Original Article

Systemic Radionuclide Therapy of Painful Prostate Cancer Bone Metastases With Samarium-153-EDTMP

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Abstract

Most patients with prostate cancer (PC) will develop painful bone metastases, which alters their quality of life. **Objective**: This study aimed to evaluate the efficacy and toxic hematological profile of samarium for the treatment of PC metastases' bone pain. **Methods**: Twenty-nine PC patients (median age: 69 years, range: 46-84; Gleason score equal to or higher than 7 in 66.7% and under 7 in 33.3% of patients presenting multiple painful bone metastases were treated with intravenous injection of ^{153}Sm-EDTMP. Response to treatment was defined as either a reduction of at least 25% in patient's pain score, using a 0 to 10 scale (score 0: no pain, score 10: maximum pain), or in daily analgesic dosage. Complete blood counts were performed before ^{153}Sm–EDTMP administration and 4 and 8 weeks after treatment with the purpose of evaluating hematological side effects of the agent. **Results**: Twenty-five patients (86.2%) responded to treatment (median time: 1.5 month, range: 1.0 to 2.0 months). A reduction equal to or higher than 25% in post-treatment values compared to baseline values was seen in hemoglobin (Hb) of 3 (12.0%) patients, in leukocytes (Lo) of 16 (64.0%) patients, and in platelets (Pl) of 19 (76.0%) patients. Hb under 10g/dl, Lo under 2.0x10^3/ul, and Pl under than 50.0x10^3/ul were seen in 7 (28.0%), 3 (12.0%) and 2 (8.0%) out of 25 patients analyzed after ^{153}Sm–EDTMP, respectively. No infectious or bleeding episodes were seen in any patient during the study. **Conclusion**: ^{153}Sm-EDTMP is effective for acute control of PC patients' bone pain. However, additional studies with bone marrow assessment before and after ^{153}Sm–EDTMP are necessary to clarify the origin of cytopenias found in our cases.

Keywords: Prostate cancer. Bone metastasis. Bone pain. ^{153}Sm-EDTMP. Samarium.

Introduction

More than 50% of patients with prostate cancer (PC) will develop painful bone metastases.[1,2] The purpose of treating bone metastases is to relieve pain, reduce use of analgesics and maintain motion.[1] The use of high doses of opioid causes severe side effects, including nausea, vomiting, constipation and sedation, besides decreasing quality of life.[3]

Radiotherapy helps to reduce opioid doses.[3] External beam irradiation is highly effective for bone pain relief and may occasionally result in reduction of tumor mass,[1,4] but it should not be used in multifocal metastases.[4,5] Hemibody radiation is usually indicated as a therapy for these cases, but it is associated with an unpredictable degree of toxicity, particularly when the lungs and the gastrointestinal tract are irradiated.[4]

Radionuclide therapy for pain caused by bone metastases seems to be a good option for treatment of

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multifocal metastases. Radionuclides are deposited in the metastatic lesion at a rate of 17:1 in comparison with normal bone, so radiation to the normal bone marrow (BM) outside the lesion is very low.[6] BM suppression seems to be mild and reversible after 6-8 weeks of treatment with radionuclides.[7] The interest on this issue has recently increased after the description of improvement in survival of advanced PC patients with myelotoxic regimens, such as docetaxel with prednisone or estramustine,[8,9] which seem to require a BM with good functional reserve of hematopoietic cells. Therefore, the aim of this study was to evaluate the efficacy and safety of samarium-153-EDTMP (^{153}Sm-EDTMP) for treating PC metastases' bone pain.

Materials and Methods

Patients

Twenty-nine male patients with painful bone PC metastases were enrolled in the study after Informed Consent was given. Their pertinent clinical and hematological data are presented in Tables 1 and 2. Median age was 69 years (range: 46-84 years). Gleason score was equal or higher than 7 in 14 patients (66.7%) and under 7 in 7 patients (33.3%), but was not available in the remaining 8 patients enrolled in the study. All patients were refractory to androgen deprivation with cyproterone and flutamide. No patient was under second-line hormonal therapy with estrogen, glucocorticoid or ketoconazole. Patients previously treated with radiotherapy for pain of bone metastasis and those under platelets antiaggregant or anticoagulants were excluded from the study. Four (cases 4, 10, 20 and 29) and 9 patients had received the last dose of mitoxantrone or biphosphonate, respectively, at least three months before entering in the study. Pain intensity was quantified by a 0 to 10 numeric scale (score 0: no pain, score 5: moderate, score 10: maximum pain), based on a arbitrary questionnaire involving the following information: if no pain was referred (score 0), if the patient was still walking (score 1 to 4), if the patient used to wake up because of pain (score 5 to 9), and if the patient needed help for eating, walking and personal hygiene (score 10: maximum pain). The questionnaire was applied to each patient enrolled in the study by one of the authors (ECSCE) on the day of ^{153}Sm–EDTMP infusion and 4 and 8 weeks after the infusion of the radionuclide. All patients had bone metastases detected by a bone scan with 99mTc-MDP (Figure 1A) and presented Hb higher than 5.0g/dl, Lo equal to or above 2.0x 10^3/ul, and Pl equal to or above 50.0x10^3/ul.

