ORIGINAL ARTICLE

Efficacy of ^{153}Sm-EDTMP on Bone Pain Palliation in Metastatic Patients: Breast and Prostate Cancers

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Abstract

Purpose: This study aimed to evaluate the effect of samarium-153-EDTMP (^{153}Sm-EDTMP) on pain relief bone metastases of Breast Cancer (BC) and Prostate Cancer (PC) patients.

Materials and Methods: Thirty patients aged 40-77 years (62.6±10.2 years) with intractable metastatic bone pain were included in the current study. A checklist of patient information and a standard questionnaire for the assessment of pain and quality of life were completed before and after four and eight week's palliative treatment with 37 MBq/kg of ^{153}Sm-EDTMP. To analyse the data, parametric and non-parametric tests were used in SPSS software.

Results: Twelve females with BC (40%) and 18 males with PC (60%) were included. Four and eight weeks after palliative treatment of ^{153}Sm-EDTMP, the mean pain score reduction and quality of life were statistically increased compared to before the intervention (P-value < 0.05). Notably, the amount of pain reduction in the fourth week was more than in the eighth week; however, the quality of life was better in the eighth week, without significant variation (P-value >0.05). In addition, there was no statistically significant relationship between pain reduction and the type of primary diseases, BC, and PC (P-value >0.05).

Conclusion: The injection of ^{153}Sm-EDTMP had therapeutic efficacy for bone pain palliation in patients with diffuse bone metastases at the end of the 4th and 8th week post-infusion.

Keywords: Breast Cancer; Prostate Cancer; Bone Metastasis; ^{153} Samarium Ethylenediamine Tetra (Methylene Phosphonic Acid).

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1. Introduction

Breast Cancer (BC) and Prostate Cancer (PC) commonly cause bone metastases, and bone pain due to metastases is one of the most debilitating symptoms [1]. These pains often lead to other symptoms such as movement disorders, respiratory failure, fear of death, and anxiety and depression, which can eventually decrease the quality of life [2, 3]. Therefore, controlling bone pain metastases is an effective step. Several therapeutic approaches, such as radiotherapy, chemotherapy, and analgesics are commonly used to treat various diseases. However, they can cause side effects due to a large field of radiation and are ineffective in some advanced disease cases [4,5].

It has been shown that the administration of radiopharmaceuticals emitted beta radiation can be an effective method in the treatment of bone metastases with fewer side effects and with an average response rate of 70% [6]. Generally, treatment with radiopharmaceuticals has several benefits such as reducing pain, increasing the quality of life, reducing the use of painkillers, reducing the need for additional complementary therapy techniques like radiotherapy and chemotherapy, and increasing the prognosis and survival of patients [7]. Studies reported that radiopharmaceuticals would disappear after about 2 to 7 days or even a few months after injection [6,8]. Among the wide range of radiopharmaceuticals used to relieve pain for bone metastases, the physical properties, including their half-life and ability to radiate gamma/beta radiation are of great importance to reducing the pain score. Phosphorus-32 and strontium-89 with a half-life of 12 to 50 days, as well as Samarium-153 (^{153}Sm) and Rhenium-186 with a half-life of 2 and 4 days, respectively, are employed for this purpose.

^{153}Sm is a radiopharmaceutical that emits beta rays with the maximum beta energy of 0.81 MeV and gamma rays with 103 KeV, which are allowed for therapeutic. ^{153}Sm is used in combination with Ethylene Diamine Tetra Methylene Phosphonate (^{153}Sm-EDTMP) [9,10]. This compound accumulates in the skeletal system in proportion to the osteoblastic activity, so that 65% of the absorbed dose of this radiopharmaceutical is absorbed in the skeletal tissue. The aim of the current study was to evaluate the efficacy of bone palliative after treatment with 37 MBq/kg ^{153}Sm-EDTMP radiopharmaceutical in patients with prostate and breast cancer bone metastases.

