Acta Oncologica 27 (1988) Fasc. 4

FROM THE DEPARTMENTS OF ONCOLOGY, RADIATION PHYSICS, AND UROLOGY, UNIVERSITY HOSPITAL, S-22185 LUND, SWEDEN.

PALLIATION OF MULTIPLE BONE METASTASES FROM PROSTATIC CARCINOMA WITH STRONTIUM-89

J. TENNVALL, L. DARTE, R. LUNDGREN and A. MOHAMED EL HASSAN

Abstract

The efficacy of strontium-89 in relieving pain caused by disseminated bone metastases was studied in 11 patients with prostatic carcinoma. The therapy consisted either of 3 i.v. injections of 100 MBq strontium-89 chloride in intervals of 4 weeks in 8 patients or 200 MBq i.v. administered on one occasion in 3 patients. The study suggests that 1–3 i.v. injections of 100 MBq strontium-89 may be a worthwhile and fairly atoxic treatment for palliation of bone pain from metastatic prostatic carcinoma.

Key words: Prostate cancer; bone metastases, ^{89}Sr treatment.

After failure of hormonal therapy, patients with prostatic carcinoma often suffer from pain due to multiple bone metastases. Pain control to improve quality of the remaining life, and postpone immobilization becomes important for these patients.

The beta emitter strontium-89, a bone seeking radionuclide with especially high uptake in osteoblastic metastases, has been reported to provide pain relief (3, 4, 7). Some recent investigations (6, 12, 13) have more systematically confirmed the potential of ^{89}Sr for palliation of multiple painful bone metastases without causing bone marrow depression or other side effects. Most of the patients in these studies have received activities of ^{89}Sr below 1.5 MBq/kg.

The aim of the present report was to explore the efficacy of ^{89}Sr in alleviation of pain from multiple bone metastases in carcinoma of the prostate, and also to investigate if an increased activity of ^{89}Sr could produce more effective pain relief without haematologic toxicity.

Material and Methods

The series included 11 patients with disseminated prostatic carcinoma who were referred during the period August 1985 to August 1986 to the Department of Oncology, University Hospital, Lund, because of failure of conventional therapy to control their pain. The patients fulfilled the following criteria: 1) Severe and intractable pain. 2) Chemotherapy and/or hormonal treatment was no longer effective. 3) Local radiotherapy was considered fruitless due to pain from multiple bone deposits. 4) ^{99}Tc^{m} MDP bone scintigram showed disseminated metastases accumulating the radionuclide. 5) Pathologic fractures or large bone-destructions were roentgenologically excluded. 6) Expected survival exceeded 1–2 months.

The median age of the patients was 66 years (range 50–85 years). The median Karnofsky index was 70% (40–90%). Two patients were initially totally bedridden and hospitalized. The others were at home but nursing care was required for 3 patients with a Karnofsky index below 70%.

Hormonal therapy and/or chemotherapy was continued if it was considered clinically appropriate.

Two different therapy regimens were employed: A) 3 i.v. injections of 100 MBq ^{89}Sr chloride (Amersham International, Code SMS. 2P) with intervals of 4 weeks in the first 8 patients, or B) 200 MBq i.v. on one occasion in the last 3 patients. The regimen was changed for practical reasons. The median Karnofsky index was 75% in treatment group A and 60% in group B. At the start of therapy, the median weight of the patients was 70 kg (range 59–103 kg). Thus, the patients received on average a total activity of 4.3 MBq/kg in regimen A and 2.9 MBq/kg in regimen B.

Each patient's performance was evaluated prior to treatment, and then every 4 weeks during 12 or 16 weeks after the initial treatment, by the same physician (JT). The patients were asked to complete a questionnaire each

Accepted for publication 6 February, 1988.

