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^{153}Sm-EDTMP for Pain Relief of Bone Metastases from Prostate and Breast Cancer and Other Malignancies

Luis Correa-González,[a] Consuelo Arteaga de Murphy,[b] Pablo Pichardo-Romero,[a] Martha Pedraza-López,[b] Claudia Moreno-García,[a] and Luis Correa-Hernández[c]

[a]*Unidad Médica de Alta Especialidad "Hospital de Oncología" Siglo XXI, Instituto Mexicano de Seguro Social, México, D.F., Mexico*
[b]*Nuclear Medicine Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, D.F., Mexico*
[c]*Ciclotrónica Mexicana, Morelos, Mexico*

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Background and Aims. Approximately 85% of patients with cancer suffer severe metastatic bone pain for which radionuclide therapy has been employed for pain palliation. We undertook this study to evaluate the pain relief effect of ^{153}Sm-EDTMP in Mexican patients with severe and painful bone metastases from mainly prostate, breast, and renal cancer and other malignancies.

Methods. Patients (277) with intense sustained pain caused by bone metastases were referred to the Nuclear Medicine Department of the Oncology Hospital of the Mexican Social Security Institute. The patients had to have acceptable physical conditions, a previous positive ^{99m}Tc-MDP scan and blood values within normal range. ^{153}Sm-EDTMP was prepared at the Instituto Nacional de Investigaciones Nucleares (ININ) and 37 MBq/kg of body weight was injected intravenously. Pain palliation was evaluated with a visual analogue scale (VAS) and a verbal rating scale (VRS) before treatment and 3 and 12 weeks after treatment was started.

Results. The age interval of the patients was 24–92 years with a mean age of 64 ± 12 years. Mean values for hemoglobin, leukocyte and platelet counts did not statistically differ at zero time, 3 and 12 weeks after treatment. Pain intensity and relief assessment were statistically different: 9.1 ± 0.61 units initially; 4.2 ± 1.3 units 3 weeks later (54%) and after 12 weeks the pain diminished to 2.4 ± 1.4 units (74%) in the pain relief score scales.

Conclusions. ^{153}Sm-EDTMP was readily available, safe and well tolerated. We conclude that ^{153}Sm-EDTMP was an adequate palliative agent and was the best option for our Mexican patients to relieve their severe metastatic bone pain.

Key Words: ^{153}Sm-EDTMP, Pain relief, Bone metastases, Prostate cancer, Breast cancer.

Introduction

Bone metastases from solid malignant tumors are responsible for most of the morbidity and mortality in ~65–70% of patients with advanced prostate gland and breast cancer; ~85% of these patients suffer severe metastatic bone pain. It has been reported that pain is produced by indirect stimulation of sensory nerve endings by released cytokines and other biological compounds in response to the invasion of tumor cells in the bone marrow (1).

For localized bone pain palliation, the gold standard is external beam radiation therapy and for diffuse bone pain the gold standard is pharmacological management, alone or in combination with other therapies. According to multiprofessional clinical guidelines, the effective pharmacological treatments for pain relief are several, including

Address reprint requests to: Consuelo Arteaga de Murphy, Ph.D., Instituto Nacional de Ciencias Médicas y Nutrición Dr. Salvador Zubirán, Vasco de Quiroga 15, Delegación Tlalpan, C.P. 14000, México, D.F., Mexico; Phone: (+52) (55) 5487 0900; FAX: (+52) (55) 5655 1076; E-mail: camurphy53@yahoo.com.mx

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morphine, analgesic medication, bisphosphonates, hormonal agents and cytotoxic chemotherapy. Invasive measures (e.g., neuroaxial blockage) are rarely necessary but are an important option if patients with cancer pain syndromes are refractory to pharmacologic management and radiotherapy (2–6). More recently, the synergy of radiotherapy with immunological strategies has been reported as a good option for pain relief and the synergy of radiotherapy plus cytotoxic chemotherapy has been known as a better pain relief tool. The combination of chemotherapy and radionuclides is thought to be a better treatment for pain palliation (7,8). Patients who do not fully respond to standard treatments are given the option of bone-seeking radionuclides that specifically target osteoblastic lesions (2).

Radionuclide therapy with bone-seeking radiopharmaceuticals is one of the oldest interventions in nuclear medicine and has been in use for many years as an effective method of palliating painful bone metastases. Beta-emitting radionuclides are an efficient pain palliation treatment with low myelotoxicity (9,10).

