

Metastatic Bone Pain Management with Radioactive Isotopes

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ABSTRACT

Pain is the commonest clinical manifestation of bone metastases. Its treatment is palliative in nature, and consists of chemotherapy, radiotherapy, hormonotherapy, diphosphonates, and drug therapy (i. e., opiates). Radioactive isotopes represent an appealing alternative to conventional treatment modalities. Among the different types of isotopes, wide clinical experience with ^{153}Sm has been obtained in this laboratory. In the present study, 94 patients (mean age = 65 years), who had been diagnosed of having breast, prostate and other malignant tumors, were evaluated. These patients were treated with 37 MBq/Kg ^{153}Sm -EDTMP. All of them complained of bone pain and had scintigraphic evidence of metastatic bone dissemination. Treatment efficacy was evaluated both objectively and subjectively. Eighty-five per cent (85%) of the patients reported pain relief, and analgesia was reduced by 55%. Twenty-two per cent (22%) had a complete response. Bone marrow toxicity was not a concern, with mild transient hematologic derangements in 30% of the patients. It was concluded that ^{153}Sm -EDTMP results in relief or cessation of metastatic bone pain in a majority of patients.

Key words: Metastatic bone, ^{153}Sm -EDTMP

INTRODUCTION

Bone metastases are the commonest contributor to morbidity in cancer patients, especially in those with breast and prostate cancer^{1,2}. Metastatic bone dissemination give rises to pain, with pain being the most frequent clinical manifestation from bone metastases³. It is estimated that about 75% of patients with advanced cancer report pain at some time point along course of their disease⁴.

Metastatic bone pain results from the increment in size of bone metastases and destruction of bone tissue by osteoclasts, which, in turn, result in increased osteolytic activity. This gives rise to the occurrence of a certain number of substances such as prostaglandins, bradykinin, citokines, tumor

growth factors, tumor necrosis factor, platelet growth factor, potassium ions, and osteoclast triggering factors^{5,6,7,8}. All these substances are associated with nerve end sensitization at the periostium in response to chemical and thermic stimuli, whereby the neuron membrane threshold decreases and peripheral nociceptive receptors are stimulated. Since these receptors are usually silent, the above substances cause primary hiperalgesia^{9,10,11,12}.

Metastatic bone pain is somatic in nature¹³. Because of the preexisting attendant bone destruction, bone metastases may cause pathologic fractures, which, in turn, increase bone pain. On the other hand, bone metastases result in pain activated by movement of the bones involved. Of

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note, the psychological and emotional component of metastatic bone pain should also be borne in mind¹⁴.

Metastatic bone pain is associated with a major reduction in patients' life quality. Its treatment is palliative in nature, the major aim not being complete eradication, but rather relief. A multidisciplinary team (i. e., Departments of Medical Oncology, Urology, Radiation Therapy, Surgery and Nuclear Medicine and Palliative Care Unit) should be involved in metastatic bone pain management.

Classically, metastatic bone pain has been successfully treated by chemotherapy, hormonotherapy, radiotherapy, diphosphonates, and drug therapy (i.e., opiates). Currently, radioactive isotopes are also favored as a treatment modality for metastatic bone pain.

Chemotherapy, with the use of tamoxifen, can reduce tumor size, thereby relieving bone pain in most cancer patients. Its major drawback is bone marrow toxicity¹⁵.

Hormotherapy is effective only for metastatic bone pain patients with breast or prostate cancer. However, the pain may become refractory to this kind of treatment¹⁵.

Radiotherapy is usually the first-line treatment modality for focal lesions. The radiotherapist may achieve complete pain control in 50% of the patients, and pain control duration is approximately 3 months¹⁶. Radiation therapy results in decreased inflammation and lesion size. However, radiotherapy efficacy is often limited by the inability to deliver the scheduled dose because of the attendant toxicity to adjacent organs.

