Strontium-89 Therapy for the Pain of Osseous Metastases

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A Phase I and II study has been conducted of the safety and efficacy of ^{89}Sr (injected i.v. as the chloride) to alleviate bone pain due to osseous metastatic disease. Potential attendant hematologic toxicity was also examined. Strontium-90 impurities were always less than 1.5%, employing a new quality control technique which detects the ^{90}Y "daughter." Thirty-eight patients with pain due to osseous metastases requiring regular narcotic more than twice a day, documented by an abnormal bone scan and radiography, received 45 doses (1–4.5 mCi, 16–70 μCi/kg) of ^{89}Sr after informed consent. The performance status (Karnofsky scale) ranged from 20–80%. One patient had complete pain relief while 22 other doses yielded at least a 25% reduction in narcotic requirement lasting at least 1 mo and/or 20% improvement in Karnofsky scale rating. Two patients had marked to complete relief in tumor sites which were not fractured, with no change in fracture pain. Twenty-two did not respond. Response was independent of narcotic requirements, tumor type, or Karnofsky status. No hematologic toxicity occurred. Strontium-89 may be useful as adjuvant therapy for diffuse bone pain, but a double-blind study comparing it to other nonnarcotic modalities is required.

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The problem of pain related to chronic osseous metastases is all too familiar to health professionals in all areas of oncology. Attempts to control bone pain usually are initiated with focal radiotherapy and systemic chemotherapy. If the pain persists, nonnarcotic analgesia may be of assistance, but opiates eventually are prescribed in many instances. Along with some degree of opiate-induced analgesia comes tolerance to the initial dose, and troublesome constipation and somnolence as the dose is increased. Phosphorus-32 (^{32}P) has been employed for this purpose for many years but has significant hematologic toxicity, since the marrow dose is 24 rad/mCi delivered over a far shorter time than with strontium-89 (^{89}Sr) (*1*). The percent of activity of ^{32}P activity and ^{89}Sr decaying at 3, 7, and 14 days appears in Table 1.

Strontium-89, a bone-seeking radionuclide, has been reported to provide pain relief in several clinical trials (*2–7*), but the end points to determine pain relief in these studies were apparently subjective. The difficulties of measurement of pain and analgesia in cancer patients are considerable; some new approaches have been recently reviewed (*8*). We have performed a trial of ^{89}Sr therapy in 38 patients with clearly defined criteria for response in an attempt to more objectively evaluate the clinical role of ^{89}Sr therapy for pain related to osseous metastases.

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MATERIALS AND METHODS

The results of 45 courses of therapy with ^{89}Sr chloride in 38 patients were evaluated. Five patients received two treatments and one was treated three times. These patients all had tissue-proven metastatic disease. The primary site was prostate in 17, breast in 11, lung in four, with single cases of colon, salivary, and cervical adenocarcinoma, melanoma, lymphoma, and myeloma. All patients were referred for pain not well controlled by opiates and had received prior chemotherapy or hormonal manipulation (eight), radiotherapy alone (eight), or both (22), with no significant palliation of pain, or pain recurrence with inability to tolerate further such treatment at the time of referral. The median Karnofsky

TABLE 1
Percent of Activity of ^{32}P and ^{89}Sr Decayed at a Given Time

Elapsed time (days)	% Activity decayed at elapsed time	
	^{32}P ($t_{1/2}$ 14.3 d.)	^{89}Sr ($t_{1/2}$ 50.5 d.)
3	13.5	4.0
7	28.8	9.2
14	49.3	17.5

score was 50, range 20 (three patients) to 80 (two patients). All patients showed abnormal technetium-99m (^{99m}Tc) diphosphonate uptake in the painful areas by bone scintigraphy within 6 wk prior to therapy. Thus patients with painful bone lesions which were purely osteolytic, and where the calcium analog would not be deposited, were not candidates for therapy.

Since there was concern about potential marrow toxicity, treatment doses were begun at 16–20 μCi/kg with gradual dose escalation as high as 70 μCi/kg. The strontium was administered as a single i.v. injection over 15–30 sec. All patients had complete blood counts repeated every 1–2 wk over an 8-wk period and then at least monthly for the duration of their life. A repeat serum alkaline phosphatase level was obtained as well, whenever possible. No patients were lost to follow-up.

Strontium-89 total-body retention varies widely, ranging from 30 to 80% in one series of patients with osteoblastic metastases (*4*), so we did not routinely measure this value.

Criteria for response were as follows:

1. A reduction of narcotic intake over a 24-hr period of 25% or more from pretreatment level and/or

2. An improvement of 20% (two stages) in performance (Karnofsky) scale with or without a reduction in narcotic dosage, but with no increase in 24-hr narcotic requirement. More complex psychometric measurements (*8*) were not employed.

