

Effectiveness and complications of ^{153}Sm -EDTMP in palliative treatment of diffuse skeletal metastases

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ABSTRACT

Introduction: The aim of the present study was to evaluate the efficacy and safety profile of bone palliative therapy following administration of ^{153}Sm -EDTMP in patients with intractable metastatic bone pain.

Methods: Sixteen patients (9 male, 7 female) aged 29-80 years (57.3 ± 16.7 years) with severe metastasis-related bone pain resistant to analgesic medications were enrolled in the study. All patients having multiple bone metastases, positive bone scans, and estimated life expectancy of more than 2-3 months were entered the study. All patients received intravenous injection of 1.5 mCi (56 MBq)/kg of ^{153}Sm -EDTMP. Four subscales for the intensity of pain were recorded: one as the *present pain score* (PPS) and the other three as *maximum pain score* (Max PS), *minimum pain score* (Min PS) and *average pain score* (APS) over the last 24 hours. Also the mean value of these 4 subscales was calculated as the *mean total pain score* (MTPS). The *pain mental interference* (PMI) was also assessed in 9 separate.

Results: Seven patients with breast cancer (43.75%), seven with prostate cancer (43.75%), one with papillary thyroid carcinoma (6.25%) and one with malignant paraganglioma (6.25%) were included in the study. A significant response to therapy, i.e. 2-point reduction in pain score and/or remarkable reduction ($\geq 25\%$) in the equivalent narcotic dose, was observed in 11 out of 16 patients (68.7%) by the 2nd week and in 12 patients (75%) by the 8th week. Regarding the palliative response to treatment and equivalent narcotic dose reduction, no significant difference between two major types of underlying malignancies (breast and prostate cancer) was found. There was no significant difference regarding response to therapy between two genders and among different age groups. The severity of bone marrow suppression was graded ≤ 2 in all patients.

Conclusion: Response to palliative treatment with ^{153}Sm -EDTMP in prostate and breast cancers is the same at the rate of 75% at the end of 8th week post-infusion. Hematologic toxicity is mild to moderate and no life-threatening side effect is observed.

Key words: ^{153}Sm -EDTMP; Palliative therapy; Pain; Bone metastasis

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INTRODUCTION

Metastasis related bone pain is one of the most debilitating symptoms in patients with advanced malignancies. It is seen in more than 70% of patients with advanced breast and prostate cancers and more than 30% of advanced lung, bladder and thyroid malignancies [1-4].

Palliative treatment of metastatic bone pain, including analgesic medications, surgery, chemotherapy, hormonal manipulation (including orchiectomy), bisphosphonates and radioisotopes are ineffective in some cases of advanced disease, which needs employment of other palliative strategies [5, 6].

Radiation therapy, including external beam radiotherapy and radionuclide therapy, has been introduced and employed as the last resort for these patients. External beam radiotherapy provides significant palliation with a success rate of 70-90% in case of solitary metastases [6]. The treatment is also effective for cases with multiple skeletal metastases; however, due to the large field of radiation, it is accompanied by a higher rate of complications and adverse effects, such as significant cytopenia [5-7]. Therefore in such cases, β -emitter bone seeking radiopharmaceuticals have been suggested as an effective alternative therapy.

The response rate to radionuclide therapy has been shown to be 40-95% (average of 70%), depending on the type of radiopharmaceutical administered, underlying cancer, age, number of metastases, and some other determinants [1, 5-25].

A number of bone seeking agents, such as Strontium-89 (Sr-89), Phosphorus-32 (P-32), Samarium-153 (Sm-153), Rhenium-186 (Re-186) and Rhenium-188 (Re-188) have been tested and employed for this purpose [7-16].

The exact mechanism of radionuclide pain palliation is still to be determined; however, a cytotoxic effect on normal bone cells, inhibiting the release of pain mediators and shrinkage of metastatic lesions leading to a decrease in stimulation of the mechanical pain receptors [1, 13, 16] have been suggested as the possible mechanism of their efficacy.

^{153}Sm -EDTMP is a new and less expensive bone-seeking radiopharmaceutical with physical half life of 46 hrs and maximum beta energy of 0.81 MeV [5, 6, 11, 12]. It has also a gamma emission with 103 KeV photon energy allowing imaging with this therapeutic isotope. However, this radiopharmaceutical has not been extensively studied and data on its efficacy and safety is still needed [26-30].

