Original article

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A comparative study of ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr in the treatment of painful skeletal metastases

Knut Liepe and Joerg Kotzerke

Aim **The surface bone-seeking radiopharmaceuticals ^{188}Re-HEDP, ^{186}Re-HEDP and ^{153}Sm-EDTMP, and the volume seeker ^{89}Sr were investigated to determine the efficacy and toxicity in pain palliation of bone metastases.**

Method **The effect of treatment with ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr on pain symptoms, quality of life, and bone marrow function were studied. In total, 79 patients (18 with breast cancer and 61 with prostate cancer) were treated (31 patients with ^{188}Re-HEDP, 15 patients each with ^{186}Re-HEDP and ^{153}Sm-EDTMP, and 18 patients with ^{89}Sr). All patients were interviewed using standardized sets of questions before and after therapy weekly for 12 weeks. Blood counts were taken weekly for 6 weeks and after 12 weeks.**

Results **In total, 73% of patients reported pain relief (77% after ^{188}Re-HEDP, 67% after ^{186}Re-HEDP 73% after ^{153}Sm-EDTMP, and 72% after ^{89}Sr). Fifteen percent of patients could discontinue their analgesics and were pain-free. Pain showed a decrease from 3.6 ± 1.7 to a maximum of 2.2 ± 1.8 at visual analogue scale in 10 steps ($P < 0.01$). Patients described an improvement on the Karnofsky performance scale from 70 ± 10% to 78 ± 14% 12 weeks after treatment ($P = 0.15$). There were eight patients with a thrombocytopenia grade I, two patients with grade II and one with grade III. The maximum nadir of platelet and leukocyte counts were observed between the 2nd to 5th week after treatment and was reversible within 12 weeks. There were no significant differences in pain palliation, Karnofsky performance status (KPS) and bone marrow toxicity between the different radionuclides ($P = 0.087–0.449$).**

Conclusion **All radiopharmaceuticals were effective in pain palliation, without induction of severe side effects or significant differences in therapeutic efficacy or toxicity. *Nucl Med Commun* 28:623–630 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Skeletal metastases occur in many patients with different malignant tumours, especially in the advanced stages of prostate, breast and lung cancer. The resulting bone pain interferes with the patient's quality of life and requires effective treatment. Modern chemotherapy schemes can lead to a pain response in up to 50% of patients [1]. Studies with bisphosphonate as a standard therapy in bone metastases showed a higher pain response than placebo and a lower rate of skeletal-related events [2]. Unfortunately, various non-radiotherapeutic modalities such as analgesics, hormone therapy, orchidectomy, cytostatic and cytotoxic drugs, bisphosphonates and surgery are not effective in all cases, especially in the late stage of the disease [3–5]. External-beam radiotherapy is suitable for well-defined localized bone metastases and a pain response in 70–90% was reported [6,7]. Extended-field radiation may be useful in patients with diffuse metastases, but is often accompanied by serious side effects [8]. Therefore, systemic radionuclide therapy represents a valuable and effective therapeutic option in the treatment of widespread skeletal metastases.

The management of acute and chronic pain is a major problem in oncological practice [9] and leads to a decrease of quality of life in cancer patients. Pain secondary to bone metastatic tumour growth is one of the most intractable cancer pain syndromes. In addition to the periosteal invasion and increase in intraosseus pressure due to invading tumour, various biochemical mediators and cytokines, e.g., prostaglandin, bradykinin, osteoclast activating bone factor, interleukin I, and tumour necrosis factor play a role in the genesis of bone pain [10]. Systemic radionuclide therapy affects all these factors and produces pain relief in an average of 70–80% of treated patients [3,8,11–16].

