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Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma

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Abstract. Forty-nine patients were treated with either 3×75 MBq ^{89}Sr or saline as placebo. Analysis of results 1 to 3 years after therapy revealed the ineffectiveness of ^{89}Sr to relieve pain from metastases. Unexpectedly, a higher survival rate was found after Sr application (46% vs 4% after 2 years). Covariate analysis underlines the effect of ^{89}Sr therapy on life expectation.

Key words: Radionuclide therapy – Skeletal metastases – 89-strontium

Following a report by Firusian et al. (1976) in 1976 we started therapy with ^{89}Sr for pain from skeletal metastases of prostatic carcinoma. After early enthusiastic results (Correns et al. 1979), further evaluations including analysis of consumption of analgesic drugs were less convincing, showing an effectiveness of only 55% to 65%, and even lower figures in patients with exhausted hormonal therapy (Correns et al. 1982; Buchali et al. 1984; Silberstein and Williams 1985). Therefore we felt encouraged to start a double blind study in order to evaluate the effects of ^{89}Sr among other therapeutic methods (Correns et al. 1986).

Patients and methods

Forty-nine consecutive patients suffering from bioptically proven prostatic carcinoma with multiple skeletal metastases were included in the study. Diagnosis of metastases included scintigraphy (^{99m}Tc-EHDP) and X-ray film. Treatment consisted of 3 injections of 75 MBq ^{89}Sr chloride each at monthly intervals (Sr group, 25 patients) or application of saline as placebo (Pl group, 24 patients). Patients were selected randomly, and the group they were in was not uncovered earlier than one year after the start of treatment. Effects on pain were evaluated by patients' subjective reports. Controls of scintigrams and X-ray films were performed 9 to 12 months after the start of treatment and at annual intervals. Metastatic spreading was graded according to: 1: sites in pelvis and lumbar spine, 2: additional sites in trunk skeleton, 3: generalization.

Histological type was graded from prostatic biopsy according to UICC recommendations. Blood cell count was checked before the injections, and 3, 6 and 12 months after the start of treatment.

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Results

For characterization of both groups, age, natural history (time from diagnosis to start of ^{89}Sr treatment), spreading of metastases, and histological type were evaluated. Data are listed in Table 1. No parameter was significantly different between the groups. Besides four patients, all were staged T3 or T4, therefore this factor was neglected.

Relief of skeletal pain

Forty-one patients suffered from pain requiring analgesic therapy. Relief or subjective amelioration were reported as indicated in Table 2. Subdividing groups into recently diagnosed patients (history less than one year) and longer lasting disease metastatic spread showed no differences, probably due to low figures. Summing all patients regardless of Sr or Pl therapy, a significant difference was revealed, related to the duration of the disease ($P < 0.01$). Effect on skeletal scintigraphy: controls of scintigrams were performed in 26 patients. Regression or stable assessment was found in 8 of 15 (Sr group) and in 5 of 11 (Pl group). Differences are insignificant.

Table 1. Basic data on strontium (Sr) or placebo (Pl) treated patients (mean values)

	Sr	Pl	
Total number	25	24	
Age (at start of treatment)	67.4 ± 10.0	66.5 ± 6.9	n.s.
Natural history of disease (y)	1.82	2.19	n.s.
Extension of metastases	2.16	2.50	n.s.
Histological type	2.11	2.05	n.s.

Table 2. Relief of pain in both groups (relief/number of patients)

	Sr	Pl	
Total groups	7/19	11/22	n.s.
Natural history ≤ 1 year	6/11	8/10	n.s.
>1 year	1/ 8	3/12	n.s.
Extension of metastases (1 or 2)	5/12	7/11	n.s.
(3)	2/ 7	4/11	n.s.

