A Comparative Study of Samarium-153-Ethylenediaminetetramethylene Phosphonic Acid with Pamidronate Disodium in the Treatment of Patients with Painful Metastatic Bone Cancer

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Key Words

Samarium-153-ethylenediaminetetramethylene phosphonic acid ($^{153}\text{Sm-EDTMP}$) · Pamidronate disodium · Bone metastases

Abstract

Objective: To assess the therapeutic efficacy and toxicity of samarium-153-ethylenediaminetetramethylene phosphonic acid ($^{153}\text{Sm-EDTMP}$) and pamidronate disodium in patients with painful metastatic bone cancer. **Subjects and Methods:** Eighteen patients with histopathologically confirmed malignancy and multifocal bone metastases were randomized into two equal groups of 9 patients each. Group A was treated with $^{153}\text{Sm-EDTMP}$, while group B was treated with pamidronate disodium. The pain score for each patient was recorded before and after therapy using visual analogue scales that graded both the intensity and frequency of the bone pain. Therapeutic response was classified as inefficient, mild, effective and excellent. **Results:** Pain score in each group prior to therapy was more than 6. In group A, 2 (22.2%) and 7 (77.8%) cases showed mild and effective response, respectively. The therapeutic efficacy of $^{153}\text{Sm-EDTMP}$ was adjudged

to be 77.8%. Transient myelosuppression was generally mild and reversible with white blood cells and platelets recovering after 6 weeks. In group B, palliative response in 4 cases (44.4%) was inefficient, in 1 case (11.1%) mild, in 3 cases (33.3%) effective and in 1 case (11.1%) excellent, with a therapeutic efficacy of 44.4% for pamidronate disodium. No hematological toxicity was noted. **Conclusion:** The data showed that the therapeutic efficacy of $^{153}\text{Sm-EDTMP}$ was higher than that of pamidronate disodium (for pain relief maintained more than 3 weeks) and its incidence of blood toxicity was also higher than that of pamidronate disodium.

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Introduction

Metastatic bone cancer is a common complication of malignant tumor. It has been reported that 60–80% of cancer patients develop bone metastases [1]. Malignant bone pain is still a challenging clinical problem. Pain due to bone metastases greatly decreases the patient's quality of life because of gradual deterioration, local body dysfunction, mental and physical collapse. Several treatment

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regimens for bone pain palliation including radionuclides, narcotic medication and anticancer drugs have been reported [2–6]. These studies, however, were generally heterogeneous trials involving different stages of cancer, radiopharmaceutical dosages, combination with other therapeutic modalities and methods of pain assessment.

A variety of new radiopharmaceuticals have been developed in recent years for treatment of painful bone metastases. Four are commercially available: strontium-89 chloride ($^{89}\text{SrCl}_2$), rhenium-188-(Sn)-hydroxyethylene diphosphonate ($^{188}\text{Re-HEDP}$), $^{186}\text{Re-HEDP}$ and samarium-153-ethylenediaminetetramethylene phosphonic acid ($^{153}\text{Sm-EDTMP}$). $^{89}\text{SrCl}_2$ is still the most widely used agent. It has a longer physical half-life ($t_{1/2} = 50.5$ days) than ^{188}Re , ^{186}Re or ^{153}Sm . It is a pure beta-emitter and is expensive. ^{188}Re ($t_{1/2} = 16.9$ h) obtained from ^{188}W - ^{188}Re generator is convenient in routine clinical practice, because its gamma rays can be used for imaging and dosimetric studies. ^{186}Re has favorable physical ($t_{1/2}$ 90 h, β : 1.07 MeV, γ : 137 keV with 9% abundance) and biological characteristics. These characteristics allow relatively high doses to the target with low systemic radiotoxicity, even with repeated treatments, and easy performance of dosimetric studies and scintigraphic imaging. $^{186}\text{Re-HEDP}$ permits selective localization in bone cancer lesions by bridging the hydroxyapatite crystals and has proven efficacy in relieving pain associated with bone metastases, but clinical experience with $^{186}\text{Re-HEDP}$ is limited [7–9] $^{153}\text{Sm-EDTMP}$ has relatively ideal physical, chemical and biological properties similar to ^{188}Re except of slightly longer half-life ($t_{1/2} = 40.4$ h). The 0.103 MeV γ ray is suitable for imaging its in vivo distribution. The benefit of the favorable clinical experience with $^{153}\text{Sm-EDTMP}$ has been reported in several multicenter trials [10, 11]. However, few reports comparing the therapeutic efficacy of $^{153}\text{Sm-EDTMP}$ radionuclide therapy with that of pamidronate disodium for treatment of patients with painful bone metastases are available [12, 13]. Therefore the aim of this study is to compare the pain palliation effect, toxicity and adverse reaction of $^{153}\text{Sm-EDTMP}$ with pamidronate disodium.