2. Materials and Methods

The current work was approved by the National Research Ethics Board with registration number "IR.MUBABOL.REC.1399.484". The study was based on questionnaires, and the patients (referred to one Nuclear Medicine center) were informed about the procedure.

2.1. Patients, Inclusion and Exclusion Criteria

Thirty patients with severe bone pain associated with metastasis resistant to analgesics participated in this study. All patients had multiple bone metastases and positive bone scans (based on dual-head SPECT imaging) with areas of abnormally increased radioactive uptake associated with the site of bone pain. Exclusion criteria were pregnant or lactating women, patients with a history of bisphosphonate therapy, chemotherapy or radiotherapy (during 4-6 weeks before ablative therapy), and patients who had received radionuclide therapy for the past 8 weeks. Additionally, the exclusion criteria were individuals with evidence of acute or chronic renal failure, spinal cord suppression, extensive soft tissue metastases, impending pathological fractures, severe anemia (less than 7 g/dL), leukocytopenia (less than 2500/mm^3), and thrombocytopenia (less than 60,000/mm^3).

2.2. Methodology

All patients received an intravenous injection of 1 mCi or 37MBq/kg of ^{153}Sm-EDTMP. This radiopharmaceutical has been prepared by the Atomic Energy Agency of Iran. All executable protocols were performed according to the provider's instructions. Before receiving and injecting radiopharmaceuticals, all patients with 1 liter of intravenous fluid were hydrated, and then kept for 12 hours after treatment and discharged at a distance of 2 m if the radiation exposure reached less than 1 mSv.

2.3. Evaluating the Pain Score and Function

The level of bone pain and general function were recorded using a questionnaire checklist that each patient filled out before radionuclide administration as well as 4 and 8 weeks after treatment. In the checklist, the pain level was recorded in 12 areas of the body

including head and neck, shoulders and clavicle, left and right arms, left and right ribs, spine, lumbar and pelvis, left and right femurs, and left and right legs. The level was performed based on the visual analog scale (VAS), ranging from 0 (painless - no discomfort) to 10 (worst pain - worst discomfort), to measure the pain index in subjects. The validity of this questionnaire was confirmed through content validity and its reliability was obtained using Cronbach's alpha coefficient as 91% [11].

One of the main scales used to assess the functional status and effectiveness of different therapies is Karnofsky Performance Scale Index, used in the present study [12]. This tool has three sections and 11 terms that measure the level of activity and performance status from zero to 100 points. This is how the tool was scored; a score of 80-100 can perform normal activities without the need for special care, a score of 50-70 is the inability to perform activities (needs help to various degrees but can meet personal needs), a score of 0-40 is unable to take care of itself and need for care in medical centers [13].

2.4. Statistical Analysis

After collecting and registering the data, they were plugged into SPSS software (version 16, IBM, USA). The normality of the data was assessed by Kolmogorov-Smirnov (K-S) statistical test. For parametric tests, T-test and ANOVA, and for the non-parametric tests, Mann Whitney were used. The significance level of the tests was considered to be 5%.

3. Results

Thirty patients with an average age of 62.6 ± 10.2 years (40 to 77 years), including 12 females (40%) with BC, and 18 males (60%) with PC participated in the current study.

Figure 1 shows the mean values of pain score before ^{153}Sm-EDTMP injection, four and eight weeks after administration. Also, the parameter of patients' quality of life, which was obtained from the Karnofsky questionnaire, was specified at the mentioned times.

As can be seen in Figure 1, four and eight weeks after the intervention, the mean pain score parameter improved statistically compared to before the intervention (P-value <0.05). Comparing the pain score between four and eight weeks after radionuclide palliative treatment, the mean pain score increased slightly (not significant) at eight weeks. The quality of life parameters of patients, both four and eight weeks after the intervention, showed a statistically significant improvement (P-value < 0.05). In detail, the amount of pain relief was greater in the fourth week than that in the eighth week (26.6% vs. 23.2%). The percentage of quality of life in the eighth week was higher than in the fourth week (13.2% vs. 10.5%), which indicates that the value of this parameter has improved over time.

