Bone Pain Palliation with ^{85}Sr Therapy

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The aim of this retrospective study was to evaluate the efficacy of ^{85}Sr in the palliation of metastatic bone pain. ^{85}Sr decays by electron capture with a gamma emission of 514 keV and associated x-ray emissions of 10–15 keV; physical half-life is 64 d. **Methods:** Between 1977 and 1992, 119 doses of ^{85}Sr chloride (mean activity 335 MBq [9 mCi]) were intravenously administered to 108 patients with hyperalgic generalized bone metastases from prostatic carcinoma (52 patients), breast carcinoma (41) or other cancers (15). Pain, performance status, blood and urinary excretion values were investigated during follow-up, and survival time was recorded. Strontium bone scans were obtained up to 8 wk after injection to document isotope biodistribution and to estimate absorbed doses. **Results:** At 12 wk, 72.2% of patients showed significant benefit from treatment, i.e., enhanced quality of life and pain relief; 49.1% became free of pain. These beneficial effects lasted from 1 to 36 mo (mean 4.3 mo). The best symptomatic improvement was seen in patients treated at an early stage of metastatic skeletal disease and in prostate cancer patients. No evidence of a significant dose-response relationship was found in the data analysis. The mean absorbed dose ratio of metastases to marrow was estimated at 8.2. We found no evidence that hematological toxicity was a major problem; however, all patients experienced a reduction in blood counts, especially in platelets. **Conclusion:** Systemic radionuclide therapy using ^{85}Sr is a feasible, effective and well-tolerated palliative treatment in patients with refractory bone pain. We attained at least the same response rate as that reported with bone-seeking β-emitting radionuclides such as ^{89}Sr. The patients who benefited the most from ^{85}Sr treatment were in an early stage of metastatic disease or had prostate cancer. Our clinical findings could not be linked to either the total injected activity of ^{85}Sr or the estimated absorbed dose delivered to metastases.

Key Words: ^{85}Sr; radionuclide therapy; bone pain palliation

J Nucl Med 1999; 40:585–590

The palliation of pain in patients with painful bone metastases is of primary importance in the clinical management of advanced cancer. Internal therapy with radionuclides, which concentrate at sites of increased bone turnover, is used to control pain and improve quality of life as an alternative to conventional therapies. The β-emitter ^{89}Sr was first used in 1941 for the palliation of pain from metastasized prostatic carcinoma (*1*). The effectiveness of ^{89}Sr therapy has been demonstrated by many researchers, suggesting that typically about 75% of patients have a clinical benefit (*2–8*). Although ^{32}P has been abandoned, because of severe bone marrow depletion, new agents like ^{186}Re-hydroxyethylidene diphosphonate (HEDP), ^{153}Sm-ethylene diamine tetramethylene phosphonate (EDTMP) or ^{117m}Sn-diethylenetriamine pentaacetic acid (DTPA) have shown good results in human trials (*9–11*). In our institution, from 1977 to 1992, ^{85}Sr was administered at therapeutic doses to patients with hyperalgic generalized bone metastases. ^{85}Sr, formerly used for bone scanning, is a bone-seeking radionuclide that decays by electron capture, with a gamma emission of 514 keV and a physical half-life of 64 d. The associated x-ray emissions of 10–15 keV allow an effective internal radiotherapy, with a maximum dose delivered to the target within a range of 10 mm (*12–17*). Although little is known about ^{85}Sr dosimetry in normal or pathological conditions, this isotope has the advantage of documenting the metastatic extension with a bone scan, which allows a macroscopic estimation of the absorbed dose to lesions (*12,18*).

The aim of this retrospective study was to evaluate the efficacy of ^{85}Sr for the palliation of metastatic bone pain.