^{89}Sr

^{89}Sr (Metastron) is a pure beta emitter with a maximum energy of 1.49 MeV and a physical half-life of 50.5 days

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[17]. The largest study was described by Robinson *et al.* [18]. Six hundred and twenty-two patients had been treated and an overall response rate of 81% was reported, with 15% rate of complete response. In a randomized, double-blind 'Trans Canada' trial [16] 126 patients with prostate cancer received local field radiotherapy and either ^{89}Sr as a single injection of 400 MBq (10.8 mCi) or placebo. There were statistically significant differences regarding analgesic intake, pain relief, improved quality of life and increased time to the development of new bone metastases in patients receiving strontium compared to placebo. Haematological toxicity was greater in the strontium group, but there was no increased incidence of life-threatening events, including cord compression and pathological fractures.

^{186}Re-1,1-hydroxyethylidenediphosphonate (^{186}Re-HEDP)

^{186}Re decays with a maximum beta energy of 1.07 MeV, a low abundance gamma emission of 137 keV and a physical half-life of 89.3 h. A double-blind, crossover, placebo-controlled trial reported a response rate in 80% of patients with a mean duration of response of 7 weeks [19]. The only major toxicity was a mild reversible thrombocytopenia. In a dose escalation study by de Klerk *et al.* [20] a fixed applied activity of 1295 MBq was compared with escalating activity increasing incrementally by 555 MBq to a maximum 3515 MBq.

^{153}Sm-ethylenediamine-*N,N,N′,N′*-tetrakis (methylene phosphonic acid) (^{153}Sm-EDTMP)

^{153}Sm-EDTMP had a lower beta emission (0.81 MeV (20%), 0.71 MeV (49%), and 0.64 MeV (30%)), a 28% abundance gamma emission of 103 keV (28%) and a physical half-life of 46.3 h. In two large studies with more than 550 patients a response rate of 73% and 86% was reported [11,21]. Enrique *et al.* [11] documented pain relief in 50% of patients with a duration of response between 4 and 8 weeks, and in the other 50% of patients of more than 8 weeks. In 227 patients with an administered activity between 18.5 MBq·kg^{-1} and 55 MBq·kg^{-1}, 19.7% showed a thrombocytopenia grade I or II and 6.9% a grade III or IV.

^{188}Re-HEDP

^{188}Re-HEDP represents a new, interesting radiopharmaceutical in pain palliation, but it is not approved for routine use. It has a short physical half-life of 16.9 h and a maximal beta energy of 2.1 MeV with a 15% gamma component of 155 keV. As a product of an in-house ^{188}W/^{188}Re generator, similar to a technetium generator, ^{188}Re-HEDP shows potential advantages in availability. In several papers a similar therapeutic efficacy to the other radiopharmaceuticals has been described [12,22,23]. Results with repeated treatments showed an improvement in progression-free and overall survival as compared to a single injection treatment [24]. This could be a new interesting approach in systemic radionuclide therapy.

In this study the volume seeker ^{89}Sr and the surface bone seeking radiopharmaceuticals, ^{153}Sm-EDTMP and ^{186}Re-HEDP as a commercially available radiopharmaceutical and ^{188}Re-HEDP, used in a clinical study, were investigated. We compared all radiopharmaceuticals regarding bone marrow toxicity and pain palliation effect.

Methods

Patients

In this prospective non-randomized study 79 patients (18 with breast cancer and 61 with prostate cancer) with evidence of bone metastases and symptomatic pain were treated with a single administration of radiopharmaceutical. Only patients using long-term analgesics and measurable pain symptoms were included. All patients were selected according to the following strict inclusion/exclusion criteria.

Eligibility criteria were a positive ^{99m}Tc-HMDP bone scan with at least three lesions; bone pain symptoms requiring the long-term use of analgesics; sufficient bone marrow function (platelet count $\geq 100 \times 10^9\,l^{-1}$, leukocyte count $\geq 3.0 \times 10^9\,l^{-1}$ and haemoglobin $\geq 6.0\,mmol \cdot l^{-1}$) ($9.67\,g \cdot dl^{-1}$)); and normal renal function.

Criteria for exclusion were metastatic bone fractures, spinal cord compression, and soft tissue tumours elsewhere causing nerve compression.

In accordance with the Declaration of Helsinki, all patients were informed comprehensively about the study and possible side effects and were provided with a leaflet. Consent approval had been obtained from the local ethics committee.