Patients received only one intravenous injection of 37 to 59.2MBq/Kg (1.0 to 1.6mCi/kg) of ^{153}Sm–EDTMP. Twenty-six patients (89.7%) received 37 MBq/Kg, 2 patients (6.9%) received 44.4MBq/kg, and 1 patient (3.4%) received 55.5MBq/Kg. Whole body images in the anterior and posterior positions were obtained 4 hours after dose administration. Two nuclear medicine physicians separately read the images of each patient.

Response to treatment was arbitrarily defined as a reduction of at least 25% in patients' pain score or in daily analgesic dosage used. Complete blood count (CBC) was performed before ^{153}Sm-EDTMP administration and 4 and 8 weeks after treatment. Reduction in Hb level, and Lo and Pl counts after treatment was considered significant if equal to or 25% higher than baseline values.

Table 1 - Distribution of 29 metastatic prostate cancer-hormone refractory patients according to treatments received before ^{153}Sm-EDTMP administration

Treatment	Patients
Androgen deprivation therapy	
Orchiectomy	24
Lutinizing hormone reducing therapy	5
Antiandrogen therapy	
Flutamide	6
Cyproterone	13
Cyproterone followed by flutamide	10
Chemotherapy	
Mitoxantrone plus predinisone	4
Biphosphonate	
Clodronate	5
Zoledronic acid	1
Clodronate followed by zoledronic acid	3

Results

All patients had a good uptake of ^{153}Sm-EDTMP by bone metastases (Figure 1B). Eighteen (62.1%) patients were under morphine as therapy for bone pain; anti-inflammatory and/or codeine or tramadol was given to the remaining 11 (37.9%) patients with bone pain. Median pain score was 8.0 (range: 2 to 10) before and 3.5 (0 to 4) after 8 weeks of ^{153}Sm-EDTMP ($p < 0.001$). Twenty-five out of 29 (86.2%) patients were considered responders: all of them achieved reduction of at least 25% in pain score and 4 (13.8%) patients experienced an additional reduction of at least 25% in daily analgesic dosage.

Table 2 - Distribution of 29 metastatic prostate cancer-hormone refractory patients by age, Gleason score, and baseline blood counts and blood counts performed four and eight weeks after the ^{153}Sm-EDTMP treatment

Patient	Patient Characteristics		Blood Count								
			Baseline			4th week			8th week		
	Age	GS	Hb (g/dl)	Lo (x10^3/ul)	Pl (x10^3/ul)	Hb (g/dl)	Lo (x10^3/ul)	Pl (x10^3/ul)	Hb (g/dl)	Lo (x10^3/ul)	Pl (x10^3/ul)
1	77	8	10.5	3.7	96.0	10.8	2.9	96.0	11.8	3.0	85.0
2	81	6	13.0	8.9	365.0	11.6	9.4	196.0	12.4	6.5	372.0
3	73	10	13.4	12.7	469.0	11.5	5.3	180.0	11.6	8.0	360.0
4	71	8	7.5	3.7	84.0	6.6	1.6	17.0	6.7	1.9	22.0
5	84	NP	11.8	6.1	202.0	13.1	4.7	160.0	12.6	4.1	127.0
6	76	8	7.9	7.1	137.0	NP	NP	NP	NP	NP	NP
7	55	8	10.1	4.7	349.0	9.7	3.8	299.0	8.6	5.4	152.0
8	74	6	8.9	11.8	583.0	NP	NP	NP	NP	NP	NP
9	51	NP	10.4	6.9	260.0	10.1	4.9	232.0	10.0	5.8	191.0
10	69	NP	12.7	9.4	204.0	NP	NP	NP	11.5	9.7	199.0
11	50	8	11.4	7.0	221.0	10.8	4.2	200.0	11.7	7.5	218.0
12	63	8	11.0	3.6	81.0	11.1	2.8	147.0	9.5	2.3	13.0
13	65	6	9.0	10.0	290.0	10.0	1.9	56.0	NP	NP	N4.0P
14	69	NP	9.8	5.8	141.0	NP	NP	NP	NP	NP	NP
15	71	9	6.2	7.2	275.0	6.0	2.9	177.0	4.8	2.9	110.0
16	46	9	12.5	4.3	174.0	11.1	2.2	83.0	11.1	2.3	83.3
17	68	3	12.5	7.5	269.0	12.4	6.2	148.0	13.2	6.2	207.0
18	78	9	11.7	5.2	227.0	12.2	4.5	106.0	10.9	4.4	262.0
19	79	9	12.5	10.0	191.0	10.9	3.6	61.0	11.4	2.6	74.9
20	73	6	13.1	13.5	240.0	12.2	3.6	118.0	11.5	4.9	187.0
21	79	8	9.5	5.5	181.0	6.6	1.5	56.0	NP	NP	NP
22	76	NP	10.0	7.7	214.0	9.3	4.0	282.0	NP	NP	NP
23	63	NP	9.5	4.5	343.0	9.2	2.8	53.0	9.1	2.4	132.0
24	68	7	10.6	16.4	96.0	7.0	5.6	44.0	NP	NP	NP
25	72	6	13.5	6.3	240.0	12.5	3.6	93.0	13.4	3.0	141.0
26	61	6	11.7	4.7	224.0	5.3	2.5	93.0	5.9	3.3	159.0
27	52	7	6.7	3.9	200.0	9.4	3.0	109.0	9.4	5.2	199.0
28	67	NP	10.2	4.6	31.4	NP	NP	NP	NP	NP	NP
29	65	NP	11.6	17.2	110.0	NP	NP	NP	11.4	14.3	111.0

