

Palliation of Pain Associated With Metastatic Bone Cancer Using Samarium-153 Lexidronam: A Double-Blind Placebo-Controlled Clinical Trial

Serafini AN, Houston SJ, Resche I, et al. J Clin Oncol. 1998;16:574-1581.

Study Highlights

- Samarium-153 Lexidronam ($^{153}\text{Sm-EDTMP}$) provided effective pain relief in patients with pain associated with bone metastases
- Bone marrow toxicity was relatively mild and reversible

Purpose

- To evaluate the safety and efficacy of single 0.5- and 1.0-mCi/kg doses of $^{153}\text{Sm-EDTMP}$

Study Design

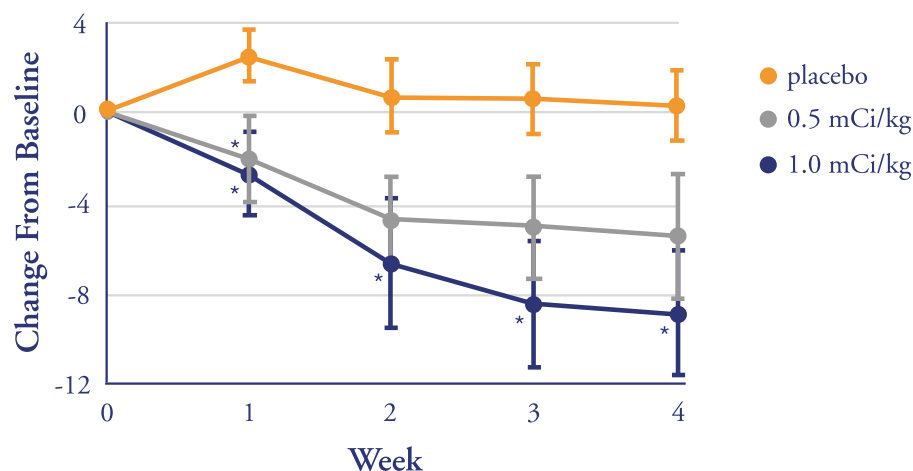
- Randomized, double-blind, placebo-controlled, prospective, multicenter clinical study of 118 patients with painful metastatic bone disease secondary to a variety of primary malignancies
 - Patients were randomized to receive either 0.5 or 1.0 mCi/kg of $^{153}\text{Sm-EDTMP}$ or placebo
- Each patient completed a daily diary, recording pain intensity and use of opioid analgesic medications
- Physicians completed clinical evaluations and global assessments at weeks 1, 2, 3, 4, 8, 12, and 16
- All patients had malignancies that had failed to respond to treatment or had relapsed after achieving remission, and had painful bone metastases
 - The primary malignancy in most of the patients studied was either prostate (68%) or breast (18%) cancer
- The majority of patients used opioid analgesics at mean oral morphine equivalent doses of 140 to 175 mg per day
- The percentages of patients receiving prior treatments were, in the placebo, 0.5 mCi/kg, and 1.0 mCi/kg groups respectively: surgery, 95%, 85%, 87%; radiation, 74%, 73%, 77%; hormonal therapy, 85%, 83%, 82%; chemotherapy, 38%, 33%, 23%

Results

EFFICACY

- Pain relief was observed in 62% to 72% of patients during the first 4 weeks in patients (including all tumor types) who received the 1.0-mCi/kg dose
 - Pain relief was statistically significant during each of the first 4 weeks ($P < .034$)
 - Pain relief was greater for patients with breast cancer at week 4 than for patients with other primary malignancies

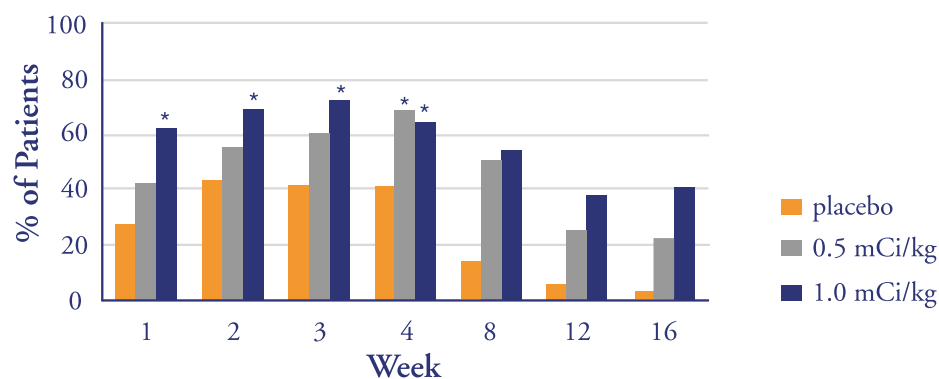
Change from baseline in patient-reported pain intensity levels



* Designates a statistically significant difference from placebo.

