Dose escalation study with rhenium-188 hydroxyethylidene diphosphonate in prostate cancer patients with osseous metastases

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Abstract. The aim of this study was to determine the maximum tolerated dose of rhenium-188 hydroxyethylidene diphosphonate (HEDP) in prostate cancer patients with osseous metastases who are suffering from bone pain. Twenty-two patients received a single injection of escalating doses of carrier-added ^{188}Re-HEDP [1.3 GBq (35 mCi), 2.6 GBq (70 mCi), 3.3 GBq (90 mCi) and 4.4 GBq (120 mCi)]. Blood counts and biochemical parameters were measured weekly over a period of 8 weeks. Haematological toxicity (WHO grading) of grade 3 or 4 was considered unacceptable. Clinical follow-up studies including methods of pain documentation (medication, pain diary) were performed for 6 months after treatment. In the 1.3-GBq group, no haematological toxicity was observed. First haematotoxic results were noted in those patients with a dose of 2.6 GBq ^{188}Re-HEDP. In the 3.3-GBq group, one patient showed a reversible thrombopenia of grade 1, one a reversible thrombopenia of grade 2 and three a reversible leukopenia of grade 1. In the 4.4-GBq group, thrombopenia of grades 3 and 4 was observed in one and two patients (baseline thrombocyte count $<200\times10^9$/l), respectively, and leukopenia of grade 3 was documented in one patient. The overall nadir of thrombopenia was at week 4. The individual, maximum percentage decrease in thrombocytes in the 1.3-, 2.6-, 3.3- and 4.4-GBq groups was 17%, 40%, 60% and 86%, respectively. In two patients, a transient increase in serum creatinine was observed (max. 1.6 mg/dl). Pain palliation was reported by 64% of patients, with a mean duration of 7.5 weeks. The response rate seemed to increase with higher doses, reaching 75% in the 4.4-GBq group. It is concluded that in prostate cancer patients, the maximum tolerated dose of ^{188}Re-HEDP is 3.3 GBq if the baseline thrombocyte count is below 200×10^9/l. In patients with thrombocyte counts significantly above 200×10^9/l, a dose of 4.4 GBq might be tolerable. Thrombo- and leukopenia are the most important side-effects. Pain palliation can be achieved in 60%–75% of patients receiving a dose of 2.6 GBq or more of ^{188}Re-HEDP. Studies in a larger patient population are warranted to evaluate further the palliative effect of ^{188}Re-HEDP.

Key words: Prostate cancer – Painful bone metastases – Rhenium-188 hydroxyethylidene diphosphonate – Haematotoxicity – Dose escalation

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Introduction

It is well documented that therapy with different radiopharmaceuticals such as strontium-89 chloride, rhenium-186 hydroxyethylidene diphosphonate (HEDP) and samarium-153 ethylene diamine tetramethylene phosphonate (EDTMP) is effective for pain palliation in patients with osseous metastases from prostate cancer [1–7]. Recently, the routine availability of tungsten-188/rhenium-188 generators which provide high levels of ^{188}Re in low volumes has been reported [8]. ^{188}Re can be used to radiolabel HEDP [8], which is already commercially available and is an approved radiopharmaceutical in Europe for therapy in the form of the ^{186}Re-HEDP analogue. In contrast to essentially carrier-free generator-obtained ^{188}Re, the reactor-produced isotope ^{186}Re always contains stable rhenium and thus ^{188}Re-HEDP shows identical chemical characteristics to ^{186}Re-HEDP only as carrier-added ^{188}Re-HEDP. An initial feasibility study with ^{188}Re-HEDP using different ^{188}Re sources demonstrated that application of ^{188}Re-HEDP in humans is safe and

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Table 1. Comparative data for ^{186}Re and ^{188}Re

	^{186}Re	^{188}Re
$t_{1/2}$	90 h	17 h
$E_{\beta\ max}$	1.07 MeV	2.12 MeV
$E_{\beta\ average}$	0.35 MeV	0.76 MeV
% β^-	93.2	100
γ (%)	137 keV (9.5%)	155 keV (15%)
Production mode	Reactor (n,γ reaction on stable rhenium)	Generator (β^- from ^{188}W parent)
Specific activity	Carrier added	No carrier added
Availability	Commercially available	Commercially available
Price per dose	High	Low