Diphosphonates are especially efficient for breast cancer-associated metastatic bone pain, and allviate the pain through their osteoclast inhibitory action¹. First-line drug therapy modalities for metastatic bone pain include opiates, which initially control pain. They are associated with important adverse effects, and may cause tolerance¹⁸. Radiopharmaceuticals are currently an appealing alternative for standard metastatic bone pain treatment modalities.

TREATMENT OF METASTATIC BONE PAIN WITH RADIOACTIVE ISOTOPES

In patients with advanced cancer in whom both radiotherapy and hormonotherapy fail (as far as radiotherapy is concerned, this failure results either because the patient has already been treated

or it is not indicated because the patient presents múltiple metastatic bone dissemination), drug therapy is not sufficiently efficient for palliative care because patients often develop tolerance or adverse effects that are unacceptable. In these cases, systemic coadjuvant treatment with radioactive isotopes may be an option.

Before initiating treatment with radioactive isotope, the patient should be evaluated to determined that the pain is occurs in the bone and cannot be explained by other causes. Radioactive isotopes have been used for metastatic bone pain palliation for more than 50 years. The isotope first used was phosphorus (³²P) in the form of sodium phosphate¹⁹. Its use in clinical practice is now discouraged because it is associated with severe hematologic severity.

In the recent 15 years, an upsurge of the interest in radioactive isotopes as an alternative treatment modality for metastatic bone pain palliation has been witnessed because, currently, many isotopes are known that bind to bone structures and exert their therapeutic action locally. The characteristics of the most relevant radioactive isotopes used for metastatic bone pain treatment^{20,21} are presented in Table 1.

The ideal isotope to be used for metastatic bone pain is the one that is a β -emissor and able to be taken up by metastases, so that high doses will be reached locally with minimal involvement of adjacent tissues. It should also selectively exert a cytotoxic effect on metastases by acting at peripheral nerve ends, where inflammatory cells, tumor cells and cells with immunity activity and chemical substances modulating the pain accumulate²². It is necessary to achieve a rapid soft tissue depuration and a peak energy exceeding 0.8 MeV and lower than 2 MeV²³.

Renium (¹⁸⁶Re)²⁴ and tin (^{117m}Sn)²⁵ are not included in the present review on radioactive isotopes for metastatic bone pain management since they have not been commercialized as yet in Spain. Therefore we lack clinical experience with these isotopes.

STRONTIUM-89

Basically, in the 90's in Spain, isotope-based metastatic bone pain management was achieved with strontium (⁸⁹Sr) (commercially known as Metastron). It is a pure β -emitting isotope based on ⁸⁹Si^{26,27,28,29} chloride. From a chemical point of

view, it is similar to calcium; thereby it fixes on bone areas in which the maximum calcium absorption occurs. Bone uptake is proportional to the bone regenerative activity, so that uptake peaks in the most osteogenic sites. Peak and mean energy are 1.46 MeV and 0.58 MeV, respectively, with a soft tissue penetration range of 2.4 mm. Between 30 and 40% of the administered dose is excreted in the urine within 48 hours, with the remaining dose being taken up by the bone. Biological half-life in metastases is somewhat longer than 50 days. Biological half-life in the healthy bone is 14 days³⁰. The use of this isotope was traditionally limited to metastatic bone pain from prostate cancer. Our clinical experience consists of only 15 patients. All these patients were given each a single dose of 148 MBq. One patient had a complete response. In 7 patients, response was partial, with different degrees of pain relief. Six patients did not have any pain palliation, and one could not be evaluated. In patients who positively responded to ⁸⁹Sr treatment, improvement started between 20 and 40 days, with a mean duration of about 4 months.

SAMARIUM-153

Samarium-153 (¹⁵³Sm) is the isotope with which the widest clinical experience in the field of metastatic bone pain has been obtained in this laboratory. In Spain, it was commercialized in the year 2000. ¹⁵³Sm has a number of advantages over ⁸⁹Sr. It is belief of the authors that ¹⁵³Sm is the most suitable isotope currently available for metastatic bone pain management.

It is a sodium salt composed of a radioactive complex consisting of samarium bound to leixidronam

(ethylenediaminetetramethylenephosphonate [EDTMP]). It is commercialized as Quadramet³¹.