Strontium-89 and phosphorous-32, both bone volume seekers, have been used for bone pain palliation. Other radionuclides that have been used as bone seekers for the same purpose, with more or less success, have been samarium-153-chelated to the phosphonate-EDTMP, rhenium-186/188-DMSA, rhenium-186/188-HEDP, yttrium-90-DOTA-, thorium-227-EDTMP, thorium-227-DOTMP and lead/bismuth-212-DOTMP (2,11). Recently, clinical trials using the radionuclide 223-radium-cloride (^{223}Ra) have been promising (12–14).

For more than two decades, ^{153}Sm-EDTMP and ^{89}Sr therapies have been evaluated for pain relief. Both radiopharmaceuticals deliver high radiation doses to bone metastases and provide similar effects for a total or partial pain relief and a better quality of life. The efficiency of these two radionuclide therapies is ~70–79% and ~25% of the treated patients may even become pain free. Both of these therapies are repeatable, depending on cell counts, and produce a significant reduction in analgesic consumption and may even have a therapeutic potential beyond simple pain palliation (6,15,16).

We studied ^{153}Sm-EDTMP because it is widely available, extensively used, is safe and allows pain relief. It stabilizes the pain and produces some pain regression plus tumor marker response. It is well tolerated in repeated doses of 37 MBq/kg body weight and is cost-effective. The hematological profiles (red blood cells, leukocytes and platelet counts) and myelosuppression are low and transient, grade 2, according to the National Cancer Institute *Common Toxicity Criteria*. The radiopharmaceutical can significantly decrease patient morbidity, prolong patient survival, may decrease the occurrence of new bone metastases, even showing a significant decrease in PSA, in tumor load and have been shown to modify progression of skeletal metastasis in several forms, especially in breast cancer and pain palliation (4,17,18).

There are data showing that the therapeutic efficacy of ^{153}Sm-EDTPM was higher than that of bisphosphonates. Pain relief with ^{153}Sm-EDTPM starts after 1 week and lasts for 2 to 17 weeks, whereas some bisphosphonate analgesics relieve pain for only 3 weeks. Other benefits of ^{153}Sm-EDTMP are that bone uptake is not affected by high-potency intravenous bisphosphonates in patients with prostate cancer refractory to castration and both treatments can be given simultaneously. This dual treatment may be more effective when combined with chemotherapy plus radiation therapy (19–22).

^{153}Sm-EDTMP treatment can be given to patients undergoing hemodialysis (23,24) and ^{153}Sm-EDTMP plus bisphosphonate therapy plus chemotherapy can have synergistic pain relief. As mentioned before, beta-emitting radionuclides have historically been proven to relieve metastatic bone cancer pain, whereas docetaxel, a chemotherapeutic drug, prolongs the life of patients with prostate cancer refractory to castration. Therefore, both therapies can be given simultaneously and the combination strategy produces better pain palliation than if either is given separately (25).

A reasonable estimation for bone tumor dosimetry given by ^{153}Sm-EDTMP is obtained with a ^{99m}Tc-MDP whole body scan. The image shows several degrees of uptake with bone tumor activity, number of metastases and a comparison with the ^{153}Sm-EDTMP scan (26,27). The calculated radiation dosimetry for bone surface is 6.8 mGy/MBq and 15 mGy/MBq for red bone marrow (3).

The aim of this research was to evaluate the pain relief effect of a solution of ^{153}Sm-EDTMP prepared in Mexico for treatment of 277 Mexican patients referred to the Mexican Social Security hospitals because of painful bone metastases from various types of cancer, mainly prostate and breast cancer and other malignancies.

Materials and Methods

Patients

Palliation of bone pain resulting from metastatic malignancies was treated with ^{153}Sm-EDTMP. From June 2005 to February 2013, 277 consecutive cancer patients were referred to the Nuclear Medicine Department of the Unidad Médica de Alta Especialidad del Hospital de Oncología del Centro Médico Nacional Siglo XXI del Instituto Mexicano del Seguro Social (Mexican Institute of Social Security) to evaluate intense, sustained pain caused by osteoblastic bone metastases refractory to previous analgesics (morphine, oxycodone and other opioids) of the World Health Organization (WHO) level III analgesic scale.

Patients were treated by the nuclear medicine physicians in collaboration with the physicians assuming overall patient management. All patients included in this study were referred with severe bone pain from metastatic cancer and