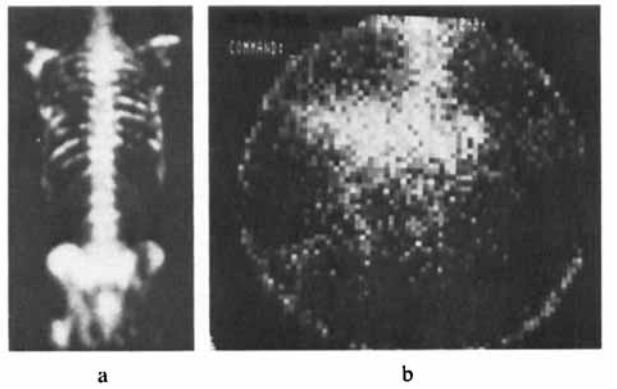

Fig. 1. Comparison between $^{99}Tc^{m}$ MDP bone scintigram (a) prior to therapy and ^{89}Sr 'Brehmsstrahlung' scintigram and (b) concerning the most painful sites, viz. pelvis and lower spine (posterior views). The ^{89}Sr scanning was made 4 weeks after the first injection of ^{89}Sr.

week regarding their analgesic consumption during a specified day of the week. Follow-up information, with special regard to possible clinical toxic effects, was later on obtained (until death) through correspondence with the referring physicians.

The evaluation of response was prospective but unblinded and the criteria were regarded as indication of positive response: 1) Improvement of at least 20% or attainment of 100% in Karnofsky index, *and* 2) reduction of analgesic requirement of 50% or more from pretreatment level, without increase of pain.

The duration of pain relief and survival time from the first course of ^{89}Sr was determined for each responder. The ratio between duration of pain relief (corrected for the time required to achieve pain relief) and remaining survival time multiplied by 100 was called 'percentage net pain relief'.

The investigation also included a qualitative estimation of the ^{89}Sr uptake in the metastases at the most painful sites by gammacamera 'Brehmsstrahlung' images made 4 weeks after the first injection. Fig. 1 shows a comparison between a ^{89}Sr 'Brehmsstrahlung' scintigram and a $^{99}Tc^{m}$ MDP scintigram performed prior to the therapy.

Four to eight weeks after the completion of the ^{89}Sr therapy the bone metastases were again studied by a repeated $^{99}Tc^{m}$ MDP scintigram.

Leukocyte (WBC) and platelet counts were repeated every 4 weeks during the study period.

Dosimetric considerations

^{89}Sr is a pure β-emitter with a physical half-life of 50.5 days. The chemical and metabolic properties are comparable to that of calcium (2, 11). The range of the β-particles in the body is less than 8 mm.

The mean radiation dose in the metastases can be calculated by using the conventional MIRD formalism (8, 14). The following expression can be derived:

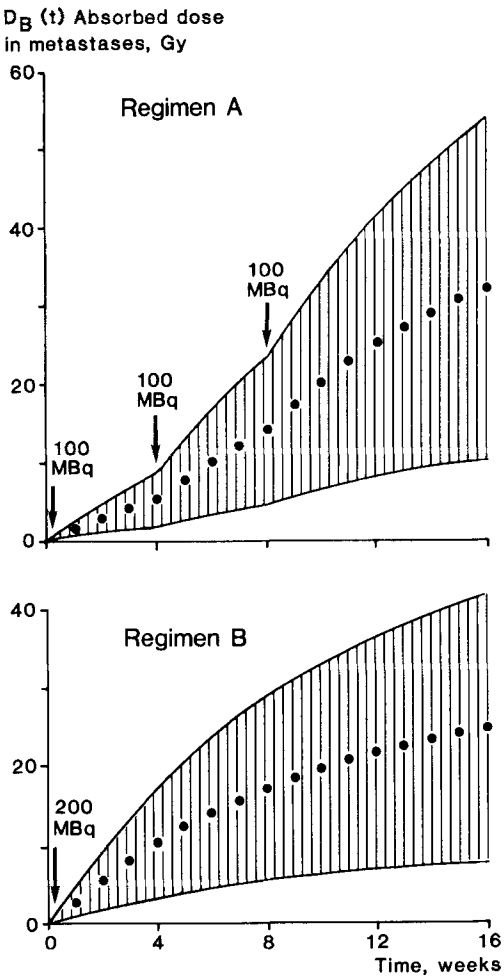

Fig. 2. The calculated accumulated absorbed doses in the metastases as a function of time after the first i.v. administration of ^{89}Sr chloride. Comparison between regimen A, viz. 3 i.v. injections of 100 MBq ^{89}Sr repeated with intervals of 4 weeks, and regimen B viz. 200 MBq administered on one occasion. The shaded areas represent possible variations in absorbed dose and ● the estimated average values.