Assay of ^{89}Sr activity (as $SrCl_2$), as well as the strontium-90 (yttrium-90) [$^{90}Sr(^{90}Y)$] impurities, was made with a liquid scintillation counter calibrated with ^{89}Sr and $^{90}Sr(^{90}Y)$ standards. Since the presence of $^{90}Sr(^{90}Y)$ in the product will not be beneficial to the patient and could cause radiation osteonecrosis over a period of years, we limit the use of this radiopharmaceutical to less than 1.5% ^{90}Sr. The relative ingrowth of this impurity in ^{89}Sr is the controlling factor in determining the shelf-life of the radiopharmaceutical.

At the completion of processing (using an energy window above 1.5 MeV to detect ^{90}Y, the decay product of ^{90}Sr) the ^{90}Sr content varied from 0.55 to 1.1%, allowing an average shelf life of 45 days (range 20 to 73 days). Monthly shipments of ^{89}Sr generally allow continuous availability of the radiopharmaceutical year round.

Strontium-85, a 514 keV gamma emitter, is another potential impurity in ^{89}Sr radiopharmaceuticals depending on its method of production. No ^{85}Sr was detected in the 13 batches of ^{89}Sr received from our vendor. Table 2 indicates the physical properties of these radionuclides.

TABLE 2
Physical Properties of ^{89}Sr and Its Radiocontaminants

Radionuclide	Half-Life	$E_{\beta max}$	E_γ
^{85}Sr	65.1 days	—	513.9 keV (99.19%)
^{89}Sr	50.6 days	1.46 MeV	909.1 keV (0.02%)
^{90}Sr	28.1 yr	0.5460 MeV	—
^{90}Y	64.0 hr	2.2730 MeV	—

RESULTS

The responses to ^{89}Sr injections as defined in the Materials and Methods section appear in Table 3. Some pain relief, as measured by analgesic reduction and/or improved performance status, occurred in 23/45 (51%) of injections. Of these, only one patient was completely relieved of his discomfort while four patients had relief in nonfractured sites only. Eighteen others had a partial response.

A dose-response relationship was sought but none was detected as noted in Table 4. Failures were as likely as responses at all dose levels and for all tumor types. The Karnofsky self-care or performance scale also failed to predict responders (Table 5). There was no difference in the percent responders with breast compared with prostate cancer ($p > 0.1$).

Since pretreatment severity of pain might affect response to ^{89}Sr therapy we related therapeutic response to narcotic dose. We defined narcotic tolerance as a 24-hr requirement for opiates in excess of the maximum suggested in the manufacturer's package insert. As detailed in Table 6 narcotic tolerance did not predict ^{89}Sr response either.

Response to ^{89}Sr never occurred before the third day and the latest response reported was the 25th day post-

TABLE 3
Response of Bone Pain to ^{89}Sr*

Item	% Response
Pain free	1 (2%)
Response in all sites but some pain persisting	18 (40%)
At least one site responding	4 (9%)
No response	22 (49%)
Total number of patients	45 (100%)

* Improvement of two grade in Karnofsky scale and/or reduction in analgesic dose/day ≥ 25%.

TABLE 4
Response to ^{89}Sr as Related to Dose

Item	Response	Dose of ^{89}Sr (μCi/kg) 10–20	21–30	31–40	41–50	51–60	61–70	Total
Pain reduction and/or activity increase	Yes	6	3	6	5	3	0	23
	No	4	3	5	6	3	1	22

* Improvement of two grade in Karnofsky scale and/or reduction in analgesic dose/day ≥ 25%.

injection; median time to respond was 9 days. The duration of response averaged 1.6 mo, ranging from 1–4 mo. In our population, median posttreatment survival was only 4 mo. Three of six patients responding to a first injection had a response to the second or third.

As previously reported (*2–7*), no hematologic toxicity was observed.

DISCUSSION

Strontium, like calcium, is in family IIA of the periodic table and, as a divalent cation, is incorporated into hydroxyapatite, with whole-body retention of 30–80%. Bone scintigraphy demonstrating increased uptake of [^{99m}Tc]diphosphonate localizes areas of increased osteoblastic activity where excessive new bone is being laid down. A radioisotope such as ^{89}Sr, with no gamma radiation, would seem ideal to substitute for calcium in reactive bone adjacent to tumor to provide a local radiotherapeutic effect. Phosphorus-32 gives higher marrow doses per mCi over the life span of these patients and is clearly myelosuppressive.

Our response rates as shown in Table 3 do not approach the complete plus partial responses published previously (Table 7). The doses injected by these European authors were equal to or less than ours. They employed an ^{85}Sr bone scan to detect treatable osteoblastic lesion, but there are no data to suggest that the [^{99m}Tc]diphosphonate radiopharmaceuticals have any different affinity for osteoblastic metastases than strontium. We used the ^{89}Sr Bremsstrahlung to scan three patients, and the abnormal areas of uptake on these (poor quality) images matched those seen with the [^{99m}Tc]diphosphonates.

