# Sm-153 EDTMP — A NEW PALLIATIVE THERAPY AGENT AGAINST PAIN IN CASES OF BONE METASTASES

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**Abstract**

During the last years exist an increasing interest in employing radiotherapeutic agents as palliative skeletal pain caused by disseminated bone metastases. Selection of an appropriate radiotherapeutic agent for one application is directly related to the biolocalization of carrier molecules.

Is estimated that the 50% of patients with mamma, prostate, and lung carcinomas can develop single or multiple bone metastases. The multiple bone metastases frequently cause intense pains that must be calmed with different analgesics.

The Physical characteristics of Samarium 153 permit be considered as excellent radiotherapeutic and diagnostic image agent.

Sm - 153 EDTMP is one of the most interesting products in the treatment of the bone metastases by the excellent biolocalization , including rapid blood clearance and bone affinity.

In some patients the relief is obtained during the first or second week of the application improving in progressive form. The benefit of the treatment can be maintained durign some months.

This radiotherapeutic agent has been applied success fully till now in near 300 patients from differents hospitals to Lima. Most of them have been experimented a progressive improvement. All patients were treated in single rooms. The dose was 1 mCi / kg in all cases according the protocol established. Images were obtained 3 hours after receiving Sm - 153 EDTMP.

## INTRODUCTION

During the last years exist an increasing interest in employing radiotherapeutic agents as palliative skeletal pain caused by disseminated bone metastases. [1], [2]. Selection of an appropriate radiotherapeutic agent for one application is directly related to the biolocalization of carrier molecules.

In Perú is estimated that 50 to 60 % of patients with mamma, prostate, and lung carcinomas can develop single or multiple bone metastases. The multiple bone metastases frequently cause intense pains that must be calmed with different analgesics ; some times combinating two or tree of them .

The physical characteristics of Samarium 153 permit be considered as excellent radiotherapeutic and diagnostic image agent.

Sm - 153 EDTMP is one of the most interesting products in the treatment of the bone metastases by the excellent biolocalization , including rapid blood clearance and bone affinity [3].

In some patients the relief is obtained during the first or second week of the application improving in progressive form. The benefit of the treatment can be maintained durign some months.

Peruvian experiences with Sm - 153 EDTMP became at the end of 1995 . This radiotehrapeutic agent has been applied success fully till now in near 300 patients from seven hospitals located in Lima and one out side of Lima . Most of them have been experimented a progressive improvement. All patients were treated in single rooms. The dose was 1 mCi/kg in all cases according the protocol established. Images were obtained 3 hours after receiving Sm - 153 EDTMP.

On the other hand in 1997, Peruvian Nuclear Center sent . Sm 153 as Samarium Trichoride to Five Latinoamerican countries under agreement IPEN and AIEA . The EDTMP was labelling with this Samarium in each country according to protocol proposed by AIEA .

## ADVANTAGES OF Sm - 153 EDTMP

The penetration range in the bone tissue is approximately 3 mm , enough to penetrate in the zone where are localized the malignant cells.

The beta and gamma emission permit the obtaining of clear images in a detection system.

Short half life in comparison with the 50.5 days of the Strontium 89 before used in Perú.

The rapid product's elimination by the kidney and the long retention in the bones make of the Sm - 153 EDTMP an ideal radiopharmaceutical in Therapeutic Nuclear Medicine.

The therapeutic dose is 30 times more economic than the dose of Sr - 89 $SrCl_2$ according to Peruvian radiopharmaceutical market. After 24 hours of the injection , the patient's urine will contain very low Sm 153 concentrations so that the treatment may be ambulatory.

## METHOD AND MATERIALS

### 1. Irradiation facilities

Samarium Trioxide enriched to 98.7% in $^{152}Sm$ from ISOTEC INC was irradiated in the RP-10 Reactor (Nuclear Center of Huarangal - Lima) at neutron fluxes of 1 - 3 x $10^{14}$ n / $cm^2$. s during 8 hours in same cases and 15 hours in others ( no continued irradiation ) . The average operating power level of the reactor during these irradiations was 7 Mw. After irradiation , the samples were left to cool for 24- 48 hours.

### 2. Target dissolution

$Sm_2O_3$ is dissolved in 1.5 ml HCl 0.1N . Ampoule quartz containing Samarium traces is washed two times with 1.0 ml bidistillate water. Both solutions are joined in a vial A.

### 3. Sm - 153 EDTMP Preparation

In the process, we usually dissolved an appropriate amount of EDTMP equivalent to 08 times molar respect to mass of Samarium irradiated [4]. This EDTMP is dissolved in NaOH 0.1N solution in a vial B.

Flask B is transfer to flask A. The pH of this solution was adjusted to 7.5 - 8.0 with NaOH 0.1N. The product thus obtained is put in a thermal bath during 25 minutes to 80°C, stirring several times the flask. The vial is opened and 2ml Buffer Phosphate (pH 7.0 - 7.5) is added into. The end product is sterilized by autoclave during 25 minutes to 120 °C. The bidistillate water must be free of pyrogenos as protocol of quality control.

## QUALITY CONTROL

### 1. Radiochemical Purity

Take a small column containing 2ml of Sephadex G-25. Put upon sephadex bed 1 - 2 mCi of label product . Column radioactivity measurement was performed in a ionization chamber. Called $A_1$ to value thus determinated.