The aim of the present study was to evaluate the efficacy and safety profile of bone palliative therapy following administration of ^{153}Sm -EDTMP in patients with intractable metastatic bone pain.

METHODS

Study population

Sixteen patients (9 male, 7 female) aged 29-80 years (57.3 ± 16.7 years) with severe metastasis-related bone pain resistant to analgesic medications were enrolled in the study. All patients had multiple bone metastases, positive bone scans (within 6 weeks of the treatment) with areas of abnormal increased radiotracer uptake corresponding to the sites of bone pain and estimated life expectancy of more than 2-3 months were entered the study. Exclusion criteria were pregnant or breastfeeding women, patients with history of bisphosphonate therapy, chemotherapy or external beam radiation during 4-6 weeks before ablative therapy and those with evidence of acute or chronic renal failure, spinal cord suppression, extensive soft tissue metastases, disseminated intravascular coagulopathy, impending pathologic fracture, severe anemia ($<7\text{g/dL}$), leukocytopenia ($<2500/\text{mm}^3$), and thrombocytopenia ($<60000/\text{mm}^3$). None of the patients had history of palliative therapy with radionuclides. The study was approved by the committee of ethics at Tehran University of Medical Sciences.

Study measurements

After obtaining informed consent, clinical history, physical examination and baseline cell blood count were taken. Consequently, a baseline *Brief Pain Inventory* (BPI) checklist [17] was applied to score the pain intensity during a semi-structured interview prior to the radionuclide palliative therapy. Four subscales for the intensity of pain were recorded: one as the *present pain score* (PPS) and the other three as *maximum pain score* (Max PS), *minimum pain score* (Min PS) and *average pain score* (APS) over the last 24 hours. Also the mean value of these 4 subscales was calculated as the *mean total pain score* (MTPS). The *pain mental interference* (PMI) was also assessed in 9 separate items including general activity, mood, walking ability, normal work, relation with people, sleep, enjoyment of life, ability to concentrate and appetite using the formal BPI checklist. All scores were achieved via a 10-point scoring system of which 0 means the best and 10 denotes the worst state. The dose of narcotic drugs was converted to equivalent oral morphine doses (mg/day).

Intervention and follow up

All patients received intravenous injection of 1.5 mCi (56 MBq)/kg of ^{153}Sm -EDTMP. The radiopharmaceutical was provided by Iranian Atomic Energy Agency. All handling protocols were done according to the provider instructions. Before

receiving the radiopharmaceutical infusion, all patients were hydrated with 1 liter of i.v. fluid. Thereafter, all patients were observed for 12 hours after the treatment and were discharged if the post-procedure course was eventless and a radiation exposure of less than 1 mSv per year in 2 m distance.

In addition to the baseline assessments, the BPI scores and the dose of analgesics were recorded in different sessions (2, 4 and 8 weeks) following ^{153}Sm -EDTMP administration. A significant response to treatment was defined as at least a 2-point reduction in pain score, keeping the average dose of analgesic drugs constant or more than 25% reduction in analgesic consumption without increasing the intensity of pain.

Hematologic toxicity was also assessed using complete blood count (CBC) before and once weekly up to the 4th week post-palliative therapy. Bone marrow suppression was graded according to the *National Cancer Institute common toxicity criteria* (NCI CTC version 2).

Statistical analysis

The statistical software package, SPSS (version 16.0), was employed for data analysis. The *general linear model (GLM) repeated measures analysis* was used to compare pain scores, analgesic doses and hematologic values in different sessions of the measurements. To determine the differences of a qualitative nominal variable in the same attribute (e.g. pain relief in different time points after therapy)

Friedman test was applied and to analyze the difference between the doses of the analgesics before and after palliative therapy, *Wilcoxon Signed Ranks* test was used. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Seven patients with breast cancer (43.75%), seven with prostate cancer (43.75%), one with papillary thyroid carcinoma (6.25%) and one with malignant paraganglioma (6.25%) were included in the study. All patients were only on analgesic palliative therapy before entering to the study and none of the patients had prior history of radionuclide or external beam radiation palliative therapy.

Efficacy of therapy

Max pain score, PMI and MTPS were improved after palliative therapy, while Min pain score, APS and PPS showed no significant improvement after radionuclide palliative therapy (Figure 1 and Table 1). A significant response to therapy, i.e. 2-point reduction in pain score and/or remarkable reduction (25%) in the equivalent narcotic dose, was observed in 11 out of 16 patients (68.7%) by the 2nd week and in 12 patients (75%) by the 8th week. Five patients (31.2%) showed significant reduction in both pain score and analgesic dose two weeks following therapy.

