The effect of repeated strontium-89 chloride therapy on bone pain palliation in patients with skeletal cancer metastases

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Abstract. One hundred and eighteen patients with painful skeletal metastases of malignant diseases (predominantly prostate, breast and lung cancer) were treated with 150 MBq of strontium-89 chloride (Metastron, Amersham, UK) intravenously. The results were evaluated according to a score considering pain relief, mobility, analgesic intake and general feeling. In only five patients (4.2%) was no improvement observed; mild improvement was noted in 48 (40.7%), and substantial or complete improvement in 56 (47.5%) and 9 (7.6%), respectively. The mean painless period after a single ^{89}SrCl dose was 3.3±2.28 months (in patients with prostate, lung, breast and other types of cancer it was 3.65±2.11, 3.29±1.27, 3.08±0.48 and 3.44±1.36 months, respectively). During a 3-year study, ^{89}SrCl treatment was successively repeated up to 5 times in some patients (total number of Metastron applications was 256) who benefited from the first Metastron administration and did not show signs of myelosuppression. Even after repeated treatment, relief was consistent and the duration of the period without pain increased (in particular in patients with breast cancer, in whom the period of relief was prolonged from 3.08±0.48 months after the first dose to 5.33±2.36 months after the fifth ^{89}SrCl administration). The increased painless period was not observed after repeated treatment in the patient group comprising miscellaneous types of cancer, and the degree of improvement was less apparent. During the course of successive ^{89}SrCl treatments, transient signs of myelosuppression indicated by a decrease in white cell and thrombocyte counts of at least 25% were observed 10 times after Metastron administration (twice in two patients), i.e. in 3.9% of all ^{89}SrCl administrations; these transient haematological changes of moderate grade were closely connected with Metastron administration. Palliative treatment of metastatic skeletal pain with ^{89}SrCl improves the quality of life in most patients suffering from prostate, lung and breast cancer and may be safely repeated with the same benefit and without significant myelosuppression. The beneficial effect of ^{89}SrCl treatment seems to be less pronounced in other types of cancer with painful skeletal metastases.

Key words: Prostate cancer – Breast cancer – Lung cancer – Bone metastases – Strontium-89 – Pain palliation – Repeated treatment

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Introduction

Metastases of certain malignant neoplasms (prostate, breast and lung cancer) show a definite predisposition for bone. In contrast to involvement of many other tissues, infiltration of bone is manifested by pain. Its character and intensity vary from distress during movement under load (simulating degenerative arthrotic symptoms) to severe pain at rest and during the night requiring permanent treatment with analgesics, including opiates. Palliation of skeletal pain together with suppression of growth of neoplastic tissue can be performed by wide-field radiotherapy; however, the inability to reach all metastatic areas with an optimal irradiation dose means that this method cannot be used safely and effectively in many patients with multiple metastases. The first application of strontium-89 chloride (^{89}SrCl) in patients with metastatic carcinoma of the prostate was promising [1]. A comparison of the effect of intravenous ^{89}SrCl and radiotherapy on skeletal bone palliation corroborated the conclusion that the administration of an appropriate radiopharmaceutical can adequately replace radiotherapy [2, 3].

Strontium kinetics in metastatic prostate carcinoma, and in particular strontium accumulation in skeletal metastatic areas, were studied by adding ^{85}Sr to pure β-emitting ^{89}Sr [4, 5]. The absorbed doses in skeletal metastases and bone marrow are dependent on the total plasma clearance rate, which is primarily influenced by

renal strontium plasma clearance. Despite varying rates of renal clearance it was shown that strontium retention slowly increases in metastatic deposits, with a peak after 10 days. High accumulation around metastatic areas and the long physical half-life (50.5 days) of ^{89}Sr increase local irradiation and contribute to the therapeutic effect.

The aim of our study was to assess the extent of pain palliation by repeated ^{89}SrCl treatment in patients with different types of cancer and skeletal metastases, paying special attention to the adverse myelosuppressive effect of repeated therapy. Haematological changes following an intravenous dose of ^{89}SrCl have been reported in some patients [3, 6–9]. Successive strontium treatment in patients with marked pain relief following ^{89}SrCl administration could therefore be contraindicated on account of the potential damage to bone marrow caused by the accumulated radiation dose.