Table 2. Formulations used for ^{186}Re-HEDP and ^{188}Re-HEDP. Values represent the concentration in the final preparation for injection in µmol/ml

	^{186}Re-HEDP	n.c.a. ^{188}Re-HEDP	c.a. ^{188}Re-HEDP
HEDP	18.3	18.3	18.3
Re	0.24–0.65	–	0.35
$SnCl_2$	7.06	7.06	7.06
Gentisic acid	8.8	8.8	8.8
Acetate	135	150	150
pH	5–6	5–6	5–6

n.c.a., No carrier added; c.a., carrier added

shows promising results in pain palliation [9]. A comparison of the two isotopes ^{186}Re and ^{188}Re is given in Table 1.

The most important physical characteristics of ^{188}Re are its high-energy beta emission with a maximal energy of 2.1 MeV and its relatively short physical half-life of 17 h [10]. The maximum range of electrons from this high-energy beta emission in soft tissue is 11 mm, with an average penetration depth of 3.8 mm, which is suitable for palliative therapy of bone metastases. Furthermore, ^{188}Re shows a 15% abundance of gamma emission with an energy of 155 keV, allowing simultaneous imaging of patients and thus direct control of drug accumulation in the bone metastases [10].

The main aim of this initial study was to perform a dose-escalation study and to evaluate the maximum tolerated dose of ^{188}Re-HEDP in patients with osseous metastases from prostate cancer as the primary tumour.

Materials and methods

Preparation of ^{188}Re-HEDP. The preparation of ^{188}Re-HEDP was performed such that the composition of the commercially available ^{186}Re-HEDP was chosen as standard with respect to comparability of the results generated by this study using the ^{188}Re-analogue to those obtained using ^{186}Re-HEDP (Mallinckrodt). Especially important in the formulation of ^{188}Re-HEDP is the use of carrier, as this nuclide is obtained essentially carrier-free by β^--decay of ^{188}W, whereas ^{186}Re is produced in nuclear reactors through neutron capture of stable ^{185}Re and thus by virtue of its mode of production is carrier-added. The presence of macroscopic amounts of stable rhenium in Re-HEDP preparations is decisive with respect to the chemical species formed [11]. In carrier-added preparations these species consist of Re–Re bonds which cannot be formed using carrier-free ^{188}Re. As a consequence of this, the biodistribution and in vivo stability of carrier-added and no-carrier-added ^{188}Re-HEDP show remarkable differences, and only the carrier-added composition accumulates at a high percentage in bone tissue [12]. The formulations used in the preparation of ^{186}Re-, no-carrier added ^{188}Re- and carrier-added ^{188}Re-HEDP are compared in Table 2.

Rhenium-188 was obtained from a commercially available 18.5 GBq (500 mCi) alumina-based ^{188}W/^{188}Re generator from Oak Ridge National Laboratories (ORNL). Depending on the specific volume activity required, the generator eluates (typically 20 ml of physiological saline) were concentrated to a volume of 1 ml or 3 ml of physiological saline using a concentration method that we have reported elsewhere [13]. Then 10 µl of a stable perrhenate solution [100 µmol $HReO_4$ (Aldrich)/ml physiological saline] was added per millilitre of the concentrated ^{188}Re solution. One ml of this carrier-added ^{188}Re-perrhenate solution (containing 1 µmol stable perrhenate) was used for the labelling reaction by adding it through a 0.22-µm sterile filter (Waters) to a kit vial containing 8.3 mg HEDP (Fluka), 3.0 mg gentisic acid (Aldrich) and 3.9 mg stannous chloride dihydrate (Merck). The vials were then heated for 15 min at 90°–100°C and cooled to room temperature. For neutralization, 1 ml of a sterile solution of 39 mg sodium acetate trihydrate (Merck) and 10 µl 32% sodium hydroxide solution (Merck) per millilitre were added, yielding a final pH in the range of 5–6.