Radiopharmaceuticals

^{188}Re-HEDP was prepared as previously described by Lin *et al.* [25]. ^{89}Sr, ^{186}Re-HEDP and ^{153}Sm-EDTMP are available commercially.

Laboratory studies

Pre-treatment laboratory tests included bone marrow status (haemoglobin, leukocyte and platelet counts and differentiation blood counts), kidney function (creatinine) and liver function (total bilirubin). In patients with prostate cancer the prostate-specific antigen (PSA) was measured. Blood counts were repeated weekly within 6 weeks and 12 weeks after treatment.

Imaging studies

All patients were evaluated with a pre-therapeutic ^{99m}Tc-HMDP bone scan within 1 month before treatment. This bone scan was repeated after 12 weeks, to document a possible decrease of number or uptake of bone metastases. Additionally, all patients treated with ^{188}Re-HEDP, ^{186}Re-HEDP and ^{153}Sm-EDTMP had a

post-therapeutic scan using the intrinsic gamma rays from the radiopharmaceuticals to visualize the distribution of radioactivity. Post-therapeutic bones scan after ^{89}Sr were not possible, because this radiopharmaceutical is a pure beta emitter.

Evaluation

Before treatment and within 12 weeks after treatment, weekly interviews with a standardized set of questions were performed. This set included the visual analogue status (VAS) in 10 steps [26], to document pain relief, use of analgesics, and KPS [27], to determine the functional status of the patients. As the primary endpoint, pain relief of two steps on the VAS at least in two consecutive weeks without increase of quantity analgesics was used.

Toxicity

For the assessment of toxicity, the toxicity criteria of the World Health Organization [28] were used. According to this toxicity scale, platelet counts of $74–99 \times 10^9 l^{-1}$, $50–74 \times 10^9 l^{-1}$, $25–49 \times 10^9 l^{-1}$ and below $25 \times 10^9 l^{-1}$ correspond to a toxicity grade of 1, 2, 3 and 4, respectively. The maximum decrease was calculated by comparison of the level of blood counts before therapy (baseline) with the lowest level within 12 weeks. All patients were asked about a reversible increase of pain symptoms within the first 14 days (flare syndrome).

Statistics

Data are presented as mean ± standard deviation. For determining a significant change in the visual analogue scale and KPS we used Student's *t*-test. Two-tailed *P* values less than 0.05 were considered to indicate statistical significance.

Results

Patients

A total of 79 patients with breast or prostate cancer and a mean age of 66 years (range, 45–87 years) were treated with a single administration of ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr. For ^{188}Re-HEDP the standard activity in accordance with the dose escalation study of Palmedo *et al.* [23] was used. Patients' characteristics are summarized in Table 1. Regarding the non-randomized manner of this study, the patient numbers were different in the four radionuclide groups. Patients were hospitalized for 2 days for administration of ^{188}Re-HEDP because of the German radiation protection regulations for using non-commercially available radionuclides. The treatment using ^{186}Re-HEDP, ^{153}Sm-EDTMP or ^{89}Sr was performed on an outpatient basis. There were five patients (6%) with an analgesic treatment step I, 29 patients (37%) with step II and 45 patients (57%) with step III using the WHO criteria [28]. All patients suffering from prostate cancer received hormone therapy for at least 6 months before therapy and also during the post-therapy observation period, or an orchiectomy. Eighty-nine percent of patients had been treated with a bisphoshonate for at least 6 months; this was discontinued 4 weeks before therapy. In addition, 19% of patients received chemotherapy and 27% of patients had external-beam radiation prior to the administration of radiopharmaceutical. All these treatments were finished at least of 5 months before the radionuclide therapy. It is unlikely that these various preceding therapies modified or altered the observed therapeutic effect in this study. There was an inhomogeneity in the analgesic intake: in the group of patients who underwent ^{89}Sr therapy there were more with analgesic level III (WHO) and lower KPS (Table 2).