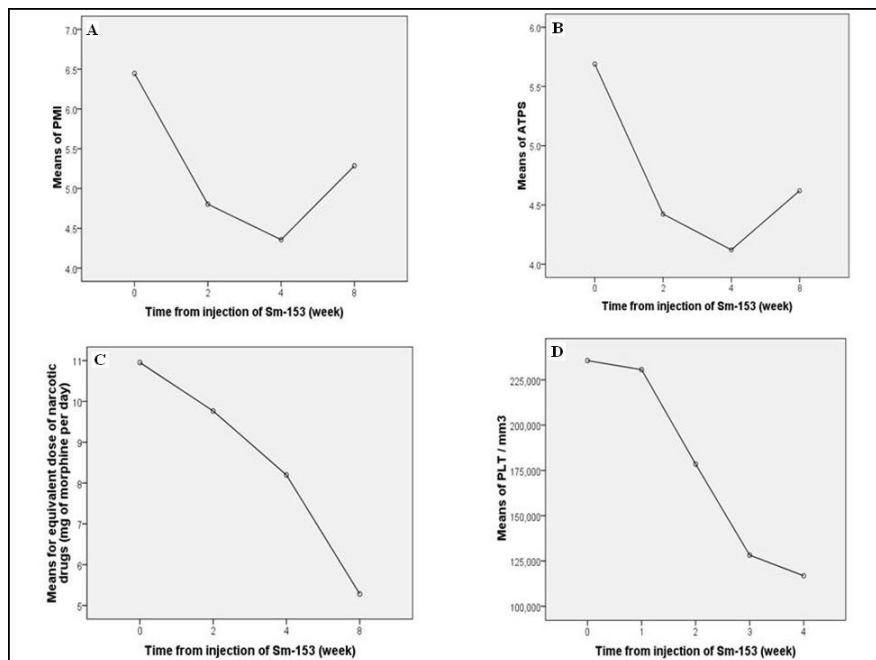


Fig 1. The palliative effects of the radionuclide therapy (A and B) reach to a significant level at the second week post-treatment. The narcotic equivalent dose reduction was significantly reduced at the eighth post-treatment week (C). A significant drop in platelet count is seen four week post-therapy (D).

Table 1. Changes in pain indicators from the baseline to the end of the follow-up period (eight weeks after the treatment, with two-week intervals).

Mean values of pain indicators	Follow-up time points				Within-subjects effects between different levels	Within-subjects contrasts between different levels	
	Baseline	2nd week	4th week	8th week	P value (Significance)	Levels	Significance
Max PS in the last 24h	7.87 ± 2.39	6.00 ± 3.01	5.88 ± 2.45	6.25 ± 2.79	0.049 (S)	2 week vs. Base	0.034 (S)
Min PS in the last 24h	3.13±2.34	3.25±2.86	2.81±2.07	2.69±1.92	0.849 (NS)	--	--
APS in the last 24h	5.56±2.19	4.19±2.88	4.06±1.8	4.62±2.18	0.087 (NS)	--	--
PPS in the last 24 hr	5.44±3.11	3.87±2.77	3.50±2.12	4.25±2.436	0.112 (NS)	--	--
PMI	6.44±1.78	4.80±2.48	4.35±2.37	5.28±2.35	0.002 (S)	4 week vs. 2 week	0.002 (S)
†Equivalent narcotic drug doses	10.95±19.84	9.76±19.20	8.19±11.74	5.28±11.46	0.209 (NS)*	--	--
MTPS	5.68±1.97	4.42±2.44	4.12±1.61	4.61±2.02	0.049 (S)	2 week vs. base 4 week vs. 2 week	0.048 (S) 0.032 (S)

Max PS: Maximum Pain Subscore, Min PS: Minimum Pain Subscore, APS: Average Pain Score, PPS: Present Pain Score, PMI: Pain Mental Interference, MTPS: Mean Total Pain Score, S: Statistically significant ($p < 0.05$), NS: Non-significant, * Greenhouse-Geisser correction was used since the sphericity was not assumed due to significant Mauchly's Test. †: mg equivalent of oral morphine per day.

Table 2. A significant progressive drop in blood cell counts during the four weeks of post-treatment monitoring was seen.