MATERIALS AND METHODS

Patients

Between 1977 and 1992, 108 patients (62 males, 46 females; age 16–88 y, mean age 62.5 y) with hyperalgic generalized bone metastases (not satisfactorily relieved by drug therapy, including opiates) received a therapeutic dose of ^{85}Sr chloride; 11 patients with a good response after the first treatment received a second dose because of recurrence of pain 3–9 mo later, hence a total of 119 doses (mean dose 335 MBq, 9 mCi). The primary sites of tumor were prostate (52 patients, mean age 69.0 y; 60 doses, mean activity 335 MBq, 9 mCi), breast (41 patients, mean age 56.2 y; 43 doses, mean activity 355 MBq, 9.5 mCi) or others (15 patients, 10 males and 5 females, mean age 57.8 y; 16 doses, mean activity 290 MBq, 7.8 mCi) (Table 1). Only patients with performance status ≤ 2, a life expectancy of at least 3 mo and acceptable blood counts (leukocytes > 2.5×10^9/L: range 3.2–13.2 × 10^9/L, mean 5.3 × 10^9/L; thrombocytes > 75×10^9/L: range 108–580 × 10^9/L, mean 189 × 10^9/L) were eligible (Table 2). To document the extent of the metastatic disease, all patients underwent a ^{99m}Tc-methylene diphosphonate (MDP) bone scan a few days before the therapeutic injection of ^{85}Sr. We counted 8 cases of paucifocal extension (<5 lesions), 27 of plurifocal extension (5–10 sites) and 84 of diffuse metastatic involvement (more than 10 sites) (Table 3). Before radionuclide therapy, all patients had received chemotherapy or hormonal therapy, plus radiotherapy on painful sites.

Received Mar. 24, 1998; revision accepted Oct. 3, 1998.

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TABLE 1
Patient Characteristics

Site	Age (y)	No. of patients	Doses	Activity in MBq
Prostate	52–88 (mean 69.0)	52*	60	45–780 (mean 330)
Breast	31–78 (mean 56.2)	41†	43	155–555 (mean 355)
Others	16–78 (mean 57.8)	15 (10*, 5†)	16	75–740 (mean 285)
Total	16–88 (mean 62.5)	108 (62*, 46†)	119	45–780 (mean 335)

*male.
†female.

Dosimetry

Because of the hematological toxicity of the treatment, the standard dose of 370 MBq (10 mCi) was reduced empirically in cases of high risk of bone marrow depletion (advanced age, recent chemo- or radiotherapies, large extent of the metastatic disease on bone scans). Conversely, the dose was increased in cases of severe pain or if the metastatic extension to bone was low. Therefore, the mean activity administered was 335 MBq, but the range varied from 45 to 740 MBq (1.2–20 mCi) (Table 1).

Follow-up

To avoid environmental contamination after the injection, all patients were admitted to hospital isolation facilities for at least 7 d (mean 10 d), until radiation doses returned to the permitted levels (25 μSv/h at a distance of 1 m from the body). During hospitalization, urine was collected and its activity measured. Strontium bone scans, obtained up to 8 wk after injection, allowed documentation of isotope biodistribution and estimation of absorbed doses. For each patient, a clinical follow-up was performed at 4, 8 and 12 wk. A blood count was also obtained. Any modification in bone pain, mobility and use of pain medication was recorded. Pain relief was evaluated subjectively by the patient and objectively by the reduction of the analgesic dose and the change in performance status. The response to treatment was defined as complete (complete pain relief, a decrease in performance status [unless it was already 0] and at least a 50% decrease in opiate doses during at least 4 mo, unless patient died sooner than 4 mo with persisting efficient pain control), partial (significant improvement of pain control during at least 2 mo) or none (all others), and the duration of the remission was recorded.

TABLE 2
Performance Status

Performance status (WHO)	No. of cases (%)
0	13 (10.9)
1	68 (57.1)
2	38 (31.9)

WHO = World Health Organization.