Materials and Methods

Patients. ^{89}SrCl (Metastron, Amersham, UK) was administered intravenously to 118 patients (80 men, 38 women) with a mean age of 66 years (39–86). All suffered from painful bone metastases. The most frequent disease was prostate cancer, followed by lung cancer (usually adenocarcinoma) and breast cancer. The remaining patients had kidney neoplasms, colorectal cancer and cancer diseases of another or unknown origin (Table 1). The type of disease had been diagnosed by clinical investigation including x-ray examination and corroborated in most patients by postoperative histology. Prior to the first ^{89}SrCl administration the general status of all patients was evaluated according to the Karnofsky Performance Scale. Most of them needed medical analgesic treatment (scale <70) due to marked signs of the disease.

All patients with prostate cancer had undergone prostatectomy and been continuously treated by hormonal therapy. One-third of the patients with lung cancer had previously been treated by thorax irradiation, and one-third with chemotherapy only. Mastectomy was carried out in all patients suffering from breast cancer, followed by radiotherapy and chemotherapy; only those patients who had undergone surgery within last 4 years were continuously treated by tamoxifen. Patients with other types of cancer had usually undergone chemotherapy that was completed shortly or immediately before the first ^{89}SrCl administration. The patients' current status was determined by routine medical investigation including basal biochemical and haematological data, ECG, and routine x-ray investigation. Their skeletal metastatic disease was confirmed by technetium-99m methylene diphosphonate whole body scintigraphy (dual-head gamma camera DST-XL, Sopha Médical, France). The study period was 3 years. Seventy-six patients (64.4%) died during this time due to disease progression.

Drug administration. The indication for ^{89}SrCl administration (Metastron, Amersham, UK) was bone pain caused by skeletal metastases which were diagnosed by routine skeletal scintigraphy and x-ray investigation while important signs of bone marrow depression (platelet count $<100\times10^9$/litre and leucocyte count $<2.5\times10^9$/litre) were absent. These criteria were valid even for repeated radiopharmaceutical administration. ^{89}SrCl was not administered to patients in the terminal stage of disease who were expected to die within 3 months. Prior to drug administration all patients were informed by a manufacturer's leaflet about the possible increase in bone pain within next 1–2 days (this transient pain increase happened in one-third of patients). A dose of 150 MBq of ^{89}SrCl was injected intravenously at 8 a.m. to all 118 patients. A second ^{89}SrCl dose was injected in 76 patients, a third in 36, a fourth in 21, and a fifth in 8 patients. The total number of ^{89}SrCl administrations was 256. Repeated strontium injections were administered for recurrence of bone pain under the above criteria but not before 3 months following the first injection. All patients were hospitalized for 1 week after drug administration and were regularly checked as out-patients thereafter.

Evaluation of results. The response to the first ^{89}SrCl administration was evaluated based on a score used in some multicentre studies [3, 10] (Table 3). The general condition of patients was assessed according to the subjective description of their overall physical and mental health status. The change in analgesic intake was objectively determined by the medical staff and the patients themselves. Changes in mobility of patients were dependent on pain sensation during walking with or without support. Pain palliation was subjectively evaluated by patients and by change of their analgesic demand (permanent pain, night-time pain, pain only occurring during movement etc.). The sum of ratings was expressed as the overall score. Because the patients who did not show any improvement after the first dose were not selected for

Table 1. Type of cancer disease and Karnofsky performance scale (*n*=118 patients)

