

# Palliation of bone pain in patients with metastatic cancer using strontium-89 (Metastron)

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*Bony metastasis is the most common cause of cancer pain. Strontium-89 (Sr-89), or Metastron, therapy has been shown to be effective for the palliation of pain due to skeletal metastases. By reducing opioid analgesics intake and restoring mobility, Sr-89 improves the patient's quality of life. Sr-89 is given conveniently as an outpatient procedure, and when necessary it can be repeated at 3-month intervals. Sr-89 is useful as an adjunct to local external beam radiation (EBR) because Sr-89 will target all skeletal metastases, including those not included in the EBR field. Because Sr-89 is a beta-emitting radionuclide with a long physical half-life (50.5 days), precautions should be taken by the caretaker(s) against Sr-89 contamination from the patient's blood or excretions, particularly if the patient is incontinent.*

**Key Words:** Radionuclide therapy—Strontium-89—Radiation safety—Nursing care—Bone pain—Pain palliation—Incontinence

The development of pain is a common problem for the cancer patient, leading to psychological and physiological hardship and resulting in a poor quality of life (1). Approximately one-third of patients in active therapy and two-thirds of patients with advanced disease experience significant pain (2). Bony metastases are the most common cause of cancer pain, with nearly 50% of all patients who present with breast or prostate cancers eventually developing bone metastases (1). These patients may survive months or years after the development of metastatic disease, and their pain requires appropriate management.

## THERAPEUTIC OPTIONS

Therapy for patients with advanced disease is not curative, but focuses on palliative procedures to reduce pain and improve the patient's quality of life (1,3). Although chemotherapeutic agents have proven effective for treating bony metastases from breast carcinoma, their utility for pain palliation is not clearly documented; and although hormonal therapy is initially effective for ~70% of prostate cancer patients, most eventually become refractory as hormone-resistant tumors develop (3). Opioid analgesics are often required to alleviate pain for these patients.

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Accepted for publication December 8, 1994.

As tolerance develops or disease progresses, however, higher doses are often necessary, leading to common gastrointestinal (GI) side effects and somnolence.

Local external beam radiation (EBR) therapy is often used to reduce pain in patients with regional bone metastases (1,3). However, most patients require multiple visits, and many will develop new sites of pain requiring more extensive radiotherapy such as hemibody irradiation (HBI) or total body irradiation. Typically, wide field radiation results in side effects such as nausea, vomiting, diarrhea, significant myelosuppression, and potential lung toxicities (4).

In the early 1940s, radiopharmaceuticals such as strontium-89 (Sr-89) and phosphorus-32 (P-32) were introduced by researchers for pain palliation in cancer patients (5,6). Although P-32 was well accepted in managing hematological proliferative disorders such as polycythemia vera, the resulting bone marrow suppression limited its use for the treatment of bone metastases (7).

### Sr-89

Since its introduction in the 1940s, Sr-89, with a physical half-life ( $T_{1/2}$ ) of 50.5 days, has proven to be a superior radiopharmaceutical for the palliation of painful bone metastases. As a calcium analog, it is taken up by bone tissue, thereby delivering therapeutic radiation for several months. It has been retained longer at metastatic bone sites than in normal osseous tissue (3,8–10).

Sr-89 has been clinically evaluated for safety and efficacy in medical centers throughout Europe, Canada, and the United States (3,11–13). These studies led to the June 1993 approval of Sr-89 chloride injection (Metastron, Amersham International, Medi-Physics, Inc., Arlington Heights, IL, U.S.A.) by the United States Food and Drug Administration (FDA) for the palliation of pain due to skeletal metastases (14).

The availability of Sr-89 has prompted significant interest by patients, their family members or friends, physicians, nurses, and other health professionals. This article serves as an introduction to Sr-89 therapy, with some emphasis on nursing care and safety issues.

## CLINICAL TRIALS OF SR-89

### Early Studies

In 1974, Schmidt and Firusian (15) administered 0.01–0.015 mCi/kg (0.37–0.56 MBq/kg) of Sr-89 in patients with various primary lesions, and clinical improvement was noted in eight of 10 patients. In

1976, Firusian et al. (16) also reported good pain palliation in nine of 11 patients with metastatic prostate carcinoma. Using stricter assessment criteria, Silberstein and Williams (17) later reported a response rate of 51% in 38 patients receiving a total of 45 Sr-89 treatments.

### Pharmacokinetics of Sr-89 as a Palliative Agent

In 1986, Blake et al. (8) showed that, in patients with disseminated carcinoma of the prostate, the retained portion of Sr-89 in the skeleton was substantial (11–88%). Robinson et al. (9) later estimated that 10-fold more Sr-89 radiation is absorbed by bone metastases than by normal marrow.