Blood marker	Monitoring intervals					Within-subjects effects between different levels	Within-subjects contrasts between different levels	
	Base	1st week	2nd week	3rd week	4th week	Significance	Levels	Significance
Hb (gr/dl)	11.7±2.5	11.5±2.5	11.0±2.2	11.0±2.4	10.7±2.3	<0.0001 S	2 week vs. 1 week 4 week vs. 3 week	0.003 S <0.0001 S
PLT (x1000/mm ³)	235±58	230±69	178±43	128±46	116±37	<0.0001 S	2 week vs. 1 week 3 week vs. 2 week 4 week vs. 3 week	0.004 S <0.0001 S <0.0001 S
WBC (x1000/mm ³)	5958±1814	4675±2001	3891±2037	3983±1766	4133±1717	<0.0001 S	1 week vs. base 2 week vs. 1 week 3 week vs. 2 week	0.001 S <0.0001 S <0.0001 S

Hb: Hemoglobin; PLT: Platelet; WBC: White Blood Cell; S: Statistically significant difference.

Regarding the palliative response to treatment and equivalent narcotic dose reduction, no significant difference between two major types of underlying malignancies (breast and prostate cancer) was found (p values for Max PS, PMI, MTPS equivalent narcotic dose were 0.975, 0.146, 0.105 and 0.095, respectively). There was no significant difference regarding response to therapy between two genders and among different age groups (all P values > 0.05).

Adverse effects

No side effect was observed during ¹⁵³Sm-EDTMP infusions, except for a flare reaction in one patient, which resolved spontaneously. Post-treatment monitoring of platelet count, white blood cell (WBC) count and hemoglobin (Hb) level showed a

significant drop during the four weeks of post-therapy period (Table 2). As per NCI CTC, the severity of bone marrow suppression was graded ≤ 2 in all patients.

DISCUSSION

Systemic therapy with beta-emitting agents is currently one of the most widely employed methods to control intractable metastatic bone pain. Among the most commonly used agents for internal radiotherapy, i.e., ⁸⁹Sr and ¹⁸⁶Re-HEDP, ¹⁵³Sm-EDTMP, the latter shows less hematologic toxicity, which at least is partly explained by the lower maximum energy of its beta emissions (0.81 Mev). The lower toxicity along with the equal efficacy in

providing pain relief are the main reasons why some authors have suggested ^{153}Sm -EDTMP as the ideal agent for palliative internal radiotherapy of metastatic bone disease [31]. On the other hand, ^{153}Sm -EDTMP is one of the beta-emitting agents with more availability in some countries, like Iran. Despite of these facts and simplicity of administration, Anderson and Nunez believe that, ^{153}Sm -EDTMP is underutilized for improving cancer pain in the skeleton [32]. Especially in developing countries with limited availability of resources, a single course of treatment could be quite effective with a reasonable cost, provides palliation for a considerable duration of time and improves quality of life of patients with advanced metastatic disease.

Our study showed 75% of patients achieve some degrees of therapeutic response in two months, which is compatible with the previous reports (Table 3): Dolezal showed that ^{153}Sm -EDTMP treatment leads to pain relief of varying degrees in 72% of patients with metastatic breast cancer to skeleton [30]. There are a number of measures, which are used to assess the efficacy of treatment with beta-emitting agents. Among these measures, pain scores and average analgesic medication usage are the most common variables. The pain scores are more of a kind of subjective measure and analgesic medication usage more of an objective measure that can be quantified rather easily and practically. In our study, patients showed response to treatment in both subjective and objective measures, a fact which is compatible with the previous reports (Table 2). In the study of Baczyk et al. analgesic drugs consumption 2 months after radionuclide therapy decreased by about 50% in comparison to the initial values [5], which is compatible with what we found. Also Enrique et al. reported pain relief in 73% of patients with a parallel 82% reduction of analgesic intake [26].

The analgesic medications are divided into two groups of narcotics and non-narcotics. In our study, the average dose of narcotics consumption showed 50% reduction and a significant drop was seen between two related dose measurements at the baseline and 8th week of palliative therapy ($p=0.045$) (Figure 1c). However, due to over the counter availability of non-narcotics and inaccurate registration of their consumptions by our patients, a reliable analysis was not possible. Our study findings are in accordance with the report of Turner et al., as onset of pain relief was observed within 14 days of administration of ^{153}Sm -EDTMP and clinical response was maximal at 6 weeks [33].