Toxicity

Regarding the early signs of bone marrow toxicity, no patient had adverse side effects greater or equal to grade III [28] with the exception of one breast cancer patient with multiple bone metastases and previous three cycles of chemotherapy, who showed a thrombocytopenia grade III. However, the bone marrow toxicity was reversible within 12 weeks after treatment. In total, 10% (8/79) of patients had a thrombocytopenia grade I, 2% (2/79) a thrombocytopenia grade II. Leukopenia and anaemia play a minor role in bone marrow toxicity. There were only two patients with leukopenia grade I and one patient with leukopenia grade II (Table 3). Most of the patients showed a grade I anaemia according to the WHO criteria before treatment, with no significant worsening within 12 weeks after therapy. Generally, we could not find any

Table 2 Analgesic intake of patients according to the WHO level [26]

WHO level	^{188}Re-HEDP	^{186}Re-HEDP	^{153}Sm-EDTMP	^{89}Sr
Step I	2/31	2/15	1/15	0/18
Step II	11/31	5/15	7/15	5/18
Step III	18/31	8/15	7/15	13/18

Table 1 Patients' characteristics

Radiopharmaceutical	Patients (*n*)	Prostate cancer (*n*)	Breast cancer (*n*)	Applied activity (MBq)	Age (years)	Range (years)
^{188}Re-HEDP	31	25	6	3194 ± 387	68	56–87
^{186}Re-HEDP	15	12	3	1358 ± 158	69	45–83
^{153}Sm-EDTMP	15	9	6	2940 ± 545	61	48–71
^{89}Sr	18	15	3	152 ± 19	63	47–76
Total	79	61	18		66	45–87

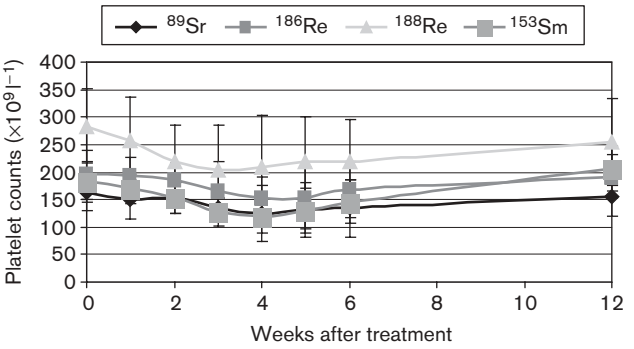
significant decrease in platelet and leukocyte counts or a significant difference between the four radiopharmaceuticals ($P = 0.059$–0.470). After ^{188}Re-HEDP administration, patients showed a 30% decrease in platelet counts from the baseline level to the nadir. After ^{188}Re-HEDP the decrease was 29%; after ^{153}Sm-EDTMP the decrease was 33%; and after ^{89}Sr it was 26% (Tables 4 and 5). Regarding the late toxicity, 12 weeks after treatment administration the platelet counts returned to 95% and the leukocyte counts to 93% (Fig. 1).

There was no evidence of either local or systemic intolerance to treatment, whilst a flare reaction with a reversible increase of pain within 14 days after therapy was noted in 15/79 (19%) of patients.

Response

In total, pain relief (decrease of pain symptoms at two steps on the VAS at least in two consecutive weeks without increase of analgesics intake) was achieved in 73% (58/79) of patients and 15% (12/79) of patients were pain-free. The detailed response rate is summarized in Table 6. The VAS in 10 steps showed a mean decrease from 3.6 ± 1.7 (baseline level) to a maximum of 2.2 ± 1.8 ($P < 0.01$). The pain symptoms were 2.5 ± 2.0 twelve weeks after systemic radionuclide treatment. The duration of response was > 12 weeks in 14/24 patients with response for ^{188}Re-HEDP, 5/10 for ^{186}Re-HEDP, 6/11 for ^{153}Sm-EDTMP and 6/13 for ^{89}Sr. For the other patients

Fig. 1



Time course of platelet counts.