$$D\beta(t) = 0.02 \times E \times T \times C \times (1 - e^{-\lambda t}),$$

where $D\beta(t)$ is the mean absorbed dose in the metastatic lesion expressed in Gy; E is the average energy of the β-particles from ^{89}Sr (0.5833 MeV); T is the effective half-life of ^{89}Sr in the metastasis expressed in days and λ is the corresponding decay rate; C is the concentration of ^{89}Sr in the metastatic lesion expressed in MBq/kg; and t is the time after intravenous administration of the radionuclide. The formula is essentially in agreement with the calculations of Firusian et al. (5).

The parameter T varies between 40.4 and 46.5 days according to calculations from figures in the paper by Blake et al. (2). The concentration C is estimated by the formula: $C = A \times \alpha \times s \times m$, where A is equal to the injected activity (in MBq) divided by the body weight (70 kg); α is the share of the injected activity that is stored in the

Table

Clinical data for 5 patients responding to ^{89}Sr treatment

Case No.	Change of Karnofsky index %	Analgesic requirement	Time to achieve pain relief after 1st treatment (weeks)	Duration of pain relief after 1st treatment (weeks)	Survival-time (weeks)	'Net pain relief' %
1	(60→90)	80% less narcotic requirement	2	7	31	23
3	(90→100)	Painfree without analgesics during 4 weeks, and after that only minor analgesic requirement	2	14	41	34
5	(70→90)	75% less narcotic requirement	3	7	54	13
6	(40→90)	83% less cortison medication. No other analgesies used. Initially hospitalized	2	14	44	32
4	(40→90)	50% less narcotic requirement. After 2 courses of ^{89}Sr with a complementary single fraction external radiotherapy (8 Gy) to the most painful site. Initially hospitalized	6	6	14	43

skeletal system; s is the transfer factor from body weight to the skeletal system (and is equal to 7); m is the transfer factor from the skeletal system to the metastases. Based on the results of Blake et al. (2) the factor α ranges between 0.49–0.95. The transfer factor m varies between 2 (6) and 5 (2, 5).

Fig. 2 shows the calculated mean absorbed dose in a metastatic lesion, based on formulas and the assumptions made above and with respect to regimen used, viz. A or B. The variation of calculated mean 'metastatic-dose' at a special time is defined by the minimum and maximum values of the variables T, α and m. These variables are specific to each individual metastatic lesion. The average accumulated mean absorbed doses in a metastatic lesion after 16 weeks and one year (maximum attained) were for regimen A, 32 Gy and 45 Gy respectively, and for regimen B, 25 and 30 Gy respectively. Similar values were obtained by using the assumptions and formalisms of Firusian et al. (5), viz. for regimen A, 28 and 42 Gy respectively, and for regimen B 22 and 28 Gy respectively.

The estimated mean absorbed doses received by different organs after an i.v. injection of 100 MBq ^{89}Sr are: for bone surfaces 1.6–1.7 Gy (13); for red bone marrow 1.1 Gy (1, 13); for whole body 0.08 Gy (1); and for bladder wall 0.005 Gy (1).

Results

Response to ^{89}Sr therapy was observed in 5 out of 11 patients (45%). None of the 3 patients treated according to the regimen B responded. Of the 5 responders only one was completely relieved of his discomfort without any analgesic medication, but the others had a marked decrease of both bone pain and analgesic medication. The characteristics of the responders are listed in the Table.