Subjects and Methods

Subjects

Eighteen patients with histologically proven metastatic bone cancer were randomized into two groups: A (treated with $^{153}\text{Sm-EDTMP}$) and B (treated with pamidronate disodium). Recruitment criteria were bone pain, bone metastases intensively positive in a recent bone scan or determined by magnetic resonance imaging

(MRI) and computed tomography (CT) scan; pain refractory to analgesics; therapies not changed and/or modified; pain not originating from pathological bone fracture; absence of signs of spinal cord compression; life expectancy ≥ 3 months; absence of hepatic and renal insufficiency and signs of disseminated intravascular coagulation; white blood cells (WBCs) $\geq 3.0 \times 10^9/\text{l}$, platelets $\geq 80 \times 10^9/\text{l}$; and absence of signs of rapid depletion of bone marrow reserve. Patients treated by chemotherapy or external radiotherapy in the 3 months prior to the beginning of the study were excluded. Simultaneous hormone therapy, as long as it had been started or changed at least 3 months earlier, was allowed.

Therapeutic Drug and Administration Modalities

The study was carried out by using the recommendation of the National Radionuclide Therapy Committee of China. The $^{153}\text{Sm-EDTMP}$ provided by the Department of Isotope, China Institute of Atomic Energy was used in a standard single dose of 37 MBq/kg (radiochemical purity $>98\%$). The pamidronate dosage (30 mg/500 ml saline) and the infusion protocol were according to the manufacturer's directions (Shenzhen Haiwang Pharmaceutical Company Ltd., China). The study was approved by the Ethics Committee, Peking University First Hospital, and was performed according to the ethical standards of the State Drug Administration. Most of the subjects were out-patients. Written information about therapy and radiopharmaceuticals was given to the patients. All patients gave their written informed consent prior to inclusion in the study.

The patients given $^{153}\text{Sm-EDTMP}$ were kept in isolation and 2 of them were kept under close observation for at least 3 h during administration of the radiopharmaceutical.

All patients were instructed to report any discomfort or side effect which occurred after the injection of the drug. Blood counts, especially WBCs, and platelets, and serum titers of alanine transaminase, aspartate aminotransferase, and creatinine and blood urea nitrogen were determined for each patient.

Pretherapy Assessment

For each patient the following data were collected: previous and current tumor and pain palliation treatments, coexisting diseases, hematological and biochemical profiles, and analgesic drugs and hormones. Routine whole-body bone scan was performed at 3 h after injection of 925 MBq $^{99\text{m}}\text{Tc-MDP}$ using GE STARCAME 300i SPECT. Either CT or MRI was done.

Using previously validated methods [14, 15] intensity of bone pain was graded as follows: mild = 1 point; moderate = 2 points; severe = 3 points; and unbearable = 4 points and frequency as occasional = 1 point; intermittent = 2 points; frequent = 3 points, and constant = 4 points for each skeletal segment. A regional pain index (intensity $\times$ frequency) was then calculated for each skeletal segment. Pain assessment also included information about the dosage and type of analgesic drugs administered, as well as an evaluation of the patient's general state of health and physical activity, according to the Karnofsky Index.