Table 3 Bone marrow toxicity documented by the platelet and leukocyte counts

Radiopharmaceutical	Thrombocytopenia			Leukopenia	
	Grade I (*n*)	Grade II (*n*)	Grade III (*n*)	Grade I (*n*)	Grade II (*n*)
^{188}Re-HEDP	2 (6%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
^{186}Re-HEDP	2 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
^{153}Sm-EDTMP	2 (13%)	0 (0%)	0 (0%)	1 (7%)	1 (7%)
^{89}Sr	2 (11%)	1 (5%)	1 (5%)	1 (5%)	0 (0%)
Total	8 (10%)	2 (2%)	1 (1%)	2 (2%)	0 (0%)

Thrombocytopenia and leukopenia are in accordance with the toxicity criteria of the World Health Organization [26]; *n*, number of patients.

Table 4 Value of platelet counts with the nadir, the value after 12 weeks and the maximal percent drop within 12 weeks after treatment

Radiopharmaceutical	Baseline value ($\times 10^9 l^{-1}$)	12 weeks after treatment*($\times 10^9 l^{-1}$)	Maximum nadir** ($\times 10^9 l^{-1}$)	Maximal drop within 12 weeks***(%)	Time of nadir (weeks)
^{188}Re-HEDP	277 ± 71‡	263 ± 79	194 ± 86	32 ± 15	2.7 ± 0.9
^{186}Re-HEDP	199 ± 50	181 ± 81	140 ± 33	35 ± 14	3.6 ± 1.0
^{153}Sm-EDTMP	193 ± 37	206 ± 40	130 ± 30	35 ± 11	3.4 ± 1.1
^{89}Sr	163 ± 63	156 ± 49	125 ± 42	37 ± 19	4.4 ± 1.0

Results are given as the mean value and standard deviation.
*Absolute value of platelet counts 12 weeks after treatment.
**Maximum decrease within the period of 12 weeks after treatment.
***Percent decrease from the baseline to the maximal nadir.

Table 5 Value of leukocyte counts with the nadir within 12 weeks and the value 12 weeks after treatment

Radiopharmaceutical	Baseline value ($\times 10^9 l^{-1}$)	12 weeks after treatment* ($\times 10^9 l^{-1}$)	Maximum nadir** ($\times 10^9 l^{-1}$)	Maximal drop within 12 weeks***(%)	Time of nadir (weeks)
^{188}Re-HEDP	6.8 ± 1.2‡	6.5 ± 2.6	5.2 ± 1.3	27 ± 16	2.9 ± 0.6
^{186}Re-HEDP	5.7 ± 1.4	5.2 ± 1.1	4.2 ± 0.5	32 ± 15	4.1 ± 1.2
^{153}Sm-EDTMP	4.3 ± 1.9	3.9 ± 1.6	3.3 ± 1.6	28 ± 14	3.9 ± 0.9
^{89}Sr	6.1 ± 2.9	5.7 ± 2.0	4.4 ± 1.2	30 ± 10	4.9 ± 1.2

Results are given as the mean value and standard deviation.
*Absolute value of leukocyte counts 12 weeks after treatment.
**Maximum decrease within the period of 12 weeks after treatment.
***Percent decrease from the baseline to the maximal nadir.

Table 6 Rate of pain relief (decrease of two steps on the visual analogue status in at least two consecutive weeks without increasing the number of analgesics)

Radiopharmaceutical	Pain response		Pain free	
	Number of patients	Percent	Number of patients	Percent
^{188}Re-HEDP	24/31	77	5/31	16
^{186}Re-HEDP	10/15	67	2/15	13
^{153}Sm-EDTMP	11/15	73	2/15	13
^{89}Sr	13/18	72	3/18	17
Total	58/79	73	12/79	15

Table 7 Pain value on the 10 steps visual analogue scale (0 = no pain, 10 maximal pain)