Responses in regimen A occurred between 2 and 3 weeks after the first injection in all 5 patients but one. The duration of response averaged nearly 10 weeks, ranging 6–14 weeks. There were no changes in systemic treatment involving either hormones or chemotherapy during the study period.

One patient achieved pain relief on all sites but the lower back after the first injection. A re-examination of the radiogram and the scintigram revealed large destructions in the first and second lumbal vertebrae and an increased uptake of radionuclides in these locations. The same day he received the second injection of ^{89}Sr, he also received external radiotherapy with a single fraction 8 Gy tumour dose (10) in the upper lumbal vertebrae. Two weeks later the patient was almost free of pain and could heavily reduce the dose of narcotics; after another 2 weeks he was able to leave the hospital. This patient was included as one of the 'responders' to ^{89}Sr therapy (case No. 4, Table).

For the 5 patients who achieved pain relief, the average survival time was 37 weeks and the average duration of pain relief was 10 weeks. This yielded an average 'net pain relief' of 27%, range 13–43% (Table).

The uptake of ^{89}Sr in the most painful metastatic sites was estimated by gammacamera 'Brehmsstrahlung' images 4 weeks after the first injection. There was a close correlation with the ^{99}Tc^{m} MDP scintigram performed prior to the therapy in all cases.

Concerning relation between the uptake and the clinical response, 4 of the 5 responders had an increased uptake of ^{89}Sr corresponding to the examined painful sites. However, also 4 out of 6 non-reponders showed an uptake in these sites. $^{99}Tc^{m}$ MDP scintigram carried out 8 to 16 weeks after the initial treatment showed progression of bone dissemination in all cases, though the uptake had in some cases decreased in the initially most painful sites and in one case even normalized.

Three of the patients experienced a short transitory worsening of pain 2 or 3 days after treatment. Twelve weeks after the initial injection the 8 patients treated according to regimen A had a median of 31% decrease in WBC-counts, and 24% decrease in platelet counts; the lowest values observed were 2.2×10^{9}/l and 110×10^{9}/l respectively. During the follow-up until death one patient had low platelet count probably due to extensive bone marrow invasion, verified at autopsy.

The 3 patients treated according to regimen B had at 12 weeks a slight decrease in the WBC counts (median 36%), and dangerously low platelet counts. This was probably attributed to pronounced bone marrow involvement in the terminal phase of the disease. In two instances the involvement was histopathologically verified at autopsy or by bone marrow biopsy.

Discussion

^{89}Sr treatment probably gave the responding half of the patients a higher quality of life during, on average, one fourth of their remaining lives (Table).

The present results are in agreement with observations made by Robinson (12), who treated 73 patients with disseminated bone metastases from prostatic carcinoma. Almost 10% of the patients became painfree, and in a further 30% a marked decrease of bone pain and pain medication was observed. The response rates in the report of Silberstein & Williams (13) are similar, but the results are not comparable since metastases from other primary malignancies were also included. In some previous studies of prostatic carcinoma (3, 4, 7) a higher response rate (pain relief) was reported but the recording was not based on prospective, specific criteria.

Though most of the patients in the present study received a higher activity of ^{89}Sr (2.9–4.3 MBq/kg) compared to Robinson's report (1.5 MBq/kg) and to the other reports cited above (0.5 MBq/kg–1.4 MBq/kg), we did not observe higher response rates. This observation does not, however, exclude a relationship between activity and response, since we might have treated patients with more advanced disease.

In accordance with the report of Robinson (12), favourable response in pain level was generally not seen until the second or third week after injection. This is to be expected as the long physical half life of ^{89}Sr means a very protracted treatment. The early analgesic effects of ^{89}Sr reported by some authors (3, 7) might probably be explained as placebo effects and/or possibly in some cases by very high metastatic uptake (Fig. 2).