Natural history	≤ 1 year	>1 year	
All patients (Sr and Pl)	14/21	4/20	$P < 0.01$

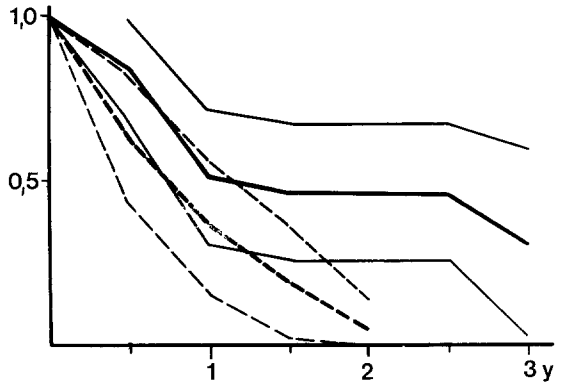

Fig. 1. Survival rates of patients after ^{89}Sr (*solid lines*) or placebo application (*dashed lines*). Thinner lines correspond to standard deviation (± 2 s)

Effects on survival

Ten patients died whilst under treatment (one after the first and nine after the second injection), three of them received Sr and seven Pl. Calculation of survival data using the actuarial method revealed a difference between the groups ($P < 0.05$) (Fig. 1). Survival rate 2 years after the start of treatment was 0.46 in Sr and 0.04 in Pl groups. Analysis of covariates (Cox 1972) was performed excluding those ten patients, who did not receive three injections. Application of ^{89}Sr, grading, and natural history of the disease proved to be significant parameters influencing survival. An additional analysis of 33 ^{89}Sr treated patients (3×75 MBq) including patients before the start of the double blind study revealed grading, natural history, and extension of metastases as significant covariates.

Effects on blood cell count

Patients with thrombocytopenia (<100 Gpt/l) before treatment were excluded. After treatment, thrombopenia was detected in 11 of 22 patients of the Sr group, and in 4 of 17 of the Pl group. The difference between groups did not prove significant. In some patients thrombopenia appeared after the first injection and proved irreversible in five (Sr-group) and two (Pl-group) patients. Leucocytopenia (<4 Gpt/l) was found in three (Sr) and one (Pl) patient and was always associated with thrombopenia. Changes of hematocrit were inconsistent.

Discussion

Up to now the main indication for application of ^{89}Sr was relief of pain, as reported by several groups (Firusian et al. 1976; Firusian 1979; Kutzner et al. 1977; Correns et al. 1979, 1982; Buchali et al. 1984). In most cases it was achieved within a few days. Calculations (Kaul et al. 1973; Firusian et al. 1976) led to a total dose of 17 to 20 Gy/75 MBq to injured bone. From an effective half time of 25 days in metastatic regions, a dose of about 3 Gy may be calculated for the 1st week, following a fast uptake within 30 min after injection (Blake et al. 1986). Therefore, the effects on pain were achieved with low doses, resembling anti inflammatory radiations. These calculations led to the introduction of a nuclide with a shorter half time into therapy: ^{90}Y (Kutzner et al. 1982). Our results reported here give strong support to a placebo effect, the placebo group effects are in the same range as those in the Sr group, this may be due to the special performance of therapeutic nuclide application influencing the patient psychologically. The recognition of natural history as an important factor, indicating duration and effectiveness of basic therapy, strongly underlines our interpretation.

Skeletal scintigraphy is an important factor in the evaluation of therapeutic effects (Levenson et al. 1983). Schmid et al. (1982) reported a reduction of scintigraphic activity by basic therapy in 57% of patients using similar criteria (Langhammer et al. 1978) as used in our study. Our results are in the same range for the Sr and Pl groups, and most of our patients evaluated by scintigraphy (21 of 26) belong to the group with a short natural history of the disease. Therefore, an effect of hormonal therapy cannot be ruled out.

If we take into account the radiation dose to bone marrow, which is in the same order as for bone itself (Snyder et al. 1975), the suppression of blood cell count is not surprising. It restricts the use of the nuclide to treatments with proven effectivity.

Therefore, the unexpected effect on survival rate is of special importance. It leads to a new concept to use ^{89}Sr in patients with skeletal metastases in order to raise their life expectation, irrespective of pain.

Our results in moribund patients (three of them died under the treatment) are questionable. Life expectation in these patients is often limited by the fulminant generalization of the metastatic process, as the primary tumour cannot be influenced by ^{89}Sr treatment.

As the extension of metastases into bone determines the relative nuclide dose and appears as an important parameter of survival, the amount of ^{89}Sr should be adjusted to the volume of metastases. Such a study is currently under way.

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