Type of disease, total number (%)	Karnofsky performance scale						
	30	40	50	60	70	80	90
Prostate cancer 43 (36.4%)	4 (9.3%)	8 (18.6%)	8 (18.6%)	10 (23.3%)	5 (11.6%)	7 (16.3%)	1 (2.3%)
Lung cancer 31 (26.3%)	2 (6.4%)	12 7	6 (22.7%)	2 (38.7%)	2 (19.4%)	– (6.4%)	(6.4%)
Breast cancer 23 (19.5%)	3 (13.0%)	8 (34.8%)	4 (17.4%)	1 (4.4%)	5 (21.6%)	1 (4.4%)	1 (4.4%)
Other cancer type 21 (17.8%)	7 (31.3%)	2 (9.5%)	5 (23.8%)	6 (28.6%)	1 (4.8%)	–	–
Sum of groups	16 (13.5%)	25 (21.2%)	29 (24.6%)	23 (19.5%)	13 (11.0%)	10 (8.5%)	2 (1.7%)

repeated ^{89}SrCl administration, the detailed score evaluation used in the first treatment period was simplified for further drug applications, and the results of repeated ^{89}SrCl treatment (including the first dose) were expressed in four steps. A fall in white cell and platelet counts greater than 25% of baseline values was considered to be significant.

Results

Changes in general condition, analgesic intake, mobility and pain palliation after the first Metastron administration in all 118 patients are summarized in Table 2.

Nearly all patients said they felt better after radiopharmaceutical administration, with mild or definite improvement of their general condition. All analgesics were completely discontinued only in three patients, but a marked decrease in their requirement was evident in most patients. The most obvious benefits of ^{89}SrCl were improved mobility and pain palliation. The response is best illustrated by the overall score (Table 3). No significant change was observed in only five patients (4.2%). Mild improvement occurred in 48 patients (40.7%) and substantial improvement in 56 (47.5%). Dramatic improvement, i.e. feeling of complete absence of disease, was reported by nine patients (7.6%). No obvious difference in degree of improvement was observed in patients with prostate, lung and breast cancer; however substantial and dramatic improvement was less frequent in the fourth group of patients with other cancer diseases.

Table 2. Changes after first administration

	Score	Prostate cancer	Lung cancer	Breast cancer	Other cancers	No. of patients
General condition						
Deterioration	–1	–	–	–	–	0
No change	0	1	–	–	3	4 (3.4%)
Mild improvement	+1	13	8	10	18	49 (41.5%)
Definite improvement	+2	29	23	13	–	65 (55.1%)
Analgesics						
Quantity increased	–1	–	–	–	–	0
Unchanged intake	0	3	–	–	4	7 (5.9%)
Quantity decreased by 20%–45%	+1	19	12	15	13	59 (50.0%)
Quantity decreased by 50%–80%	+2	20	18	7	4	49 (41.5%)
Analgesics discontinued	+3	1	1	1	–	3 (2.6%)
Mobility						
Deteriorated	–1	1	1	–	–	2 (1.7%)
Unchanged	0	5	–	2	4	11 (9.3%)
Less restricted	+1	35	29	20	17	101 (85.6%)
Unrestricted	+2	2	1	1	–	4 (3.4%)
Pain palliation						
Pain more intense	–1	–	–	–	–	0
Unchanged	0	–	–	2	2	4 (3.4%)
Mild pain relief	+1	8	3	3	7	21 (17.8%)
Marked pain relief or no pain	+2	35	28	18	12	93 (78.8%)

Table 3. Overall score after first administration

	Score	Prostate cancer	Lung cancer	Breast cancer	Other cancers	No. (%)
Deterioration	< –1	–	–	–	–	0
No significant change	–1...+1	1 (2.3%)	1 (3.2%)	–	3 (14.3%)	5 (4.2%)
Mild improvement	+1...+ 3	16 (37.2%)	12 (38.7%)	10 (43.5%)	10 (47.6%)	48 (40.7%)
Substantial improvement	+4...+ 6	22 (51.2%)	16 (51.7%)	10 (43.5%)	8 (38.1%)	56 (47.5%)
Dramatic improvement	+7...+ 8	4 (9.3%)	2 (6.4%)	3 (13.0%)	–	9 (7.6%)