GS: Gleason score; Hb: hemoglobin; Lo: leukocyte; Pl: platelet; NP: not performed

Seven out of 29 (24.1) patients found complete remission of bone pain with low doses of anti-inflammatory or codeine, but refused complete withdrawn of analgesics. No difference in response to ^{153}Sm-EDTMP was seen in patients treated with morphine or in those treated with codeine or tramadol, as well as in patients previously treated with chemotherapy or untreated patients. Similar uptakes of ^{153}Sm-EDTMP by bone metastases and relief of bone pain with therapy were seen in patients previously treated or untreated with biphosphonates. Median duration of response to treatment during the 2 months of observation of each patient enrolled in the study was 1.5 months (range: 1.0 to 2.0 months).

At the study entry, anemia was identified in all

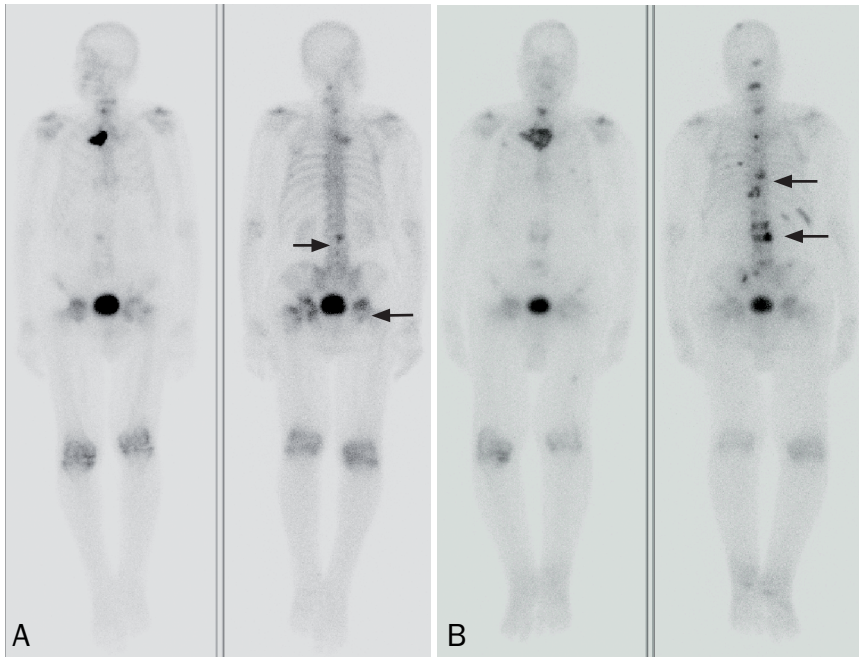

Figure 1 - A: bone metastases of prostate cancer (arrows) on bone scan with 99mTc-MDP. B: good uptake of 153Sm-EDTMP by the bone metastases (arrows).

patients, leukopenia in 5 patients and thrombocytopenia in 5 patients. CBC was performed after 4 and 8 weeks of treatment in 23 and 21 patients, respectively. Hematological toxicity was not evaluated in 4 patients. Variations in Hb levels and Lo and Pl counts after the treatment are presented in Table 3. The most severe variations were seen in counts of Lo and Pl. Reduction higher than 25% in post-treatment values compared to baselines values was seen in Hb of 3 (12.0%) patients, in Lo of 16 (64.0%) patients, and in Pl of 19 (76.0%) patients. Variations in Hb level and Lo and Pl counts were detected at 4 weeks after treatment in 3 patients, in 15 patients and in 13 patients, respectively. The remaining patients had reductions in hematological parameters detected at 8 weeks after ^{153}Sm-EDTMP. Hb under 10 g/dl, Lo under $2.0x10^3$/ul, and Pl under than $50.0x10^3$/ul were seen in 7 (28.0%), 3 (12.0%) and 2 (8.0%) out of 25 patients, respectively, analyzed after treatment, being detected predominantly in patients with previous cytopenias. No infectious or bleeding episodes were seen in any patient during the study.