### Recent Efficacy Data

In 1989, Robinson et al. (9) treated bony metastases arising from prostate ( $n = 100$ ) or breast carcinoma ( $n = 28$ ) with significant pain relief in 80% and 89%, respectively, of patients treated. Two other studies also achieved favorable clinical response rates (75–77%) in patients with metastatic prostate cancer (10,18). McEwan et al. (18), in 1990, reported that the safety and efficacy of Sr-89 therapy was similar when patients were previously treated with local or wide-field radiotherapy. In a double-blind crossover study in 1991, Lewington et al. (19) demonstrated that therapeutic responses to Sr-89 were not due to placebo or stable strontium effects ( $p < 0.01$ ).

In 1993, Robinson et al. (3), based on 15 years of clinical experience with Sr-89 for pain palliation at the University of Kansas Medical Center, demonstrated an ~80% response rate in evaluable patients with prostate ( $n = 240$ ) and breast ( $n = 47$ ) cancer treated with Sr-89 (Table 1). In addition, 15% of patients who received Sr-89 therapy reported being free of pain, and >50% experienced a dramatic reduction in pain and improved quality of life.

### Comparative Trials

In a 1993 multicenter United Kingdom study, the efficacy and safety of Sr-89 and radiotherapy was

TABLE 1. Recent Sr-89 clinical trials

Study	Dose	n	Overall response rate
Porter et al., 1993 (12)	10.8 mCi (or 400 MBq)	68	70%
Bolger et al., 1993 (13)	5.4 mCi (or 200 MBq)	305	61%
Robinson, 1993 (3)	30–80 $\mu$ Ci/kg (or 1.11–2.96 MBq/kg)	287	~80%

compared in 305 patients with metastatic prostate cancer (13). The investigators concluded that Sr-89 (5.4 mCi, or 200 MBq) was equally effective to local radiation (20 Gy in five daily fractions or a single fraction of 8 Gy) or HBI (single fraction of 6 Gy upper half, or 8 Gy lower half) in reducing existing bone pain. However, patients receiving Sr-89 experienced a significant reduction in the need for follow-up radiotherapy ( $p < 0.01$ ) compared with those treated with local radiation. In addition, more Sr-89-treated patients were free of newly painful sites as compared to patients receiving local radiation (65% vs. 46.5%,  $p < 0.05$ ). There was a higher incidence of GI side effects such as nausea, vomiting, and diarrhea after EBR than following Sr-89.

#### Sr-89 as an Adjunct to Radiotherapy

Sr-89 therapy has also been evaluated in combination with local EBR in a recent trans-Canada trial (11,12). Sr-89 (10.8 mCi, or 400 MBq) or placebo was administered to 126 patients (68 received Sr-89, whereas 58 received placebo) with advanced prostate cancer after radiotherapy for bone pain. Sr-89 was found to significantly increase the proportion of patients who were free of new sites of pain (58.7% vs. 34% for placebo,  $p < 0.002$ ). At 3 months, 40% of the patients receiving Sr-89 were pain free, compared to only 23% of the patients receiving placebo. Over the first 3 months following therapy, significantly more patients in the Sr-89 group showed a  $>50\%$  reduction in levels of prostate-specific antigen (PSA). In addition, the placebo group required additional EBR well before the Sr-89 group (mean time, 20.3 versus 35.3 weeks, respectively;  $p = 0.006$ ). These data demonstrate that Sr-89 is a useful agent as an adjuvant to EBR.

#### Effect of Sr-89 on Survival

Although most of the studies discussed have not shown significant improvements in patient survival with Sr-89 therapy, Buchali et al. (20) treated 49 patients with skeletal metastases of prostatic carcinoma and reported a significantly higher survival in the Sr-89 group ( $3 \times 2$  mCi, or  $3 \times 75$  MBq) compared with the placebo group (46% vs. 4%,  $p < 0.01$ ) (20). In addition, data from a comparative U.K. trial of metastatic prostate cancer discussed earlier demonstrated a trend of superior median survival time among patients who had received Sr-89 (33 weeks) compared with radiotherapy (28 weeks) (13), but the difference was not statistically significant ( $p = 0.11$ ).

#### PATIENT SELECTION

Currently, candidates for Sr-89 therapy must be experiencing painful bony metastases that can be demonstrated as areas of increased uptake (hot spots) on bone scans (Table 2) (9,14). In addition, it is recommended that platelets should be  $>60,000$  and WBCs  $>2,400$ . Life-threatening complications are extremely rare as judged from the results of clinical trials (14). Although anemia is not a contraindication for Sr-89 therapy, transfusions may be desirable in patients with a hemoglobin of  $<10$  g (3).

Terminal patients with very short life expectancy ( $<3$  months) are less likely to benefit from Sr-89 therapy because 7–20 days are typically required for a therapeutic response (14).