Before deciding to employ ^{89}Sr, we recommend a bone scan with $^{99}Tc^{m}$ labelled phosphate, radiography of the painful sites, and a careful clinical examination. The $^{99}Tc^{m}$ MDP bone scan was in our study found to be a valuable tool for determining whether the painful lesions will accumulate ^{89}Sr. Radiography and thorough clinical examination were considered necessary, as ^{89}Sr therapy cannot relieve pain caused by pathologic fractures, large bone destructions, and tumour invasion of peripheral nerves (13).

In agreement with previous studies utilizing lower activity of ^{89}Sr (3, 4, 6, 7, 12, 13), haematologic toxicity was only seen in cases with pronounced bone marrow involvement. No serious haematologic toxicity was observed after 3 i.v. injections of 100 MBq with intervals of 4 weeks. The absorbed radiation dose in red bone marrow is estimated to 1.1 Gy per 100 MBq ^{89}Sr (1, 13). However, the biological effect is probably lower than from external irradiation, mainly due to differences in dose rates (9).

In conclusion, the present study suggests that one to three i.v. injections of 100 MBq ^{89}Sr may be a worthwhile and fairly atoxic adjunct for alleviation of bone pain from metastatic carcinoma.

Request for reprints: Dr Jan Tennvall, Department of Oncology, University Hospital, S-221 85 Lund, Sweden.

REFERENCES

1. Amersham International Booklet, 1985. Amersham product literature PLF, UK 1985.
2. Blake G. M., Zivanovic M. A., McEwan A. J. and Ackery D. M.: Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate. Eur. J. Nucl. Med. 12 (1986), 447.
3. Correns H. J., Mebel M., Buchali K., Schnorr D., Seidel C. and Mitterlechner E.: Strontium-89 therapy of bone metastases of carcinoma of the prostatic gland. Eur. J. Nucl. Med. 4 (1979), 33.
4. Firusian N.: Endoossale Isotopen-Therapie maligner Skeleterkrankungen. Z. Krebsforsch. 91 (1978), 143.
5. — Mellin P. and Schmidt C.: Results of strontium-89 therapy in patients with carcinoma of the prostate and incurable pain from bone metastases: A preliminary report. J. Urol. 116 (1976), 764.
6. Hayek D., Ritschard J., Zwahlen A., Courvosier B. and Donath A.: Emploi du strontium-89 dans le traitement antalgique des métastases osseuses. Schweiz. Med. Wochenschr. 110 (1980), 1154.
7. Kutzner J., Grim W. and Hahn P.: Palliative Strahlentherapie mit Strontium-89 bei ausgedehnter Skelettmetastasierung. Strahlentherapie 154 (1978), 317.
8. Loevinger R. and Berman M.: A schema for absorbed-dose calculations for biologically distributed radionuclides. MIRD Pamphlet No. 1 (1968).
9. Orton C. G.: Re-assessment of normalization between fractionated and continuous radiotherapy for the CRE and TDF equations. Br. J. Radiol. 53 (1980), 374.
10. Price P., Hoskin P. J., Easton D., Austin D., Palmer S. G. and Yarnold J. R.: Prospective randomised trial of single

and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother. Oncol. 6 (1986), 247.
11. REEVE J. and HESP R.: A model-independent comparison of the rate of uptake and short term retention of Ca-41 and Sr-85 by the skeleton. Calcif. Tiss. Res. 22 (1976), 183.
12. ROBINSON R. G.: Radionuclides for the alleviation of bone pain in advanced malignancy. *In:* Nuclear Medicine in Oncology, chapter 3. Clinics in Oncology Series, Vol. 5, No. 1. Edited by D. C. Ackery and V. Batty. W. B. Saunders Co, Ltd. East Sussex, England 1986.
13. SILBERSTEIN E. B. and WILLIAMS C.: Strontium-89 therapy for the pain of osseous metastases. J. Nucl. Med. 26 (1985), 345.
14. SNYDER W. S., FORD M. R., WARNER C. G. and WATSON S. B.: 'S', Absorbed dose per unit cumulated activity for selected radionuclides and organs. MIRD. Pamphlet No 11 (1975).