TABLE 3
Metastatic Extent to Bone

No. of metastatic sites on ^{99m}Tc bone scan	No. of cases (%)
<5	8 (6.7)
5–10	27 (22.7)
>10	84 (31.9)

Statistics

A statistical program was used for calculations of medians, ranges and the analysis of variance. χ^2 test was also used where specified. P value < 0.05 was considered as statistically significant. When using χ^2 test, partial response and complete response were considered as one group. No valid control group could be set up because most eligible patients in our institution received ^{85}Sr treatment.

RESULTS

Clinical Results

The quality of the post-therapeutic ^{85}Sr bone scans was mostly acceptable (Fig. 1). Whole-body distribution of ^{85}Sr

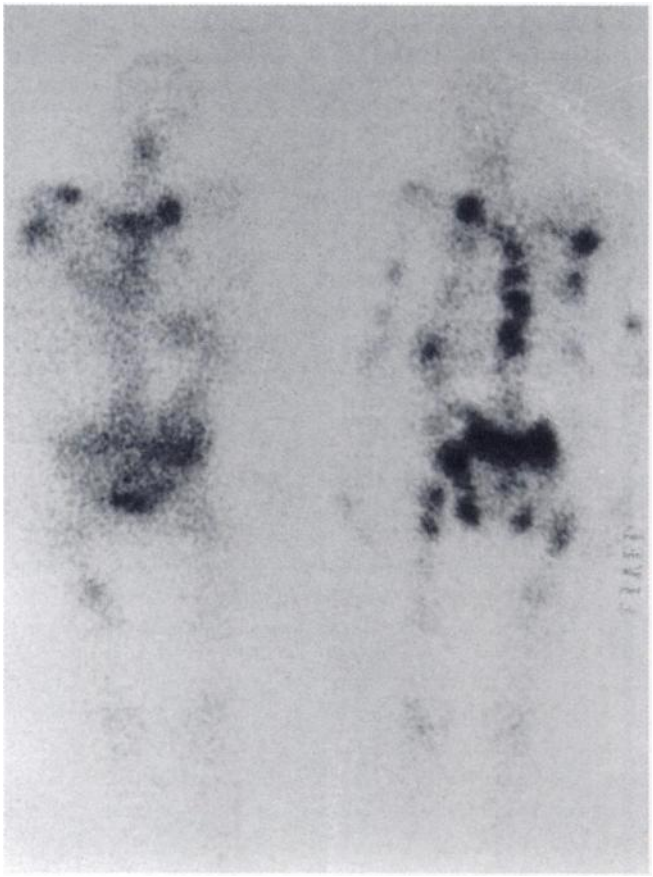

FIGURE 1. Images of 55-y-old man with metastatic prostatic carcinoma were obtained 14 d after intravenous injection of 445 MBq (12 mCi) ^{85}Sr, using large field-of-view gamma camera with high-energy collimator rated to 514 keV. Anterior and posterior whole body images show multiple focal areas of increased uptake at metastatic sites.

was similar to that of ^{99m}Tc-MDP. Overall results showed pain relief 12 wk after the first ^{85}Sr administration in 78 of 108 patients (72.2%): 53 patients (49.1%) became effectively pain free, and 25 patients (23.1%) had partial pain relief. After the second dose, only 6 of 11 patients (54.5%) showed some benefit from treatment (Table 4). A flare response was observed in 4 patients (3.7%) between the second and the fourth day. Symptomatic improvement, when it did occur, usually occurred between the fourth and the eighth day. A couple of patients reported some relief as soon as the following day (this may partly account for a decrease in activity of patients confined in their room). Beneficial effects lasted from 1 to 36 mo with a mean of 4.3 mo (4.7 mo in cases of complete response and 3.4 mo in cases of partial response).