#### Sr-89 Therapy and Nursing Care

Sr-89 should be given by physicians who are qualified by training and experience in the safe use and handling of radionuclides. I prefer to use a scalp vein needle (gauge 23 or 25) with plastic wings (butterfly needle) prefilled with saline from a 10-ml syringe. After introducing the butterfly needle into a peripheral vein (usually in the forearm), one may secure the needle by taping the plastic wings to the skin. I routinely test for any extravasation by verifying good blood drawback from the butterfly needle and ensuring the absence of any local swelling after introducing 2–3 ml of saline through the needle. Then I inject the Sr-89 over  $\sim 2$  min, followed by several milliliters of saline. There is little published information regarding any adverse effect if the Sr-89 dose is infiltrated during injection. If this does happen, one may consider the use of a warm towel, local massage, or exercise of the affected limb to improve the local circulation and thereby promote absorption of the infiltrated dose.

I prefer not to inject the Sr-89 through any central venous access line or device, if at all possible.

**TABLE 2.** Selection of patients for Sr-89 therapy

1. Patient has substantial pain due to bony metastases and not due to nerve root compression or musculoskeletal problem
2. Recent bone scan shows "hot" areas in the painful locations
3. Patient is not pregnant
4. Platelets  $> 60,000/\text{mm}^3$
5. WBC count  $> 2,400/\text{mm}^3$
6. Patient does not have any spinal cord compression since cord compression is considered an emergency requiring steroid therapy, immediate external beam radiation (EBR) or surgical decompression (21)
7. Patient is not terminal and has a life expectancy of  $\geq 3$  months

**TABLE 3.** *Nursing guidelines following Sr-89 therapy*

1. Beware of "flare" response occurring 2–3 days after Sr-89 therapy. This requires increasing the patient's pain medications for a few days.
2. Take precautions against contamination from the patient's blood or excretions.
3. CBCs should be performed every 2 weeks or more frequently in the presence of significantly low platelets or WBCs.
4. Watch for signs of spinal cord compression due to disease progression (loss of bowel or bladder control or weakness in the lower extremities). Such patients may require steroid therapy, urgent EBR, or surgical decompression (21).

Because the central venous access route is frequently used for blood drawing and fluid or drug delivery, I am concerned about the potential chance of Sr-89 contamination if Sr-89 is also given by the same route.

Immediate adverse effects are rare with Sr-89 therapy. If Sr-89 is infused rapidly (<30 s), patients may experience a flushing sensation similar to the side effects noted by patients receiving calcium solutions intravenously (14). I routinely infuse Sr-89 over 2 min and have rarely encountered this phenomenon. In my practice, outpatients following Sr-89 infusion are asked to wait for ~15 min before leaving the Nuclear Medicine Department in case an unexpected reaction should occur.

Patients may occasionally experience a transient pain-flare phenomenon 48–72 h after Sr-89 infusion (3,14) (Table 3). This can be managed by temporarily increasing analgesics. Patients experiencing a pain-flare are usually good responders to Sr-89 therapy (3).

As the therapeutic benefits of Sr-89 are achieved, many patients can decrease their analgesics and increase their daily activities (3). After Sr-89 therapy, patients typically experience a 20–30% reduction in platelets as well as a 15–20% drop in WBCs (3). Blood counts are recommended every 2 weeks after Sr-89 treatment to detect any significant bone marrow toxicity (3,14). More frequent tests may be necessary for those patients with low platelets and white cell counts. The nadir of platelet depression in most patients is found at 12–16 weeks following Sr-89 therapy (14). Clinically, the patient should be watched for any bleeding tendency or infection.

### SAFETY PRECAUTIONS

Because Sr-89 is a pure beta emitter with maximum range in tissue around 8 mm, there is no

significant external radiation coming from the patient (14). However, Sr-89 has a relatively long physical half-life of 50.5 days, and appropriate precautions should be taken by any caretakers to prevent contamination by the patient's excretions (Table 4). Sr-89 is excreted in the urine and feces in a 2:1 ratio in patients with bony metastases (14). Patients should be instructed to avoid urinals or bedpans if possible. If a urinal or bedpan has to be used, it should be thoroughly rinsed after use. Any spilled urine should be wiped with a disposable tissue and flushed away. Caretakers should wear disposable gloves while handling any contaminated items.