Table 1 depicts the pain intensity of patients at different times by the type of disease (BC and PC) and determines that there is no statistically significant relationship between pain reduction and the type of primary disease (P-value <0.05).

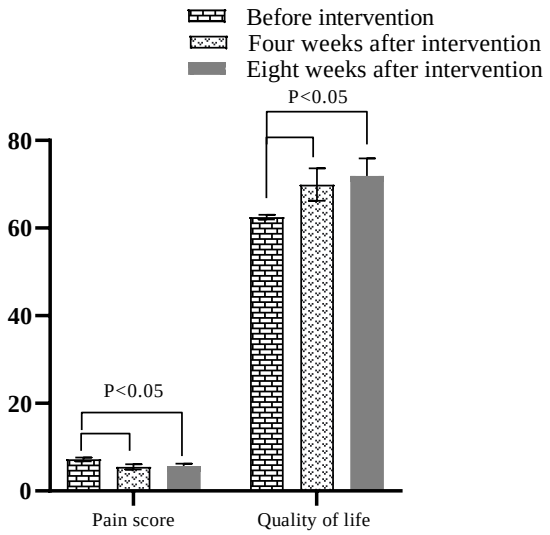

Figure 1. Mean values of pain score and quality of life parameter of patients before, four, and eight weeks after ^{153}Sm-EDTMP injection

4. Discussion

Bone is the most common site of metastasis in BC and PC. Beta-emitting agents, with fewer side effects, are commonly used to control/treat metastatic bone pain.

Among the other agents, ^{153}Sm-EDTMP shows less blood toxicity and high efficacy in pain relief. This agent is absorbed after injection into bone-forming areas by binding to hydroxyapatite, and the unabsorbed drug is rapidly excreted [12]. Inhibition of lymphocyte-

Table 1. The effectiveness of radionuclide therapy in reducing the pain score and quality of life according to the type of disease (BC and PC)

Statistics	Type of disease	Before intervention	Four weeks after the intervention	P-value	Eight weeks after intervention	P-value
Pain score	Breast cancer	7.16±0.3	5.65±0.5	0.3	5.9±0.3	0.07
	Prostate cancer	7.33±0.5	5.42±0.6	0.3	5.55±0.5	0.07
Quality of life of patients	Breast cancer	63±3.1	68.91±3.9	0.2	72.5±2.9	0.5
	Prostate cancer	62.11±3.2	70.55±3.4	0.2	71.5±4.5	0.5

associated cytokines and changes in the activity of osteoblasts and osteoclasts are mechanisms of pain relief after consumption [14]. Different parameters are used to evaluate the effectiveness of treatment with beta-emitting agents, in a way that, the pain scores and quality of life of patients are the most common variables. The use of pain score indicators is more of a mental measure, and the quality of life is an objective criterion.

In the current study, we have considered only ^{153}Sm-EDTMP because, in several studies, it was reported that ^{153}Sm-EDTMP palliation effectiveness is similar to the other agents like ^{177}Lu-EDTMP. For instance, Sharma *et al.* [15] compared the therapeutic efficacy of ^{153}Sm-EDTMP and ^{177}Lu-EDTMP in pain palliation in 30 BC/PC patients with skeletal metastases. They assessed 20 and 10 patients randomly for treatment with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP, respectively, using a fixed dose of 37 MBq/kg body weight. The pain reduction score was assessed clinically during 1, 3, 6, and 8 weeks. They have declared that both radionuclides offer an effective and comparable therapeutic which can be used interchangeably as per availability for bone pain palliation. In another study by Taheri *et al.* [10], they reported similar results following the intervention at 2, 4, 6, and 12 weeks using the two radiopharmaceuticals (^{153}Sm-EDTMP and ^{177}Lu-EDTMP).