TABLE 4
Clinical Results

Site of primary tumor	Pain relief			
	None	Partial	Complete	Total
Prostate				
Cases (%)	14 (23.3)	14 (23.3)	32 (53.3)	60 (100)
Patients (%)	10 (19.2)	13 (25)	29 (55.8)	52 (100)
Mean activity injected (MBq)	290	330	355	335
Mean duration (mo)*	—	4.2	4.7	4.6
Mean survival (mo)†	3.5	9.5	10.2	8.5
Mean survival (mo)‡	4.2	9.5	10.7	9.1
Breast				
Cases (%)	13 (30.2)	8 (18.6)	22 (51.2)	43 (100)
Patients (%)	13 (31.7)	8 (19.5)	20 (48.8)	41 (100)
Mean activity injected (MBq)	415	315	335	355
Mean duration (mo)*	—	2.9	5.0	4.4
Mean survival (mo)†	2.4	5.3	10.1	6.9
Mean survival (mo)‡	2.6	5.3	10.1	7.2
Other				
Cases (%)	8 (50)	4 (25)	4 (25)	16 (100)
Patients (%)	7 (46.7)	4 (26.7)	4 (26.7)	15 (100)
Mean activity injected (MBq)	285	370	210	290
Mean duration (mo)*	—	1.8	3.3	2.6
Mean survival (mo)†	2.0	6.8	4.8	3.9
Mean survival (mo)‡	2.6	6.8	6.0	4.9
Total				
Cases (%)	35 (29.4)	26 (21.9)	58 (48.8)	119 (100)
Patients (%)	30 (27.8)	25 (23.1)	53 (49.1)	108 (100)
Mean activity injected (MBq)	335	330	335	335
Mean duration (mo)*	—	3.4	4.7	4.3
Mean survival (mo)†	2.8	7.8	9.8	7.3
Mean survival (mo)‡	3.3	7.8	10.2	7.9

*Mean duration of the pain relief in cases of partial or complete response.
†Mean survival including those who died in the first 4 wk.
‡Mean survival excluding patients who died in the first 4 wk.

TABLE 5
Results Depending on the Performance Status and on the Extent of Metastatic Disease

Performance status	Pain relief		
	None	Partial	Complete
0	3 (23.1)	1 (7.7)	9 (69.2)
1	12 (17.6)	14 (20.6)	42 (61.7)
2	20 (52.6)	11 (28.9)	7 (18.4)
Total	35 (29.4)	26 (21.9)	58 (48.8)
Extent of metastatic disease			
<5 metastatic sites	2 (25)	1 (12.5)	5 (62.5)
5–10 metastatic sites	2 (7.4)	5 (18.5)	20 (74.1)
>10 metastatic sites	31 (36.9)	20 (23.8)	33 (39.3)
Total	35 (29.4)	26 (21.9)	58 (48.8)

With regard to the site of primary tumor, the higher symptomatic improvement was obtained in patients with prostate cancer (76.6% of pain relief, with mean response of 4.6 mo). Furthermore, the survival was longer in patients with meaningful clinical response, especially when excluding patients who died in the first 4 wk after therapy, but only in prostate ($P < 0.05$) and breast cancers ($P < 0.01$); no significant difference in survival was shown in other cancers, whether one includes or excludes patients who died in the first 4 wk. A correlation between the performance status and the response was seen: The better results were obtained in patients with good general condition (χ^2 test, $P < 0.01$) (Table 5). Another correlation between the extent of bone metastases and the response was seen: The better results were obtained in patients with fewer metastases on the ^{85}Sr bone scan (χ^2 test, $P < 0.01$) (Table 5).

For prostate cancer patients, the clinical results may seem slightly related to the injected activity (highest mean activity and best results), but a global data analysis showed no evidence of a significant dose-response relationship overall.