In the first few days after therapy, Sr-89 may be found in the patient's blood (8). Within this period, any accidental blood spill during a blood drawn or bleeding from other sources should be wiped up and disposed of through the toilet. Disposable gloves should be worn by the blood drawer or caretaker

**TABLE 4.** *Information for patients*

1. What effects will Sr-89 (Metastron) have?  
In general, the patient will feel little effect right after Sr-89 injection. The reduction of bone pain will not occur until 1–2 weeks later, and sometimes it will take longer before pain palliation occurs. Occasionally, the patient may experience a flare phenomenon with more pain than usual at 2–3 days after Sr-89 therapy. There is no need for alarm since this will last only a few days, and the attending physician may increase the pain medication temporarily.
2. Are there side effects after Sr-89 therapy?  
Side effects that patients can feel are quite uncommon. There may be a fall in the number of blood cells in the first 2–4 months, and the attending physician would check the blood counts periodically (usually every 2 weeks).
3. Is there any restriction in diet or activity before or after Sr-89 therapy?  
None.
4. What are the precautions after Sr-89 treatment?  
The following precautions are recommended for the first week after Sr-89 injection:
  - A. If feasible, the patient should use a normal toilet in preference to a urinal or bedpan. The toilet should be flushed twice. Should any urine be spilled, it should be wiped clean with a disposable tissue and then flushed away. The patient should wash the hands thoroughly after using the toilet.
  - B. If a urinal or bedpan has to be used, the urine should be emptied into the toilet and flushed away. Any dripping from the urinal should be wiped with disposable tissue and then flushed through the toilet. The urinal should be rinsed several times and dried before reuse. If a urine collection device is used, the patient should check with the attending physician or consult the Nuclear Medicine Department for advice.
  - C. If the patient has an accidental cut, the spilled blood should be washed away or wiped clean with a sterile gauze, which should be flushed through the toilet afterwards.

during cleaning. Any clothing contaminated with blood should be thoroughly washed and dried separately from other clothing.

Sr-89 should not be administered to an incontinent patient due to potential Sr-89 contamination of the patient's clothing, bedding, and environment (22). In the exceptional case where Sr-89 therapy is given to an incontinent patient, the caretaker(s) must closely follow radiation safety precautions discussed below. Consultation with the institute's Radiation Safety Officer (RSO) or health physicist is highly recommended. In general, fecal incontinence is harder to handle than urinary incontinence. All fecal excretions and disposable contaminated items must be collected and flushed through the toilet whenever possible. Any contaminated bedding and clothing should be thoroughly cleaned in a designated washing machine and dryer separate from uncontaminated items. An incontinent patient should be catheterized (14) until the radiation level of the urine has essentially returned to background level. This will take at least 1 week. The urine may be emptied into the toilet and flushed, but the empty urine bags should be returned to the Nuclear Medicine Department or RSO for disposal. The required time for radioactive decay to background level is usually 10 half-lives (505 days, because the half-life of Sr-89 is 50.5 days).

Blake et al. (8) investigated the strontium kinetics in 14 patients with disseminated prostate carcinoma after Sr-89 therapy and found that the total body strontium retention at 90 days varied from 11% to 88%. Those patients with extensive bony metastases shown by bone scans had higher whole body retention of strontium than those with isolated bony metastases. In 1942, Pecher (23) measured the urinary and fecal excretion in a few patients with widespread bony metastases from prostate cancer and found that the fecal excretion was about half that of urinary excretion.

Sr-89, like calcium, is secreted into human milk, and breast feeding must be discontinued by mothers about to receive intravenous Sr-89 (14).

If the patient expires shortly after receiving Sr-89 therapy, it has been shown that cremation does not pose any significant environmental hazard (24). If an autopsy has to be performed, the pathologists and their assistants should be informed of any recent Sr-89 therapy so that appropriate radiation safety measures can be undertaken. As with cremation, burial of the body should not pose any significant radiation environmental hazard; however, the funeral home personnel should be alerted to take radiation safety precautions when embalming the body.

## DISCUSSION

The primary goal of Sr-89 therapy is pain palliation with preservation of quality of life. Many patients receiving Sr-89 can decrease or eliminate their narcotic requirements along with the associated adverse effects of the drugs.

Narcotic analgesics should be tapered slowly because of the development of physical dependence after long-term use (25). Abrupt withdrawal of opioids after prolonged administration produces an abstinence syndrome, characterized by anxiety, agitation, tremors, insomnia, fear, chills alternating with hot flashes, salivation, lacrimation, rhinorrhea, and diaphoresis. A tapering scheme has been recommended by the American Pain Society (26): one-half of the previous daily dose is given in q 6 h doses for the first 2 days. Then the doses are reduced by 25% every 2 days until a low total daily dose of 30 mg/day of oral morphine in the adult, or 0.6 mg/kg/day in a child, is reached. After 2 days at this low dose, the opioid will be discontinued.

There are minimal side effects associated with Sr-89 therapy, and, with appropriate monitoring, a patient responding to Sr-89 therapy may be able to receive repeated doses usually at intervals of  $\geq 3$  months. The Sr-89-induced pain reduction can help restore a patient's mobility, help maintain independence, and improve the patient's quality of life. □

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