We employed a high dose of 1.5 mCi/kg, which is higher from what Sinzinger et al. [34] have reported (0.5 mCi/kg v.s. 1.0 mCi/kg). However, the response to treatment is significantly different from their report. In their study all patients had response to therapy at 8th week post-infusion, while in our study the response rate was 75%. The explanation for reported higher rate of response in their study is that Sinzinger et al. followed the Vienna protocol, in which the patient is not treated just one time, but repeatedly by intravenous doses of 30 mCi (1.1 GBq) ^{153}Sm -EDTMP [34]. The treatment is on outpatient basis and is scheduled for 1-5 treatments at 3-month-intervals, 6-10 at 6-month-intervals, 11-15 at 9-month-intervals, and thereafter at 12-month-intervals. Following such a protocol, all patients will show a reasonable palliative response to treatment. Requisite for such a protocol is repeated administration of ^{153}Sm -EDTMP and acquisition of a scintigraphy (more than 6 hours after radionuclide application), which makes the protocol more time- and cost-consuming and less practical in regions with poor economic status of healthcare setting [1].

Table 3. A review on the reports of the efficacy of palliative therapy with ^{153}Sm -EDTMP in different metastatic cancers.

Study	Pathology	Response Rate	Toxicities	Sample size
Dolezal J. [30]	Breast Cancer	72% in 3 months	No grade IV, 1 grade III	43
Baczyk et al. [5]	Breast and Prostate Cancers	80% in 2 months	40% of patients showed moderate granulocytopenia and/or thrombocytopenia	30
Feng et al. [31]	Prostate Cancer	83.9%	Not available	55
Berger et al. [36]	Osteosarcoma	One-month pain palliation was only observed in a minority of subjects and in none at 4 months.	Not available	22

In some of the previous trials even a higher dose than what we administered (for example doses up to 111 MBq/kg) was used [21, 24]. However, even with such a high dose, the pain relief response within 40-50 days post-treatment period was 78-95%, which leads to the conclusion that no improvement in palliative response and survival rates with dose augmentations is seen. Conversely increased bone marrow suppression is observed. Turner et al. also found no dose-response relationship for pain relief [33]. This also confirms Sinzinger's conclusion that a higher dose is not necessarily more beneficial, but could significantly affect the bone marrow.

Although 103 keV gamma emission of ^{153}Sm could be utilized for individual pretherapeutic estimation of beta radiation absorbed dose to red marrow and subsequent dose adjustments to minimize myelotoxicity [2], in our study we did not perform pretherapeutic dosimetry, as uptake does not correlate to therapeutic benefit, and dosimetry offers no advantage to treatment planning and dose adjustment [34]. On the other hand, always there is a risk that these studies might cause stunning phenomenon (i.e. suppressing the uptake rate of the therapeutic dose, which is supposed to be administered in couple of days following the dosimetric dose) [34]. However, Vigna et al. stated that the significant variability in biodistribution and metabolism of ^{153}Sm -EDTMP suggests that dose calculation based on the patient weight does not optimize the treatment and using a predictive pre-treatment dosimetry tailored to individual patient characteristics for dose adjustment was recommended by their group [35]. Regarding these controversies, further studies to address this issue are still needed.

Based on what Vigna et al. [35] have reported, the cumulated activity of administered Sm-EDTMP in bone and red marrow are significantly higher in patients prostate cancer (in which bone metastases are osteoblastic in nature), than in patients with breast cancer (where bone metastases are more of an osteolytic or mixed lytic/blastic component). As per this finding, one could expect to have a higher pain palliation response rate in patients with prostate cancer than patients with breast cancer. However, our study did not show such a difference in response rate, which is compatible with the findings of Baczyk et al. [5]. As per Sinzinger et al. [34], no individual predictor of response to ^{153}Sm -EDTMP palliative therapy is available. Our study also confirmed that the type of the underlying malignancy, gender and age are not predictors of response to therapy.

Hematologic toxicities are the main side effect of the treatment. Previous studies showed transient mild to moderate bone marrow suppression (presenting as leukopenia and thrombocytopenia) following

radionuclide treatment which are resolved in the 5th week to 8th week interval [12, 27]. Our study confirmed that bone marrow suppression complication following ^{153}Sm -EDTMP therapy is mild (grade 1 and 2) and severe hematologic toxicity with the current doses is rare.

CONCLUSION

Response to palliative treatment with ^{153}Sm -EDTMP in prostate and breast cancers is the same at the rate of 75% at the end of 8th week post-infusion. Hematologic toxicity is mild to moderate and no life-threatening side effect is observed.

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