Washed the column with 15ml of NaCl 0.9% . The eluate contains the label product and column retains the $^{153}$ Sm free. The column activity measurement is called $A_2$

Radiochemical purity is calculated as:

$$R.P = 100 (1 - A_2/A_1) \% \qquad [5]$$

The ionization chamber factor of Capintec is 241 x 1.12 . For Vinten chamber is 374.

### 2. Radionuclidic purity

The Radionuclidic purity is carried out by gamma spectrometry employing a mutichanel equipment, where the main pick of $^{153}$ Sm is found to 101.3 KeV.

Routinely were not detected $^{152m}$ Eu, $^{154}$ Eu, $^{155}$ Eu neither $^{156}$ Eu.

If the amount of lanthanides in target material is more to 0.01% could be detectd a significative activity of $^{155}$ Eu and $^{156}$ Eu.

## 3. Biodistribution

Biodistribution was performed in winstar rats weighing 280 - 350 g at 2 , 4, 16 , 24 and 48 hours after intravenous dose of 200 μCi of Sm - 153 EDTMP. Can observed a higher uptake in skeletal system , low dose in liver and rapid blood clearance . The results were expressed in % dose/organ. See Table No 01

## 4. Toxicity evualation

A 5 mice group with an average weight 25 g are injected with a volume of 0.1 ml of Sm - 153 EDTMP . This dose is equivalent to 500 times more than human administration. Mice are maintain in observation by one week. If none animal die or none present severe reactions in behavior during evaluation period , the result is favorable.

TABLE No. 01

BIODISTRIBUTION OF 153 Sm EDTMP IN RATS (*)

| ORGANS | TIME ( h) | | | | |
|---|---|---|---|---|---|
| | 2 | 4 | 16 | 24 | 48 |
| Blood | 0.074 | 0.065 | 0.064 | 0.060 | 0.058 |
| Liver | 0.332 | 0.390 | 0.390 | 0.384 | 0.328 |
| Spleen | 0.012 | 0.013 | 0.012 | 0.011 | 0.010 |
| Lung | 0.030 | 0.028 | 0.026 | 0.024 | 0.020 |
| Kidney | 0.210 | 0.224 | 0.310 | 0.385 | 0.495 |
| Stomach | 0.048 | 0.045 | 0.042 | 0.039 | 0.034 |
| Small Intestine | 0.050 | 0.050 | 0.048 | 0.044 | 0.041 |
| Large Intestine | 0.162 | 0.160 | 0.152 | 0.148 | 0.144 |
| Bladder | 0.185 | 0.488 | 0.160 | 0.145 | 0.095 |
| Heart | 0.015 | 0.016 | 0.015 | 0.014 | 0.014 |
| Muscle | 0.340 | 0.245 | 0.244 | 0.244 | 0.238 |
| Femur | 1.856 | 1.989 | 2.112 | 2.224 | 2.229 |
| Skeletal | 46.22 | 47.18 | 49.62 | 50.16 | 51.48 |

(*) Biodistribution expressed as % Dose per organ . The data is the average for the last 12 production batchs

## PROTOCOL OF APPLICATION

### A. SELECTION OF THE PATIENT

- Positive bone scan using Technetium 99m (MDP)
- Normal or near to the normal hemogram
- Fine renal function
- Life expectancy greater than 4 months
- Previous treatment with radiotherapy and chemitherapy at least one month before the application (if exist)

### B. APPLICATION

- Dose:

  1 mCi / kg to localized metastases

  1.5 mCi / kg to multiple metastases

- Previous hydratation of the patient by oral via (1 liter in 30 minutes)

TABLE No. 02

BIODISTRIBUTION OF Sm 153 EDTMP KIT IN RATS (*)

| Batch | Time | Radiochemical Purity Sm 153 - EDTMP | Biodistribution | | |
|---|---|---|---|---|---|
| | | | Liver | Blood | Skeletal |
| 1 | 4 d | 99.60 % | 0.59 % | 1.59 % | 47.17% |
| 1 | 65 | 99.85 | 0.58 | 1.61 | 45.27 |
| 1 | 120 | 99.83 | 0.64 | 1.69 | 42.21 |
| 2 | | | | | |
| 2 | 48 | 99.85 | 0.65 | 0.92 | 48.23 |
| 2 | 130 | 99.58 | 0.59 | 0.61 | 47.92 |
| | 150 | 99.41 | 0.58 | 0.95 | 45.96 |
| 3 | | | | | |
| 3 | 26 | 99.60 | 0.66 | 1.16 | 45.85 |
| 3 | 90 | 99.52 | 0.65 | 1.25 | 45.60 |
| | 125 | 99.41 | 0.71 | 1.12 | 43.69 |

(*) 02 Horas post injection. n = 2

- Intravenous injection in 5 minutes (is recommended make a dilution with physiological serum no more than 20 ml)
- Obtaining of images at 3 and 24 hours.

## C. PATIENT POST OBSERVATION

- Control of the pain in a week post injection
- Blood sample:

  Hemograms at 2 or 3 weeks and at 3 months
- Evaluation of the pain at 2 or 3 weeks and at 3 months
- Evaluation of the medication
- Proper evaluation of the patient

## RESULTS AND DISCUSSION

Sm - 153 EDTMP has demostrated be an excellent radiopharmaceutical to palliative metastatic bone cancer pain. Images obtained additionally allow a rapid diagnostic.

Availability of the label product in the Peruvian Nuclear Center added with an economic price permit to poor patients to access to their treatment.

Studies connecting EDTMP KIT have been development lately in order to obtain a new form of product [6]. Preliminary results are showed in the table No. 02

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