Radiopharmaceutical	Visual analogue status			*P* value
	Baseline value (0 to 10)	Nadir*(0 to 10)	12 weeks after treatment (0 to 10)	
^{188}Re-HEDP	4.1 ± 1.8	2.5 ± 1.9	2.8 ± 2.2	< 0.01
^{186}Re-HEDP	1.8 ± 0.4	1.0 ± 0.7	1.2 ± 0.8	0.071
^{153}Sm-EDTMP	4.4 ± 1.3	3.1 ± 1.6	3.3 ± 2.0	0.076
^{89}Sr	2.3 ± 0.8	1.2 ± 0.8	1.7 ± 1.2	0.120
Total	3.6 ± 1.7	2.2 ± 1.8	2.5 ± 2.0	< 0.01

Results for visual analogue status are given as the mean and standard deviation.
*Maximum decrease within the period of 12 weeks after treatment.

with a response < 12 weeks, the duration was 9 ± 2 weeks for ^{188}Re-HEDP, 10 ± 2 weeks for ^{186}Re-HEDP, 10 ± 1 weeks for ^{153}Sm-EDTMP and 9 ± 2 weeks for ^{89}Sr, respectively. There were no significant differences in the response rate, the pain relief or the duration between the four radiopharmaceuticals ($P = 0.268$–0.846) (Table 7).

The Karnofsky performance scale increased from a baseline level of 70 ± 10 to 78 ± 14 twelve weeks after administration ($P = 0.015$). There were also no significant differences of the changes in Karnofsky performance scale between the different radiopharmaceuticals ($P = 0.149$–0.632). However, the increase of the scale was significant to the baseline level ($P < 0.01$) only in the group treated with ^{188}Re-HEDP; the other changes had a *P* value between 0.208 and 0.415 (Table 8).

Regarding changes in the PSA levels in patients suffering from prostate cancer, 14/61 (23%) of patients showed a decrease of more than 50% from the pre-therapeutic value. (Baseline PSA level: 163 ± 149 ng·ml^{-1}; PSA level 12 weeks after administration 149 ± 230 ng·ml^{-1}; $P = 0.95$).

There were no changes in the ^{99m}Tc-HMDP bone scan before and 12 weeks after radionuclide therapy, but in three single cases we found a decrease of bone metastases within 12 months after treatment (each of one patient with ^{188}Re-HEDP, ^{186}Re-HEDP and ^{153}Sm-EDTMP).

Table 8 Karnofsky performance status before and 12 weeks after treatment

Radiopharmaceutical	Karnofsky performance status		*P* value
	Baseline value (%)	12 weeks after treatment (%)	
^{188}Re-HEDP	73 ± 7	85 ± 9	< 0.01
^{186}Re-HEDP	72 ± 13	79 ± 12	0.251
^{153}Sm-EDTMP	68 ± 9	74 ± 8	0.208
^{89}Sr	62 ± 14	69 ± 16	0.415
Total	70 ± 10	78 ± 14	0.015

Results for Karnofsky performance status are given as the mean and standard deviation.

Discussion

Systemic radionuclide therapy with beta-emitting radiopharmaceuticals represents a therapeutic option in the management of intractable metastatic bone pain and has been used since 1942 [29]. Nowadays, ^{89}Sr, ^{186}Re-HEDP and ^{153}Sm-EDTMP are the preferred radiopharmaceuticals as they are commercially available. From a theoretical point of view ^{188}Re-HEDP offers potential as a new and attractive radiopharmaceutical for the treatment. As a generator product it has an excellent availability, which permits on-site labelling as with the routinely used ^{99m}Tc generator, resulting in low costs.

^{153}Sm-EDTMP and ^{188}Re-HEDP differ especially in the beta energy, ^{153}Sm-EDTMP with a relative low maximum energy of 0.81 MeV and ^{188}Re-HEDP with a higher maximum energy of 2.1 MeV. Some authors prefer the use of low beta energy emitters to reduce bone marrow toxicity in palliative treatment [30]. ^{89}Sr has a long physical half-life of 50.5 days in contrast to ^{153}Sm-EDTMP (shorter half-life of 46.3 h) and ^{188}Re-HEDP (shorter half-life of 17 h). ^{186}Re-HEDP has a median beta energy of 1.07 MeV and a physical half-life of 89.3 h. In our study we could not find any differences in the grade of bone marrow toxicity between the different radiopharmaceuticals we investigated. In addition, there was