Table 4. The effect of repeated Metastron administration

	1st dose (*n*=118)	2nd dose (*n*=76)	3rd dose (*n*=36)	4th dose (*n*=21)	5th dose (*n*=8)
No effect	5 (4.2%)	–	–	–	–
Mild improvement	48 (40.7%)	11 (14.5%)	5 (13.9%)	1 (4.8%)	
Substantial improvement	56 (47.5%)	61 (80.3%)	27 (75.0%)	17 (80.9%)	6 (75.0%)
Dramatic improvement	9 (7.6%)	4 (5.2%)	4 (11.1%)	3 (14.3%)	2 (25.0%)

Table 5. Mean duration of beneficial effect (in months ±SD)

Type of cancer	1st dose	2nd dose	3rd dose	4th dose	5th dose
Prostate cancer	3.65±2.11	3.95±3.42	4.42±2.81	4.17±1.32	4.30±1.25
Lung cancer	3.29±1.27	3.18±0.96	3.50±0.50	4.50±0.50	–
Breast cancer	3.08±0.48	3.58±0.92	3.88±1.21	5.63±3.00	5.33±2.36
Other cancers	3.44±1.36	3.44±1.31	3.00±1.10	–	–
All patients	3.30±2.28	3.64±2.35	4.02±1.95	4.60±2.32	4.63±1.83

Table 6. Marked haematological changes (observed in eight patients)

	1st dose (*n*=118)	2nd dose (*n*=76)	3rd dose (*n*=36)	4th dose (*n*=21)	5th dose (*n*=8)
Leukocyte decrease 25–50%	1				
Leukocyte decrease >50%	1			1	
Platelet decrease 25–50%	2	1	1	2	1
Platelet decrease >50%					

The effect of repeated radiopharmaceutical administration is shown in Table 4. The degree of pain palliation after second and subsequent drug administrations was slightly better than after the first treatment. However, it must be reiterated that only those patients with a satisfactory response after the first period of treatment were selected for subsequent strontium doses.

The duration of beneficial effect after repeated ^{89}SrCl therapy is also an important indicator of satisfactory pain palliation (Table 5). The prolongation of subjective improvement following previous drug administration was related to the increasing number of Metastron applications. This effect was evident in patients with prostate, lung and breast cancer (and especially in the last-mentioned group). In contrast to these three groups, the patients suffering from other types of cancer did not reveal any mean prolongation of period with satisfactory pain palliation.

The incidence of bone marrow depression caused by Metastron administration, as evaluated by repeated haematological investigation, was low (Table 6). A marked decrease in leucocyte and/or platelet counts was observed in eight patients only; a transient decrease in platelet count in two patients with prostate cancer was observed after two successive Metastron doses (after the first and second and the fouth and fifth, respectively). Six out of eight patients with marked haematological changes suffered from prostate cancer. As only three of these patients had been treated by chemotherapy or radiotherapy, in each case at least 6 months previously, we must conclude that the bone marrow depression resulted from ^{89}SrCl therapy alone, or that the therapy contributed to the damage caused by bone marrow infiltration in advanced disease.

Discussion

Pain palliation by intravenous administration of ^{89}SrCl in patients with bone metastases depends on the ability of radiopharmaceutical to concentrate around the metastatic lesion in osteoblastic tissue. It has been demonstrated that strontium has a specific affinity for metastatic osseous tissue and that it remains in those areas for at least 100 days [4, 11]. The uptake of ^{89}Sr in bone metastases of prostate carcinoma is 2–25 times higher than that in normal bone [11, 12]. In comparison with the previously used phosphorus-32, which caused more pronounced myelosuppression, ^{89}SrCl has a substantially better tumour-to-bone marrow concentration ratio [13].

The palliative effect did not occur until 4 days following the intravenous injection of Metastron. The duration of pain relief in our patients after the first strontium dose was 3.3 months on average (1–20 months). However, there are some variations according to cancer type. Prostate cancer patients had a mean painless period of 3.65 months (in agreement with previous multicentre studies [10, 14]). This period was longer than in patients with lung and breast carcinoma, but the group differences were not significant; similarly the three groups with prostate, lung and breast cancer did not differ in degree of improvement. A tendency toward a better effect in prostate cancer as compared with breast cancer was observed by Pons et al. [15] and was suggested by the reports of Robinson et al. [16, 17]. ^{89}SrCl failed to produce pain palliation only in 5/118 patients (4.2%), whereas more than half (65, i.e. 55.1%) had substantial or complete relief and the remaining 48 (40.7%) reported some pain palliation.