The physical half-life is 46.3 hours. It emits β particles, with peak energies of 810 (20%), 710 (50%), and 640 KeV (30%). Mean β emission is of 233 KeV, with a peak soft tissue penetration range of 3.1 mm, and a therapeutic bone penetration range of 1.7 mm^{32,33}. In addition, it emits γ photons, with a energy of 103 KeV (29%)^{31,33}.

Lexidronam shows a high affinity for bone tissue, this being similar to that of technetiated agents (e. g., diphosphonates) used for conventional bone scintigraphy. These pharmacokinetic features make ¹⁵³Sm bound to EDTMP useful for pain from

bone metastases³⁴. Thus, Lexidronam concentrates in sites with bone metabolic activity in both osteoblastic and osteolytic lesions, that is, in sites wherein there exists a high bone turnover, with a relationship of healthy bone to lesion equal to that of ^{99m}Tc-diphosphonates. Therefore, the agent can be specifically taken up by bone metastases, with a concentration of the metastases to that within the healthy bone of 5/1^{35,36}.

OUR CLINICAL EXPERIENCE

¹⁵³Sm is undoubtedly indicated for palliative metastatic bone pain treatment in patients with osteoblastic bone metastases, like those seen in prostate cancer, and in those presenting osteolytic metastases with a osteoblastic component, as is the case in many breast cancer patients. However, ¹⁵³Sm treatment should not be started if metastasis uptake of technetiated agents (i.e., those routinely used for bone scintigraphy) is not objectively visualized.

Herein, the clinical experience with Quadramet at the Department of Nuclear Medicine of La Paz University Hospital (Madrid, Spain) from November, 2000 through May, 2005 is reported. Within this period, 113 doses of ¹⁵³Sm-Lexidronam to a total of 103 patients were administered.

MATERIALS AND METHODS

Ninety-four patients (52 males and 42 females), with ages ranging from 35 to 85 years (mean age: 65 years) were evaluated. Of these 94 patients, nine received two doses, and one (a female patient with breast cancer) received three doses. The patients had been diagnosed as follows: 43, prostate cancer; 42 breast cancer; 3, bladder cancer; 1, cancer of unknown origin; 1, lung cancer; 1, chordoma; 1, pancreatic cancer; 1, head and neck cancer; and 1, pheochromocytoma.

Before initiating treatment, all patients were submitted to scintigraphy, which showed evidence of metastatic bone dissemination (Fig. 1). Bone pain was significant in all patients. In fact, the vast majority was in the level 2-3 of the World Health Organization (WHO) Analgesia Scale. All patients had a life expectancy of at least 4 months. The remaining inclusion criteria were: platelet count equal to or greater than 85,000; hematocrit exceeding 8,5 g/dl; blood white cell count equal or

greater than 3,200; serum bilirubine level not exceeding 2 mg/dl; and serum creatinine level lower than 2 mg/dl. Also, patients were required not to have received chemotherapy, radiotherapy or hormonotherapy within six weeks before initiation of treatment. In the case of child-bearing-age women, a negative pregnancy test was required. Obviously, patients who are known to be EDTMP-hypersensitive should be excluded.

¹⁵³Sm-Lexidronam administration was performed according to a protocol previously developed at the Department of Nuclear Medicine. The protocol established the following actions: informed consent signed by all patients participating in the study, admission to the rooms set aside for endometabolic treatment so that adequate rules for radioprotection be adhered to, appropriate patients' hydration, and treatment initiation. Each dose of 37 MBq/kg was slowly injected (total dose range: 1,480-3,811 MBq; mean total dose: 2,406 MBq). In the case of patients receiving more than one

dose, the second dose was given between 13 weeks and 1 year (mean interval: 7 months and a half). Total dose number was between 3,145-5,550, and mean total dose number was 4,694. As established in the protocol, urine samples were collected 4-6 hours after treatment. Five patients needed a bladder catheter. Virtually all patients had a whole-body scintigraphy performed 4-6 hours after ¹⁵³Sm-Lexidronam (Fig. 2).