Dosimetric Results

Theoretically, the absorbed dose delivered to bone (D) at infinite time, during ^{85}Sr radiotherapy, is given by:

$$D = k \times (A - U),$$

where A is the administered activity and U is the urinary excretion. For a simple estimation of the absorbed dose, we considered the cumulative urinary excretion of ^{85}Sr during only the first 7 d after injection. Therefore, we assumed, according to total-body strontium retention studies in normal subjects previously performed and using the Interna-

tional Commission for Radiation Protection model for bone dosimetry, that k = 0.35 cGy/MBq (13 cGy/mCi) for bone marrow and 1.4 cGy/MBq (52 cGy/mCi) for bone (*12*). In pathological conditions, the doses to normal (D_n) and pathological (D_p) compartments are not equivalent and one must take into account the metastatic extension M, that has a proper relative uptake R. Thus, if we imagine a homogeneous distribution of the radioisotope:

$$D = M \times D_p + (1 - M) \times D_n \quad \text{and} \quad D_p = R \times D_n,$$

knowing U (urine sample), M and R (evaluated from the ^{85}Sr bone scan), it is possible to estimate the absorbed dose to normal and pathological compartments delivered by the administered activity A at infinite time.

In this work, the estimation was impossible to make in 27 of 119 cases, because of a failure to collect the urine effectively or the bad quality of the images (Table 6). Usually, the urinary excretion of ^{85}Sr was important mainly in the first 2 d after therapeutic administration, representing about 75% of the total activity in urine collected during hospitalization. The macroscopic dose estimation suggested that the absorbed dose by normal bone marrow rarely exceeded 70 cGy for all of the patients. The absorbed-dose ratio of metastatic bone to marrow ranged from a low of 3 to a high of 15, with a mean of 8.2. Although the estimated doses delivered to lesions seemed higher in cases of complete response (mean 630 cGy, with a ratio of absorbed dose of 1.81 cGy/MBq [67 cGy/mCi]), especially in prostate cancers, this has not been proved statistically significant.

Hematological Results

In a significant number of cases, these data were sparse. A reduction in leukocyte and thrombocyte levels was observed in most patients, with a mean time to reach the nadir of about 6 wk. The mean reduction at nadir was about 30% for leukocytes and 40% for thrombocytes (Table 7). The toxicity of the treatment seemed higher with bone marrow depletion as a consequence of either previous treatments or metastatic marrow involvement. Transfusion was necessary in 24 patients, with no significant relation to dose, but 23 of them had already needed transfusions before ^{85}Sr therapy. No connection was observed between the reduction of blood counts and the extent of bone metastases. One patient with significant bone marrow involvement had a fatal myelodepression in the fourth month. In another patient, an acute myeloid leukemia was reported 11 mo after treatment.

TABLE 6
Dosimetric Results

Site of primary tumor	Pain relief			Total
	None	Partial	Complete	
Prostate				
Cases (%)	8 (17.4)	11 (23.9)	27 (58.7)	46 (100)
Mean activity (MBq)	305	340	370	350
Urinary excretion*	22.0	20.1	17.5	18.9
Dose to metastases (cGy)†	542	548	674	621
Dose to marrow (cGy)‡	69	70	72	71
Dose ratio (cGy/MBq)§	1.78	1.61	1.82	1.77
Tumor ratio¶	7.86	7.83	9.36	8.74
Breast				
Cases (%)	11 (33.3)	6 (18.2)	16 (48.5)	33 (100)
Mean activity (MBq)	415	325	335	360
Urinary excretion*	35.8	33.5	24.6	30.0
Dose to metastases (cGy)†	493	555	574	544
Dose to marrow (cGy)‡	70	75	70	71
Dose ratio (cGy/MBq)§	1.19	1.71	1.71	1.51
Tumor ratio¶	7.04	7.40	8.20	7.66
Other				
Cases (%)	6 (46.2)	4 (30.8)	3 (58.7)	13 (100)
Mean activity (MBq)	305	370	220	305
Urinary excretion*	26.1	22.3	16.3	22.7
Dose to metastases (cGy)†	491	555	534	520
Dose to marrow (cGy)‡	62	74	63	66
Dose ratio (cGy/MBq)§	1.61	1.50	2.43	1.70
Tumor ratio¶	7.92	7.50	8.48	7.90
Total				
Cases (%)	25 (27.2)	21 (23.9)	46 (50)	92 (100)
Mean activity (MBq)	355	340	350	350
Urinary excretion*	29.0	24.3	19.9	23.4
Dose to metastases (cGy)†	508	551	630	579
Dose to marrow (cGy)‡	68	72	71	70
Dose ratio (cGy/MBq)§	1.44	1.62	1.81	1.66
Tumor ratio¶	7.49	7.65	8.89	8.24

*Cumulated after 7 d, expressed as percentage of the administered activity.