Discussion

About 60% patients with metastatic cancer, including PC patients, suffer from bone pain, which may limit the individual's autonomy and social life.[10] Patients with advanced PC usually present multiple bone metastases. External beam radiotherapy can reach high rates of bone pain relief but this method cannot be used to treat multiple lesions.[11] Medical therapy may also not be effective for patients with disseminated bone metastases.[11]

Therapy with radionuclides, such as ^{153}Sm–EDTMP, deposits high doses of radiation in bone lesions compared to normal bone,[12] and are therefore of great interest in the treatment of disseminated metastatic bone disease.[1,13-15]

Almost 90% of our patients referred significant decreases in bone pain after treatment with ^{153}Sm-EDTMP, in agreement with previous reports in the literature.[4,15,16-21] We were not able to evaluate total duration of response to treatment in our patients, but relief of bone pain for 1 to 2 months characterized the responders. Duration of response to ^{153}Sm-EDTMP treatment ranging from 4 to 35 weeks was also reported.[13]

The mechanism responsible for pain relief has not been entirely elucidated. Intra-medullar pressure reduction does not account for the rapid pain relief that may occur a few days after radionuclide administration, since the absorbed radiation dose delivered has not yet destroyed a sufficient amount of tumor cells.[2] A possible explanation for this finding would be that tumor necrosis induced by radiation would result in the death of cells which participate in the inflammatory and immunologic processes, consequently reducing the release of

Table 3 - Median reduction in hemoglobin levels and leukocytes and platelets counts of 29 patients with metastatic prostate cancer-hormone refractory after four and eight weeks of treatment with ^{153}Sm-EDTMP

Blood count	4th week			8th week		
	Min	Med	Max	Min	Med	Max
Hb (g/dl)	-2.7	0.4	6.4	-1.3	0.1	5.8
Lo (x10^3/ul)	-6.2	2.0	9.9	-4.6	1.3	8.6
Platelets (x10^3/ul)	-68.0	98.0	290.0	-35.0	65.0	211.0

Min: minimum; Med: median; Max: maximum; Hb: hemoglobin; Lo: leucocyte; Pl: platelet

bradykinines, a tumor necrosis factor, prostaglandins and interleukins, substances known to increase pain.[2,3]

We found a significant acute reduction in Hb level and Lo and Pl counts in 12%, 64% and 76% of our patients, respectively. Severe cytopenias, defined as Hb level below 10.0mg/dl, Lo count below 2.0x10^3/ul and Pl count below than 50.0 x 10^3/ul, were found in less than 30% of patients enrolled in study, in agreement with previous reports.[4,13] No infectious and bleeding episodes were seen in any of our patients. It is known that one of radionuclides therapy side effects is mielotoxicity,[17] but apparently without clinical complications,[4,13] as seen in our study. In addition, severe cytopenias were seen in our study predominantly in patients who presented previous cytopenias. Since no BM analysis was performed in our patients before the study entry and after ^{153}Sm–EDTMP administration, we cannot attribute hematological abnormalities only to samarium-153 effects. BM infiltration by neoplastic cells of progressive PC or BM lesion by previous exposure to mitoxantrone could have contributed, at least in part, to the cytopenias found in our cases. Besides, we did not evaluate patients after the end of this study, and therefore were not able to describe the duration of the hematological abnormalities. BM suppression seems to be reversible after 6-8 weeks of treatment with radionuclides.[7]

More recently, an improvement in survival of advanced PC patients with myelotoxic regimens, docetaxel with prednisone or estramustine,[8,9] was seen in two large phase III trials. However, an unmanageable life-threatening myelotoxicity of these regimens in patients with ^{153}Sm-EDTMP-related hypocellular BM might hinder patients' effective treatment when radionuclide therapy really causes severe and chronic cytopenias.

We conclude that ^{153}Sm-EDTMP is an effective treatment for relief of bone pain of metastases of most PC patients, but additional studies with assessment of BM cellularity before and after treatment by biopsy and magnetic resonance, as already done by our group in hematological diseases,[22] must be conducted to clarify the acute and chronic side effects of samarium-153 on hemopoiesis.

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