Patients were followed up between 2 and 24 months (mean follow-up: 14 months). On follow-up visits, clinical and laboratory (i.e., platelets, blood white cells, hemoglobin, creatinine, etc) data were collected to assess potential treatment-related toxicity. Pain severity was evaluated based on analgesia requirements according to WHO Analgesia Scale, and patients' health status was evaluated according to the Karnofsky scale. However, the patients' subjective assessment of pain was emphasized.

Table 1 - Radioactive isotopes used for metastatic bone pain management.

ISOTOPE	EMISSION	MEAN HALF-LIFE	MEAN.β ENERGY	SOFT TISSUE PENETRATION
Phosphorus (³² P)	β	14.4 days	695 KeV	8 mm.
Strontium (⁸⁹ Sr)	β	50.5 days	583 KeV	2.4 mm.
Samarium (¹⁵³ Sm)	β and γ	4 46.3 hours	233 KeV	3.1 mm.
Renium (¹⁸⁶ Re)	β and γ	3.8 days	349 Kev	1.1 mm.
Tin (¹¹⁷ Sn)	β and γ	13.6 days	135 KeV	0.3 mm.

Table 2: Results

	Improved	Unchanged	Worsened
Subjetive	80(85%)	14(15%)	0
Karnofsky	51(54%)	43(46 %)	0
Analgesia	52(55,3%)	39(41,4%)	(3%)

Table 3 - Results: Subjective response of pain.

	PATIENTS	
Worsened	0	0%
Unchanged	14	15 %
Slight relief	22	23 %
Moderate relief	38	40 %
Complete response	20	22 %

RESULTS

No adverse effects from ^{153}Sm -Lexidronam administration were noted during the study. Pain relief started between 3 and 30 days (mean: 7 days) after treatment, and it lasted between 1 and 12 months (mean: 3 months).

Both objective and subjective patients' response to treatment, according to assessment based on WHO and Karnofsky scales are presented in Tables 2 and 3. As shown, no patients got worse, though three needed increased analgesia. Eighty-five per cent (85%) of the patients reported pain relief in different degrees, and analgesia could be reduced in 55% of them. Twenty-three per cent (23%) and 40% had mild or moderate, respectively, pain relief, and in 22% pain cessation was achieved. Four patients had been previously treated with ^{89}Sr . Three of them had moderate or complete response to ^{153}Sm -Lexidronam, and the other, who had not responded to the previous treatment with ^{89}Sr , had a moderate response to ^{153}Sm -Lexidronam.

No relevant adverse effects were noted during the follow-up. In 5% of the patients, 48-72 hours posttreatment, an initial transient increment of pain was observed. Bone marrow toxicity was mild in all cases. Thrombocytopenia was noted in 3% of the patients, anemia in 8%, and leukopenia in 19%.

DISCUSSION

Several studies (including multicenter trials) support the efficacy of ^{153}Sm -Lexidronam treatment for palliative metastatic bone pain, including its ability to improve patients' life quality, at times in the terminal phase.

The findings reported herein are similar to those reported by earlier authors, with response rates ranging from 62 to 83%^{38,39,40,41,42}.

According to criteria established by earlier authors, a dose of 37 MBq/kg, which seemed to be the most suitable, was administered. However, one can ask whether or not a higher dose would result in better clinical outcome, but data concerning the efficacy of greater doses are scanty in the literature, and it does not seem that better results have been achieved when slightly higher doses are used^{42,43}.

Clearance of 85% of the injected dose from the blood was achieved in the first 30 minutes, and approximately 65% of the dose was taken up by the bone. Thirty-five per cent (35%) of the injected dose was excreted in the urine in the next six hours^{35,36}. This, together with a short half-life and β energy from ^{153}Sm , differs from other radioactive isotopes⁴⁴, and enabled one to adjust the dose to the patient body weight, so that high activity, optimal biological radiation delivery and rapid release of a high radiation dose rate could be achieved in a short period of time.