†Mean estimated dose to metastases.

‡Mean estimated dose to normal bone marrow (the estimated dose to normal bone is four times this value (*12*).

§Mean ratio between dose to metastases and activity.

¶Mean ratio between dose to metastases and normal bone marrow.

DISCUSSION

Systemic radionuclide therapy is an optimal choice in the management of intractable metastatic bone pain. However, despite many large-scale studies, the choice of the optimal radiopharmaceutical is still under discussion. Among the potential radionuclides, ^{89}Sr and ^{153}Sm-EDTMP are approved for metastatic pain palliation by American, French and other European regulatory authorities, and new agents

TABLE 7
Hematological Toxicity 6 Weeks After Therapy

Toxicity	Leukocytes ($\times 10^9$/L)	Thrombocytes ($\times 10^9$/L)
Grade I	3.0–3.9	>75
No. of cases (%)	53 (45)	42 (35)
Grade II	2.0–2.9	50–74.9
No. of cases (%)	18 (15)	30 (25)
Grade III	1.0–1.9	25–49.9
No. of cases (%)	12 (10)	24 (20)
Grade IV	<1.0	<25
No. of cases (%)	1 (1)	1 (1)

like ^{186}Re-HEDP and ^{117m}Sn-DTPA have shown good results (*4–11*).

We wanted to review our experience with ^{85}Sr, used from 1977 to 1992 at therapeutic doses, in patients with hyperalgic generalized bone metastases.

^{85}Sr decays by electron capture with a gamma emission of 514 keV, thus allowing imaging. Obviously, ^{99m}Tc-MDP, which presents better physical (radioprotection and imaging) and logistic (cost, availability) characteristics, is the radiopharmaceutical of choice for diagnostic purposes. However, because of the associated x-ray emissions of 10–15 keV, ^{85}Sr provides an effective internal radiotherapy, with a maximum dose delivered to target within a range of 10 mm (in water and soft tissues), which is similar to that of ^{89}Sr (*12–17*). The standard dose of 370 MBq (10 mCi) ^{85}Sr was reduced empirically in cases of high risk of bone marrow depletion (i.e., advanced age, recent treatments) and increased if the bone pain was high or if metastatic extension to bone was low (estimated by ^{99m}Tc-MDP bone scan).

In this study, the global hematological toxicity of the treatment was low, the most significant factor being a decrease in platelet counts that was partially restored a few months later. However, 1 patient with significant bone marrow involvement had a fatal myelodepression in the fourth month. This patient, who had not undergone previous chemotherapy, was 77 y old and received an average dose to normal bone marrow of 49 cGy. We believe that the age of the patient and the extent of marrow involvement can explain the aplasia. One case of acute myeloid leukemia was reported after 11 mo of treatment, thus no causal relationship with the therapy can be clearly established.

Although no connection was observed between the reduction of blood counts and the extent of bone metastases, the former was incompletely documented and the latter was quoted only according to the number of sites as few, many or diffuse. Because the extent of bone metastases was not pivotal in this study, we did not expand on it as did de Klerk et al. (*19*).

Clinical results demonstrated that ^{85}Sr is effective in the great majority of patients, even when conventional treatments have failed. At 12 wk, 72.2% of patients had significant benefit from treatment in terms of enhanced quality of life and subjective pain relief; 49.1% became free of pain. Beneficial effects lasted from 1 to 36 mo (with a mean of 4.3 mo). Therefore, we attained at least the same response rate as that reported with ^{89}Sr (*2–8*). Furthermore, survival was slightly longer in patients with meaningful clinical response when excluding patients who died in the first 4 wk after therapy, but this was significant only in prostate ($P < 0.05$) and breast cancers ($P < 0.01$).