The main aim of our study was to evaluate repeated ^{89}SrCl treatments with regard to the degree of pain palliation induced and possible side-effects. Repeated Metastron administration yielded an increased satisfactory response. However, differences in the period of beneficial effect were apparent according to the type of cancer. The painless period in prostate, lung and breast cancer increased with repeated ^{89}SrCl administration, and this was particularly evident in breast cancer. Such prolongation was not observed in 21 patients with other types of cancer and skeletal metastases. It may be concluded that patients suffering from prostate, lung and breast cancer who have satisfactory pain palliation after the first ^{89}SrCl dose may benefit from subsequent doses, which can be expected to result in at least the same degree of pain palliation.

A moderate and temporary myelosuppressive effect, manifested by decreased white cell and platelet counts, is the most serious adverse event after ^{89}SrCl treatment [3, 6–9, 11]. The undesirable effect of ^{89}Sr increases with its total dose [18]; nevertheless, the therapeutic effect is augmented with a higher strontium dose [19, 20]. It has been suggested that the optimal ^{89}SrCl dose, with a marked therapeutic effect but also a minimal depressive effect on bone marrow, seems to be a single dose of 150 MBq [10]. In our study this recommended and manufacturer-supplied dose of Metastron very rarely caused a fall in white cell and platelet counts of greater that 25% (such a decrease occurred only after 10/256 Metastron administrations, i.e., in 3.9%). Haematologic changes were observed after the first as well as subsequent Metastron doses. The occurrence of white cell and platelet count decrease was not related to other previous cancer treatments (chemotherapy, radiotherapy) or to the period between such treatments and the ^{89}SrCl dose. Hematological changes were transient and closely connected with Metastron administration and this fact supports our opinion that the changes were caused by ^{89}Sr irradiation. Indeed, the cumulative effect of specific cancer treatment and radioisotope therapy could result in higher bone marrow suppression [21].

Besides ^{89}SrCl, there are now two promising radiopharmaceuticals for skeletal pain palliation. Both samarium-153 EDTMP and rhenium-186 HEDP with suitable β-particle energy but much shorter physical half-lives exhibit all the properties of drugs suitable for pain relief in skeletal metastases; moreover, their additional gamma radiation of convenient energy enables confirmation of the accumulation of radioactive tracers in bone metastases by routine scintigraphy. However, our previous experience with ^{153}Sm-EDTMP therapy shows a lower incidence of complete relief as compared with ^{89}SrCl [22] and, according to a review of relevant literature, the same seems to apply to ^{186}Re-HEDP [17]. The milder palliative effect of ^{153}Sm and ^{186}Re could be explained by their short physical half-lives (46.3 h and 90.6 h, respectively) and, consequently, shorter duration of local irradiation as compared with ^{89}Sr, with its half-life of 50.5 days.

Treatment with ^{89}SrCl strictly covers bone pain and cannot replace general chemotherapy and hormonal therapy. Life expectancy is not prolonged; the mortality of our patients within the study period of 3 years was high (64.4%). It must be remembered that even an obvious decrease in skeletal metastatic infiltration as demonstrated by routine bone scintigraphy after strontium therapy does not indicate a regression of cancer. The effect of strontium treatment is limited to skeletal metastases; the metastases in other vital organs and tissues cannot be substantially affected. Nevertheless, the quality of life of patients with painful skeletal metastatic cancer is markedly improved after Metastron therapy by pain palliation lasting months. At the same time, consumption of analgesics, including opiates, and the need for hospitalization and nursing assistance in everyday life are substantially reduced. Moreover, the financial efficacy of this procedure can be confirmed by calculating the costs and benefits of ^{89}SrCl therapy [2, 23]. It therefore can be stated that palliative treatment with ^{89}SrCl (Metastron) of painful skeletal metastases, in particular of prostate, breast and lung cancer, represents a successful and cost-effective procedure that may be repeated with the same effect and without manifest adverse reactions.

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