no evidence of influence of the uptake mechanism on bone marrow toxicity, the volume seeker ^{89}Sr showed similar leukocytopenia and thrombocytopenia as the bone surface seeker radionuclides ^{188}Re-HEDP, ^{186}Re-HEDP and ^{153}Sm-EDTMP. This is reflected in similar radiation absorbed dose for the bone marrow for the different radiopharmaceuticals: 1.7 Gy for 1285 MBq ^{186}Re-HEDP [31], 1.3–2.8 Gy for ^{153}Sm-EDTMP (using an activity of 37–111 MBq·kg^{-1}) [32] and 2.0 Gy for 3300 MBq ^{188}Re-HEDP [33].

In all patients the systemic radionuclide therapy was well tolerated and there was no evidence of either local or systemic complications and the flare was reversible within 14 days. In this study similar rate of flare syndrome (19%) were documented in comparison to other authors [11,34,35].

There are many reports on the therapeutic efficacy of the different radiopharmaceuticals in bone palliation with pain relief between 70 and 85% of cases [3,8,11,13,14, 36–38]. A study with 610 evaluated patients [37] (527 patients with ^{89}Sr and 83 patients with ^{186}Re-HEDP) showed a pain palliation of 81%; 27% of patients were pain free. The duration of pain response was 5.0 ± 3.5 months. Enrique *et al.* [11] reported effective pain palliation in 73% of 417 patients treated with ^{153}Sm-EDTMP, 82% of these patients showing palliation could reduce their analgesic intake substantially or completely. Fifty percent of patients with pain relief had duration of response of 4–8 weeks, and the other 50% for more than 8 weeks. There were no differences in the therapeutic efficacy of ^{153}Sm-EDTMP therapy between patients with prostate and breast cancer [21,35,40]. Studies only including patients with breast cancer showed similar results with a response rate of 85% [41]. In contrast, clinical data on ^{188}Re-HEDP is rare. Li *et al.* [42] used activities of 1.1–6.9 GBq of ^{188}Re-HEDP in different kind of tumours, with pain relief in 80% of patients suffering from prostate cancer and in 83% of patients with breast cancer. Similar results were observed in patients suffering from lung cancer with pain relief in 80% [43]. Using activities of 3300 MBq of ^{188}Re-HEDP in prostate cancer patients a response rate of 76% was reported [12].

The pain relief was documented with the VAS in 10 steps, which showed a decrease from a baseline level of 3.6 ± 1.7 to a maximum of 2.2 ± 1.8 ($P < 0.01$) without differences between the different radiopharmaceuticals. The functional status of the patients, documented with the Karnofsky performance status, showed a mean increase from a baseline level of $70 \pm 10\%$ to $78 \pm 14\%$ twelve weeks after administration, but only the increase of KPS in patients treated with ^{188}Re-HEDP was significant ($P < 0.01$). Tian *et al.* [21] reported in ^{153}Sm-EDTMP patients with different tumour entities a comparable increase of KPS from $58 \pm 26\%$ to $72 \pm 26\%$. The patients with strontium showed the lowest KPS and in contrast a lower baseline pain level because a stronger analgesic therapy with a higher rate of analgesics of level III (WHO). But the pain relief was comparable with the other groups in respect to the low number of patients in the groups.