Post-Therapy Assessment

A nuclear medicine physician interviewed and evaluated the patients at weekly intervals for the 1st month, 2-week intervals for the next month and then 4-week intervals for the remaining 4 months, using a previously validated method [16].

Palliative response was graded at four levels: inefficient, mild, effective and excellent. The four levels as described by Dafermou et

Table 1. The primary tumor types of patients that received ^{153}Sm -EDTMP or pamidronate disodium

Drug	Lung cancer	Breast cancer	Prostate cancer	Rectal cancer	Stomach cancer	Other	Total
^{153}Sm -EDTMP	1	2	3	1	1	1	9
Pamidronate disodium	2	3	2	1	1	0	9

Table 2. Patient population and clinical features

Drug	Male cases	Female cases	Age years	Bone metastases	Pain score	WBCs	PLTs	Follow-up period, weeks
^{153}Sm -EDTMP	6	3	52 $\pm$ 1 (21–80)	6.2 $\pm$ 6.6	8.0 $\pm$ 3.4	7.2 $\pm$ 2.5	216 $\pm$ 6.6	16.7 $\pm$ 2
Pamidronate disodium	3	6	60 $\pm$ 21 (20–81)	8.5 $\pm$ 7.2	7.7 $\pm$ 2.2	6.5 $\pm$ 1.8	202 $\pm$ 73	16.2 $\pm$ 2

PLTs = Platelets.

Table 3. Pain palliative effect of the two groups

Drug	Cases	Pain palliative effects				Effective rate %
		inefficient relief	mild response	effective	excellent	
^{153}Sm -EDTMP	9	0	2	7	0	77.8
Pamidronate disodium	9	4	1	3	1	44.4

al. [16] are as follows: (a) inefficient: post-therapy pain index not changed or increased or reduction by $\leq 25\%$, regardless of the consumption of analgesics, or reduction in the post-therapy pain index by $>25\%$ but $\leq 50\%$ with increased dosage of analgesics or change in the type of drugs to a superior grade, score 0; (b) mild response: reduction in the post-therapy pain index by $>25\%$ but $\leq 50\%$ with no variation or reduction in the dosage of analgesics, and no variation in the type of drugs, or change to an inferior grade or reduction in the post-therapy pain index by $>50\%$ but $\leq 75\%$ with increased dosage of analgesics or change in the type of drugs to a superior grade, score 1; (c) effective: reduction in the post-therapy pain index by $>50\%$ but $\leq 75\%$ with no variation or reduction in the dosage of analgesics and no variation in the type of drugs, or change to an inferior grade, or reduction in the post-therapy pain index by $>75\%$ with increased dosage of analgesics or change in the type of drugs to a superior grade, scores 2; (d) excellent relief: reduction in the post-therapy pain index by $>75\%$ or absence of pain with no variation or reduction in the dosage of analgesics, and no variation in the type of drugs or change to an inferior grade or analgesic drug therapy interrupted, score 3.

Results

Patient Population and Clinical Characteristics

The primary tumor types for each group are listed in table 1 and are essentially similar. The patient population and clinical features are comparable, and are shown in table 2. Radiological findings were available in all cases. Radiographs were negative in 2% of scintigraphically positive bony metastases.

Efficacy and Duration of Palliation

Overall results are indicated in table 3. In group A, 7 of 9 patients (77.8%) showed effective response, 2 cases (22.2%) mild response, and none showed inefficient or excellent response. The therapeutic efficacy was 77.8%. In group B, 4 cases showed inefficient response, 1 case mild (11.1%), 3 cases effective (33.3%) and 1 case excellent relief, with a therapeutic efficacy rate of 44.4%.

Table 4. WBCs and platelet toxicity after therapy

Drug	WBCs				PLTs			
	0	I	II	III	0	I	II	III
¹⁵³ Sm-EDTMP	3	6	0	0	4	3	2	0
Pamidronate disodium	9	0	0	0	9	0	0	0

PLTs = Platelets.