TABLE 5
Pain Reduction by ^{89}Sr Related to Karnofsky Self-Care Scale

Item	Karnofsky scale Response	≥50	≤40	Total
Patients with pain reduction	Yes	12	11	23
	No	14	8	22

It is likely that the patients we treated had more advanced disease than those in the studies summarized in Table 7, since survival was considerably shorter in our group. Furthermore, it is apparent that ^{89}Sr therapy cannot relieve pain caused by pathologic fractures or by tumor invasion of the spinal cord or peripheral nerves near involved bone. It was probably for these reasons that we could find no clear relationship between intensity of uptake and pain relief.

The radiation doses from ^{89}Sr, calculated according to the International Commission on Radiological Protection schema, appear in Table 8. One millicurie of ^{89}Sr appears to deliver a rather low radiation dose to osseous metastases. Other groups have calculated a somewhat higher bone dose, slightly in excess of 1,000 rad/mCi using an older schema for β-particle dosimetry (*3*). It is difficult to understand pain relief occurring in as early as 1–3 days postinjection for reasons other than the placebo effect since the dose delivered at these times is low.

Our review of hematologic responses shows no myelosuppression, in agreement with other groups using ^{89}Sr (*2–7*). We gave ^{89}Sr to patients with leukocyte counts as low as $2.2 \times 10^3/\mu l$ without any change in blood counts. When the leukocyte count occasionally dropped over a period of 2 to 3 mo from, e.g., 11.7 to $4.9 \times 10^3/\mu l$ in one case, the platelet count remained normal, excluding recognizable myelosuppression over the time period we were able to follow our patients. Pecher found

TABLE 6
Pain Reduction by ^{89}Sr Related to Presence of Narcotic Tolerance

Item	Response	Narcotic tolerance* Yes	No
No. patients with pain reduction and/or activity increase	Yes	11	12
	No	12	10
Total		23	22

* Narcotic dose in excess of manufacturer's maximum recommendation.

TABLE 7
Previous Published Data Using ^{89}Sr for Bone Pain from Osseous Metastases

Author	Journal	^{89}Sr dose	Results			Duration (mean)
			CR	PR	NR	
Kutzner et al.	*Strahlentherapie* 154:317,1978	0.8–2.7 mCi	2	14	3	4 days–5 mo
Correns et al.	*Eur J Nucl Med* 4:33, 1979	1 mCi	8	3	1	1–14 mo (6 mo)
Firusian et al.	*Z Krebsforsch* 91:143, 1978	10–30 μCi/kg	33	4	6	1–7 mo (2.6 mo)
Total			43 (58%)	21 (28%)	10 (14%)	

only mild myelosuppression with ^{89}Sr at 250 μCi/kg in rabbits and 9,000 μCi/kg in mice (*9*). The alkaline phosphatase of our patients remained stable or rose slowly as osseous tumor progressed.

Seven patients received further focal radiotherapy 3 or more weeks following ^{89}Sr, since we felt that pain relief from ^{89}Sr should have occurred by this time. However, only two benefited from this teletherapy. The pain of one patient partially responded to chemotherapy given 4 wk after ^{89}Sr.

Because of the placebo effect a double-blind study should be the next step if one believes safety and efficacy have been established. We have found that, without exception, patients (and their physicians) dealing with severe pain are unwilling to enter such a study if a saline solution is the alternative to ^{89}Sr. Strontium-89 is clearly safe in the dose range we have investigated, 16–70 μCi/kg. We believe our response rate has not been as impressive as reported by others (up to 90%) in part because our criteria were more objective. On 13 occasions the patient stated he/she felt better when actually more narcotic was being used or the patient was simply exerting himself less, with a lower Karnofsky score. If we had counted these 13 as responses, our data would have stated that the treatment was 80% effective. Other groups may have used ^{89}Sr earlier in the course of disease as well.

In summary, we have shown that ^{89}Sr is safe but not predictably efficacious in doses of 16–70 μCi/kg, contradicting more enthusiastic reports. We plan to raise the ^{89}Sr activity administered to higher levels to determine if we can produce more effective pain relief, while carefully monitoring for hematologic toxicity. Our data lead us to postulate that we can attain at least the same degree of pain relief as that possible with ^{32}P (*10*) with significantly less hematologic toxicity. Before this conclusion can be accepted, however, double-blind studies will be required.

TABLE 8
Radiation Dose from ^{89}Sr (with Maximum 1% ^{85}Sr, 1.5% ^{90}Sr) Committed Dose Equivalents*

Item	^{89}Sr	1% ^{85}Sr	1.5% ^{90}Sr†
Red marrow	39‡	0.074	35 (2.3)‡
Bone surface	59‡	0.075	78 (5.3)‡
Bone metastasis (if uptake 5× normal bone)	300‡	0.38	390 (26)‡

* rem/mCi in 50 yr.
† Includes contribution from ^{90}Y.
‡ Radiation absorbed dose in first 2 yr (rem/mCi).

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