. Department of Health and Human Services;2009.
11. Sapienza MT, Ono CR, Guimarães MIC, Watanabe T, Costa PA, Buchpiguel CA. Retrospective evaluation of bone pain palliation after samarium-153-EDTMP therapy. *Rev Hosp Clin Fac Med Savo Paulo*. 2004;59:321-8.
12. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Bertrand A, et al. Palliation of pain associated with Metastatic bone cancer using samarium-153 leixidronam: A double blind Placebo-controlled clinical trial. *J Clin Oncol* 1998;16:1574-81.
13. Tian JH, Zhan JM, Hou QT, Oyang QH, Wang JM, Luan ZS, et al. Multicentric trial on efficacy and toxicity of single dose Samarium-153 ethylene diamine tetramethylene phosphonate as a palliative Treatment for painful skeletal metastases in China. *Eur J Nucl Med* 1999;26;2-7.
14. Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, et al. Samarium-153 leixidronum complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* 2004;63;940-5.