In addition, other related studies focusing on 153Sm-EDTMP administration, for example, Kolesnikov-Gauthier *et al.* [16] assessed the efficacy of 153Sm-EDTMP for breast, prostate, lung carcinoma, or other cancers in a clinical setting. Four parameters, including VAS for pain assessment, sleep disturbance related to pain, a dose of analgesic medication, and the following question "Do you think you obtained a benefit from treatment?" were collected at each visit (before and after treatment). They reported that 153Sm-EDTMP therapy was a more effective supportive treatment in patients who suffer from bone metastases, especially in patients with BC or PC compared with other types of primary cancers. Dolezal *et al.* [17] have shown that the use of ^{153}Sm-EDTMP relieves varying degrees of pain in 72 BC patients with bone metastases. In another study by Turner *et al.* [12], they determined that pain relief was observed 4 weeks after 153Sm-EDTMP administration, and the maximal clinical response occurred 6 weeks after intervention. Additionally, in Beiki *et al.'s* study [18], 16 patients with diffuse and painful bone metastases were injected with ^{153}Sm. A significant reduction in pain score was observed in 69% of patients at the end of the second week, and 75% of patients at the end of the eighth week. The patients' quality of life clearly improved after treatment, and opioid and analgesic use significantly decreased within eight weeks of treatment. Sinzinger *et al.* [13] showed that the use of different doses of samarium (0.5 and 1 mCi/kg) could produce various responses. They have used the Vienna protocol; patients are treated repeatedly with ^{153}Sm-EDTMP intravenous at various times, which causes more pain reduction rate. In detail, in Vienna protocol, treatment is performed on an outpatient basis and planned for 1 to 5 sessions at 3-month intervals, 6 to 10 sessions at 6-month intervals, 11 to 15 sessions at 9-month intervals, and then at 12-month intervals. A prerequisite for such a protocol is the repeated administration of ^{153}Sm-EDTMP, which certainly takes more time and money and will not be cost-effective in countries with moderate to poor health care. Our study showed that the average amount of patients' pain and their quality of life reached a tolerable level at 4 and 8 weeks after ^{153}Sm-EDTMP administration in BC and PC, which had good agreement with the previous investigations. The differences in the levels of palliation with the other related studies could be related to different times of interventions and doses.

In the present study, a constant dose of 37 MBq/kg was used because, based on previous clinical studies, it has better therapeutic efficacy and safety [19]. In

addition, it has been reported that even with high doses of ^{153}Sm-EDTMP (e. g. up to 111 MBq/kg), the pain relief response at 40-50 days after treatment was not significantly different. Furthermore, high doses can increase bone marrow suppression [13], as well as Turner *et al.* [12] determined that there is no dose-response relationship for pain relief.

Vigna *et al.* [20] reported that the cumulative activity of ^{153}Sm-EDTMP administered to bone marrow in patients with PC (in which osteoblastic bone metastases) is significantly higher than that of BC (where bone metastases are mostly an osteolytic component or a mixture of lytics and blasts). Therefore, it can be expected that the rate of pain relief response in patients with PC is higher than in BC. However, our finding did not show any differences in the response rate, which is consistent with a previous result [18].

There are several limitations in the current study, such as access to patients at intervals of four and eight weeks after the intervention and the lack of cooperation of some patients to collect the questionnaires correctly. For future research, it is suggested that researchers examine the effect of higher doses of samarium on pain control, investigate the blood factors (hemoglobin, neutrophils, WBC, and platelet counts), and compare it with other similar radiopharmaceutical findings.

5. Conclusion

Based on our cross-sectional questionnaire study, it was demonstrated that a 37 MBq/kg injection of ^{153}Sm-EDTMP (at the end of the fourth and eighth weeks) significantly reduces pain and improves the quality of life in patients with diffuse bone metastases of BC and PC. In which the highest pain relief occurred after the fourth week (26.6% reduction), and the quality of life occurred after the eighth week (13.2%).

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