In general, systemic radionuclide treatment was performed in patients with advanced stage disease and severe pain symptoms needing opioid or comparable analgesic treatment. Due to the low rate of side effects some investigators suggest earlier treatment in the management of pain. Schmeler *et al.* [44] investigated the KPS and the outcome, represented by survival and pain response. Limited survival (average survival of 12.5 weeks) and poor response (only in 40% of patients) was observed in the group with a KPS of $\leq$ 50%. Patients with a pre-treatment KPS of 60% had a mean survival of 20.5 weeks following ^{89}Sr therapy and in 42% of patients there was pain relief. Those patients with a KPS $\leq$ 70% had a response rate of approximately 75%. From these data the authors concluded that patients with a pre-treatment KPS $\leq$ 50% should not be treated with ^{89}Sr and patients with pre-treatment KPS of 60% should be evaluated on a case-by-case basis. Other reports showed similar results of early treatment: in 94 patients a significantly better pain relief ($P = 0.005$), reduction of analgesics ($P = 0.018$), and a significant longer response ($P < 0.0035$) was described in patients with moderate bone involvement compared in patients with extensive bone involvement [40]. In a large Italian multicentre study [39] a response rate of 81% was shown in patients with limited skeletal metastases and higher KPS in comparison to extended metastases and lower Karnofsky performance status. In this study a better response in patients with higher KPS before ^{188}Re-HEDP therapy was found; the number of patients in the other group was too low for this evaluation. In respect of the lower number of patients, we could not find a comparison between tumour mass and response rate.

It was formerly thought that current therapy with bisphosphonates was a contraindication for systemic radionuclide therapy and in this study the bisphosphonates were also stopped 4 weeks before treatment. This recommendation was based on the hypothesis of reduced uptake of the bone-seeking agent after previous bisphosphonate administration but some results contradict this hypothesis. In a study [45] with 11 autopsied patients who had died as a result of metastatic prostate cancer, the histological and scintigraphic findings in ^{99m}Tc-HMDP bone scans in patients with and without bisphosphonates were compared. There was overall agreement between histology and bone scintigraphy of 84% in non-bisphosphonate patients and 82% in bisphosphonates patients. The authors could not find any statistical differences between the two groups regarding

the specificity, sensitivity, positive and negative predictive values of bone scintigraphy and prevalence of histological abnormality and they concluded that bisphosphonates do not generally affect the ability to detect bone metastases. In breast cancer patients the effects of clodronate on ^{99m}Tc-HMDP bone scans for detection of bone lesions were investigated. This report showed that clodronate infusion did not impair the sensitivity of a bone scan [46]. Another group reported no interference of the skeletal uptake of ^{153}Sm-EDTMP by pamidronate infusion [47]. In this study the bisphosphonate treatment was discontinued for 4 weeks to exclude a possible synergistic effect of the bisphosphonate and the systemic radionuclide therapy.

New modalities of concomitant treatment with radionuclide and chemotherapy show encouraging results. A therapy strategy in prostate cancer patients using ^{89}Sr and three cycles of chemotherapy (ketoconazole, doxyrubicin and vinblastin) could increase the pain response rate to 94% compared to a rate of 81% for chemotherapy alone [48]. There was an increase of duration of pain palliation for the combination therapy to 13.9 months (4.2–26.1 months) compared to chemotherapy alone and an increase in survival from 16.8 months (4.4–34.2 months) to 27.7 months (4.9–37.1 months). A decrease of the PSA level $>50\%$ was documented for the combination therapy of 94% compared to 81% in chemotherapy alone. Systemic radionuclide therapy (^{89}Sr) combined with chemotherapy ($100\,\mathrm{mg}\cdot\mathrm{m}^{-2}$ carboplatin) in 30 patients with prostate cancer showed significantly better pain relief for ^{89}Sr and carboplatin [49].

The repeated treatment with radiopharmaceuticals presents an interesting therapeutic option. Palmedo *et al.* [24] observed a significant extension of the median times to progression and time of survival, from 2.3 months and 7.0 months for single administration to 7.0 months and 12.7 months for two administrations with an interval of 8 weeks, respectively. There was also an increase of pain relief of 60% for single administration to 91% for two.

Conclusion

All the radiopharmaceuticals used in this study – ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr – showed similar pain palliation effects in patients suffering from breast and prostate cancer. There were no differences in bone marrow toxicity or in the decrease of platelet and leukocyte counts. The palliative treatment resulted in only mild and reversible side effects and presents a useful additional therapy to analgesic treatment. Therefore, the choice of the therapeutic bone agent may be governed by the local availability and logistics.

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