Palliative effect usually started approximately between the 7th and 15th day after administration of ¹⁵³Sm-EDTMP, and between the 3rd and 5th day after therapy with pamidronate disodium. The mean duration of pain relief was 3.5 ± 2.3 months in group A, and 2.5 ± 1.9 months in group B. One patient who underwent only one follow-up visit was excluded from this evaluation. No response and death were considered as the end points of the palliative effect. Recurring pain was usually due to new metastatic sites, as was evident on the bone scans.

Acute Adverse Reactions and Flare Phenomenon

No acute adverse reaction was observed in patients injected with ¹⁵³Sm-EDTMP or pamidronate disodium. However, a transient worsening of painful symptoms (pain flare phenomenon) was observed in 3 of 9 cases (33.3%) after ¹⁵³Sm-EDTMP administration. Most of this transient worsening occurred during the 1st week. The intensity of pain was mild or worsening, and the duration of the phenomenon lasted 3–5 days. Also, 1 case treated with pamidronate disodium experienced transient mild disturbances during relatively rapid administration.

Toxicity

No side effects were reported in the tissues except transient bone marrow suppression (table 4). Toxicity of ¹⁵³Sm-EDTMP affected primarily WBCs and secondarily the platelets. Decrease in WBCs and platelet counts usually began during the 2nd or 3rd week after radiopharmaceutical administration, with a nadir around the 6th–8th weeks and slow recovery, not always complete, in the following 2 months.

If blood counts were not at baseline values 3 months or more after ¹⁵³Sm-EDTMP, toxicity was considered persistent. Most of the patients presented with anemia (Hb baseline values of grade I in 80.5% and of grade $\geq$ II in 14.7%); the levels of Hb were not significantly modified by the administration of ¹⁵³Sm-EDTMP. In general, there

was a transient myelosuppression that was mild and reversible with WBCs and platelets recovering after week 6. Death or severe events resulting from absorbed radiation dose were not reported. No hematological toxicity was noted with pamidronate disodium.

Discussion

¹⁵³Sm-EDTMP

Pain is notoriously difficult to measure objectively. The visual analogue scale is probably the most accurate method to measure pain intensity and frequency, as it is difficult to use in patients with poor compliance [1, 16], who represent the majority in the palliative care setting. The visual analogue scale has been adequately validated and used in a multicenter study of radionuclide therapy in patients with painful bone metastases of prostate cancer [16] and as such was relied upon in this study.

The rate of response to radionuclide therapy of painful bone metastases reported by Dafermou et al. [16] was 60–80%. Our results showed an effective response rate of 77.8%, consistent with the previous report. In addition it showed a mild response rate of 22.2%. If this ‘mild response’ is included, 100% of the patients derived some benefit from the treatment. There was no ineffective or excellent response in group A probably due to the limited number of patients in the study. The therapeutic efficacy of ¹⁵³Sm-EDTMP (77.8%) was greater than that of pamidronate disodium (44.4%) although the latter had 1 case of excellent response. Equally important is the fact that bone imaging was performed during the administration of ¹⁵³Sm-EDTMP because ¹⁵³Sm emits a γ ray, 0.103 MeV, that is also useful for estimating absorbed dose to red marrow and monitoring the therapeutic efficacy.

Hematological toxicity of 62.5% for WBCs and 50% for platelets was observed mainly with ¹⁵³Sm-EDTMP, but it was transient, with a slow recovery. These results

similar to those reported in the literature [1, 15, 16] indicate that ^{153}Sm -EDTMP is a therapeutic agent with less severe side effects than other marrow-toxic therapies. The myelosuppression of ^{153}Sm -EDTMP was slight and temporary. The reduced level of myelotoxicity is a major advantage of bisphosphonates.

Conclusion

The therapeutic efficacy of ^{153}Sm -EDTMP was higher than that of pamidronate disodium (pain relief was maintained for more than 3 weeks), but the incidence of side effects was also higher than that of pamidronate disodium. No marrow toxicity was observed with pamidronate disodium.

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