Fig 1. Change from baseline in AUPC-VAS during the first 4 weeks for patients who received placebo, 0.5 mCi/kg of $^{153}\text{Sm-EDTMP}$, or 1.0 mCi/kg of $^{153}\text{Sm-EDTMP}$.

Percentage of patients who had relief of pain according to physician global assessments



* Designates a statistically significant difference from placebo during the first 4 weeks.

Fig 2. Percentage of patients who had relief of pain according to PGA. Includes categories of "slight," "moderate," "marked," and "complete" pain relief. Percentages based on the number of patients at baseline.

- 43% of patients had persistent pain relief at 16 weeks
- Significant improvements in pain scores seen in patients who received 1.0 mCi/kg were correlated with a decrease in the use of opioid analgesics, indicating that these improvements were not a result of changes in opioid analgesic use
- There was a rapid onset and durable pain relief with the 1.0-mCi/kg dose

TOLERABILITY

- The only undesirable pharmacologic effect of treatment was mild, transient, dose-related myelosuppression
 - In the active treatment groups, white blood cell (WBC) and platelet counts decreased after drug administration, reached a nadir at 4 to 5 weeks, and then recovered to pretreatment values by week 8
 - None of the patients experienced a grade 4 hematologic toxicity

Mean WBC and platelet nadirs

Treatment Group	WBCs x 10 ³ /μL			Platelets x 10 ³ /μL		
	Mean	TTN, weeks	% of baseline	Mean	TTN, weeks	% of baseline
Placebo	5.3	3	80	219	3.5	87
0.5 mCi/kg ¹⁵³ Sm-EDTMP	3.9	4	59	151	4	58
1.0 mCi/kg ¹⁵³ Sm-EDTMP	3.1	5	51	118	4	45

TTN=median time to nadir.

- The most common nonhematologic events were nausea, vomiting, constipation, asthenia, and edema, usually related to the patients' underlying disease or concomitant medications
- None of the patients discontinued due to toxicity during drug administration or during the follow-up period
- The incidence of pain flares was slightly higher in patients treated with ¹⁵³Sm-EDTMP compared to those treated with placebo (7.5% vs 5%, respectively)

Conclusions

- A single intravenous dose of 1.0 mCi/kg of ^{153}Sm -EDTMP provided efficacy with relatively mild and reversible hematologic effects in patients with pain associated with bone metastases
 - In the majority of patients who responded to treatment, pain relief occurred within 1 week and persisted for 16 weeks or longer

Indication

Quadramet® (Samarium Sm-153 lexidronam injection) is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.

Important Safety Information

Because of the unknown potential for additive effects on bone marrow, Quadramet should not be given concurrently with chemotherapy or external beam radiation unless the clinical benefits outweigh the risks. Commonly observed adverse events for Quadramet: bone marrow toxicity occurred in 47% of patients in clinical trials. Myelosuppression may increase the risk of infectious and hemorrhagic adverse events. Non-hematologic adverse events that occurred in $\geq 5\%$ of patients and greater than placebo were pain flare (7%), diarrhea (6%), infection (7%), spinal cord compression (6.5%), arrhythmias (5.0%) and hematuria (5.0%). Patients taking Quadramet should have blood counts monitored for at least 8 weeks, or until recovery of adequate bone marrow function. Quadramet should not be used in patients who have known hypersensitivity to EDTMP or similar phosphonate compounds; women of childbearing age should have a negative pregnancy test before administration of Quadramet. If Quadramet is administered to a nursing mother, formula feeding should be substituted for breast feeding. Patients who receive Quadramet should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in the environment, precautions need to be taken for 12 hours following administration.

Please see accompanying full prescribing information.