From the analysis of the results, there is some indication that the clinical response was not dose related but was correlated with patients' general condition and metastatic bone involvement; those patients in earlier stages showed the best improvement, especially in prostate cancer. Because the extent of bone metastases on ^{85}Sr bone scan was shown to represent a reliable prognostic indicator of the efficiency of the treatment, as for the other radiopharmaceuticals, there is an advantage in treating metastatic skeletal disease at an early stage (*5–11*). This finding was not reported by another author (*20*).

It is important to notice that in the 11 patients who received a second dose of ^{85}Sr after the palliation effect of the first one ended, the clinical response was generally less significant than the one seen with the first dose.

Because a simple evaluation of the results on the basis of the total administered activity seemed unreliable, we tried to evaluate the ^{85}Sr retention in the lesions. A precise dosimetric evaluation presents logistic problems (especially important with 119 cases) and questionable results because of the nonuniformity of the dose distribution within the lesions (heterogeneity of the material and of the distribution of the radionuclide [*3*]). The aim of this study of ^{85}Sr therapy efficiency was essentially clinical; therefore, we performed a macroscopic dose estimation by measuring the cumulative urinary excretion of ^{85}Sr during hospitalization and the patterns of uptake of the lesions on ^{85}Sr bone scans. Because ^{85}Sr uptake is attributed to an exchange mechanism with calcium in the bone mineral matrix, body retention, evaluated by urinary excretion, is due to the avid uptake of the radionuclide in lesion sites. For the same reason, the extension and the metabolic activity of the metastases, shown on ^{85}Sr bone scan, positively influences the absorbed dose delivered to the lesions. Two limiting factors in these dose estimations are the poor resolution of the ^{85}Sr bone scan and the short duration of the urine collection. However, these dosimetric estimations showed that the differences in pain relief could not be linked in a statistically significant way to the injected activity or the dose delivered to the metastases.

With our assumptions, we calculated that the delivered dose to metastases at infinite time ranged from 674 cGy (complete pain relief in prostate cancer patients) to 491 cGy (no response in other cancer patients), with a mean value of 579 cGy. The estimated absorbed doses are sufficiently large to expect a therapeutic benefit. Doses to red marrow were smaller by a factor of about 8. These values are similar to those published with ^{89}Sr (*5–8*). Conversely, our values of cumulative ^{85}Sr retention, 7 d after the therapeutic injection,

seemed higher than in other published data, probably because of a larger metastatic bone extension in our patients (*2–8*).

CONCLUSION

Systemic radionuclide therapy using ^{85}Sr is a feasible, effective and well-tolerated palliative treatment in patients with refractory bone pain. Almost 3 in 4 patients received a benefit, lasting up to 3 y (mean 4.3 mo) with very few serious side effects. This therapy was especially effective in patients with prostate cancer. The best results were obtained when patients received the treatment while in an early stage of metastatic disease. This has also been shown with ^{89}Sr and contrasts with the usual indications of palliative radionuclide therapy. Response was correlated neither to injected activity nor estimated dose. A major problem of ^{85}Sr therapy is related to the gamma emission of the isotope and to radioprotection problems. However, in this retrospective study, we attained at least the same response rate as that reported with bone-seeking β-emitting radionuclides. Thus the use of ^{85}Sr for therapeutic purposes should be reconsidered.

A limitation of this study is the absence of a control group. These results would theoretically warrant a prospective study to evaluate ^{85}Sr versus another bone-seeking radionuclide, but the radioprotection problem is such that it is unlikely it will be done in the foreseeable future.

ACKNOWLEDGMENTS

The authors thank the technical staff of the Nuclear Medicine Department, Centre Léon Bérard, Lyon, France, for their assistance. We acknowledge the work of the late Professor B. Lahneche, who inspired this study.

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