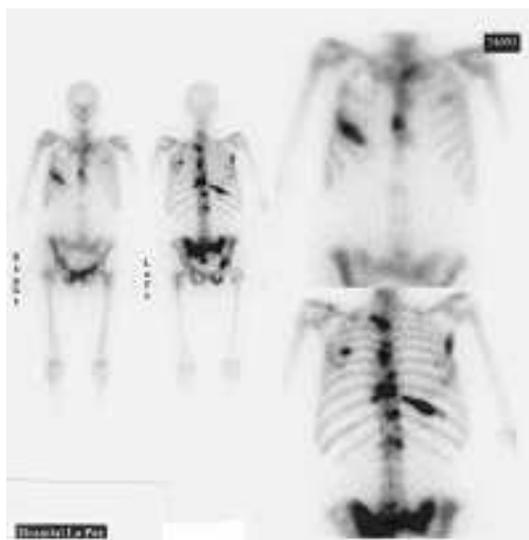


Figure 1 - $^{99\text{m}}\text{Tc}$ -HMDP

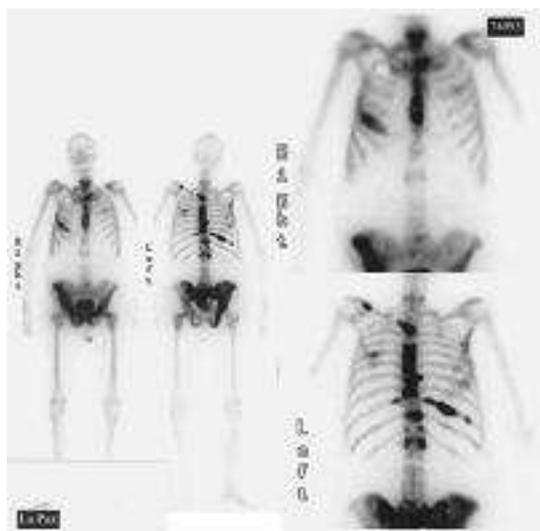


Figure 2 - ^{153}Sm -EDTMP

Thus, it is estimated that, for a dose of 2,590 MBq of ^{153}Sm -Lexidronam, the equivalent effective dose is 796 mSv³¹. This would explain the rapid response of the pain to the radioactive isotope concerned⁴¹. Because of the rapid clearance and excretion of ^{153}Sm -Lexidronam and its low exposure rate, patients can be treated on a day hospital-basis³³.

^{153}Sm γ emission permits the patient to have a scintigraphy performed after the treatment, which can show the uptake of the isotope by the metastases visualized in the conventional scintigraphy carried out before initiation of treatment. At the beginning of the present study, the scintigraphy was performed 24 hours posttreatment^{33,42}; however, because of the unsatisfactory clinical status of most patients, it was decided to perform the scintigraphy 4-6 hours before discharge, with results comparable to those achieved at 24 hours (Fig.2).

Duration of pain relief in this series was of approximately three months, which was slightly shorter than that reported by earlier authors^{37,40}. There may be two reasons for such a difference. First, some of the patients in the series had a life expectancy as short as one month, and died pain-free two months after completing treatment. Secondly, a large number of patients with a life expectancy longer than three months died between 1 and 2 months after treatment. In contrast, some authors have reported higher mean survival rates (e.g., six months)⁴².

When the treatment was initiated with radioactive isotopes, specifically with ^{153}Sm -Lexidronam, based on the results of a literature review^{40,42}, the aforementioned protocol, including inclusion criteria, was developed. However, as clinical experience expanded, it became possible to more accurately determine the risk/benefit ratio for the patient to be treated. Thus, it was no longer necessary to adhere strictly the protocol. Knowing that pain palliation may be achieved within a few days, patients with a life expectancy shorter than four months were treated, bearing in mind that clinical benefits were to outweigh the risks taken. In three patients with a life expectancy of about one month, a significant pain palliation was achieved, and in one female patient with breast cancer, total pain cessation until her death was achieved. Also, we were not strict with patients undergoing hormone therapy. Most of these patients underwent hormone therapy with no interference from ^{153}Sm -Lexidronam.

^{153}Sm -Lexidronam permits treatment not only of patients with metastatic bone pain from prostate cancer, but also patients with breast cancer and other malignant tumors^{40,41,42,43,45}, provided that metastases be detected pretreatment by conventional scintigraphy. Clinical outcome is similar regardless of the type of the primary tumor from which bone metastases originated, as these results show. However, in this series, most tumors other than prostate and breast had mild-moderate response, and very few showed a complete

response. As there were few tumors others than prostate and breast in our series, this topic warrants further investigation. Many authors report the best results for breast cancer^{37,38}.

One of the problems encountered was the modality for pain assessment. It was believed that it would not be easy for patients with intermittent pain of varying location and with bad health status and deterioration to indicate the pain degree along a scale. Nevertheless, patients were thought to be able to indicate whether they felt better, unchanged or worse, as well as whether they had lowered or withheld the analgesic medication after treatment. Therefore, while taking the scores from Karnofsky and WHO into account, everything the patient or his/her relatives reported at follow-up visits was emphasized. Eighty-five per cent (85%) of the patients reported pain relief, and 54% reported improved life quality.

The only reported toxicity associated with ¹⁵³Sm-Lexidronam treatment reported in the literature is bone marrow toxicity, it being mild and reversible in most cases, and rarely severe^{37,38,39}. In this series, bone marrow toxicity was mild in all cases. Therefore, ¹⁵³Sm-Lexidronam treatment-associated toxicity is less severe than that associated with other treatment modalities for cancer patients. In the present study, patients receiving chemotherapy within less than eight weeks before treatment did not have increased bone marrow toxicity. At any rate, it is advisable to be cautious when administering ¹⁵³Sm-Lexidronam to patients undergoing chemotherapy 4-8 weeks before treatment initiation.

In this series, 5% of the patients reported increased pain 48-72 hours after treatment, this finding being in keeping with earlier authors^{45,46}. It may be due to radiation effects, because, although it is relatively low, it negatively affects the fluid circulating within the lesion. However, pain increment was transient and responded well to a slight increase in the usual analgesic.

¹⁵³Sm-Lexidronam permits multiple doses to be delivered, as required^{47,48}. In the present study, nine patients needed a second dose, and a female patient with breast cancer received three doses. These 12 patients had a response as good as that with the first dose, with mild reversible bone marrow toxicity.

CONCLUSIONS

¹⁵³Sm-EDTMP administration is worthwhile for palliative metastatic bone pain management in patients with bone metastases from a number of primary malignant tumors because it provides relief and, is even able to stop the pain, thereby significantly improving patients' life quality. Furthermore, ¹⁵³Sm-EDTMP administration-associated adverse effects are mild and reversible.

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RESUMO

A dor é a manifestação clínica mais comum da metástase óssea. Seu tratamento é, por natureza, paliativo e consiste de quimioterapia, radioterapia, hormonoterapia, difosfonatos, e terapia medicamentosa (*i.e.* opiáceos). Isótopos radioativos representam uma alternativa atraente para as modalidades convencionais de tratamento. Entre os diferentes tipos de isótopos, temos grande experiência clínica com ¹⁵³Sm. Neste estudo, nós avaliamos 94 pacientes na faixa de 65 anos com diagnóstico de cânceres de próstata, de mamas e outros tumores malignos. Esses pacientes foram tratados com 37 MBq/Kg de ¹⁵³Sm-EDTMP. Todos eles reclamavam de dor nos ossos e apresentavam evidências de disseminação de metástase óssea. O tratamento foi analisado objetivamente e subjetivamente. Oitenta e cinco (85%) dos pacientes relataram alívio da dor, e a analgesia foi reduzida em 55%. Vinte e dois (22%) tiveram uma resposta completa. A toxicidade na medula óssea não foi um câncer e sim um transitório desequilíbrio hematológico em 30% dos pacientes. Concluímos que o ¹⁵³Sm-EDTMP resultou em alívio ou total erradicação da dor metastática na maioria dos pacientes.

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