Quality control. Quality control of carrier-added ^{188}Re-HEDP was performed using ITLC-SG strips (Gelman) developed with acetone or physiological saline. Using acetone, Re-HEDP stays at the origin and free perrhenate moves with the solvent front, while using saline as eluent, Re-HEDP and perrhenate move with the solvent front and only reduced colloids or ReO_2 remain at the origin. This two-strip system allows determination of impurities in the Re-HEDP preparation. The levels of impurities detected in patient samples were always less than 5%; thus binding of Re to HEDP exceeded 95%. In another system ^{188}Re-HEDP (and for comparison also commercially obtained ^{186}Re-HEDP) was tested using anion exchange chromatography (Sep-Pak-QMA; Waters) as a more species-defining (anionic properties) quality control. In this method a small sample of 10 µl of the Re-HEDP preparation was dissolved in 2 ml of a HEDP/ascorbic acid solution (5.5 mg ascobic acid and 8 mg HEDP/10 ml) and applied to a Sep-Pak-plus QMA cartridge. The cartidges were then rinsed with 2-ml fractions of sodium chloride solutions of increasing ionic strength (0.01, 0.05, 0.1, 0.2, 0.5, 1.0 and 2.0). The collected fractions plus the cartridge were then counted for radioactivity. A comparison of the radioactive elution profiles using the commercial ^{186}Re-HEDP and the in-house prepared ^{188}Re-HEDP is shown in Fig. 1. The two preparations show similar profiles, with the bulk of radioactivity eluting at an ionic strength of 0.5 *M* saline. Small portions of radioactivity eluted with the void volume and other small fractions

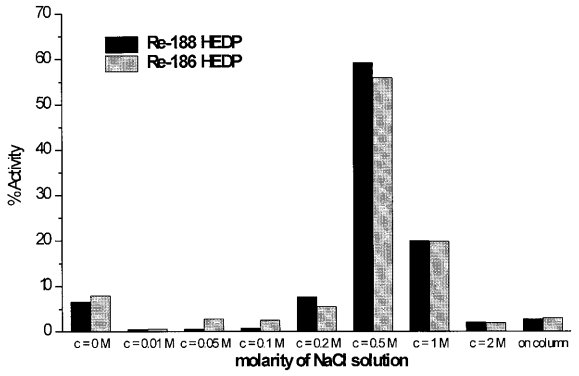

Fig. 1. Comparison of elution profiles of ^{186}Re-HEDP and ^{188}Re-HEDP from Sep-Pak QMA anion exchange cartridges using a step gradient of saline solutions with increasing ionic strength (c= concentration)

remained uneluted on the QMA column. Due to these very similar elution profiles we concluded that the formulations represented nearly identical species. This characteristic QMA elution profile was obtained in all ^{188}Re-HEDP patient preparations and was consistent throughout the study.

Sterility and pyrogenicity tests performed with concentrated generator eluates alone after radiation decay and with non-radioactive test preparations (using just sterile saline instead of radioactive generator concentrates) always revealed sterility and apyrogenicity.

Patients. Twenty-two patients with disseminated osseous metastases from prostate cancer received single injections of different doses of ^{188}Re-HEDP. Patients suffering from multifocal pain and with at least three different sites of bone metastases as proven by technetium-99m methylene diphosphonate scintigraphy and X-ray were included in the study. Patients with leucocyte and thrombocyte counts below 3.0×10^9/l and 100×10^9/l, respectively, or with impaired renal function (creatinine >1.4 mg/dl) were excluded from the study. None of the patients received chemotherapy or hemibody irradiation before the injection. All patients were informed about the experimental character of the study and possible side-effects and had given written consent in accordance with the Helsinki declaration. Approval had been obtained from the ethical committee and the radiation safety committee.

Study design. Groups of at least three patients were treated with escalating doses of ^{188}Re-HEDP, starting with 1.3 GBq. If no toxicity was observed after the treatment of three patients, the next higher dose was given. If grade I or II toxicity was observed, an additional two to four patients were treated to confirm the grade of toxicity. The dose escalation was terminated if any patient demonstrated unacceptable toxicity, which was defined as grade III or IV toxicity. In this case the previous group was considered to have received the maximum tolerated dose. For the assessment of toxicity, the toxicity criteria of the World Health Organization were used [14]. According to this toxicity scale, thrombocyte counts of $76–99\times10^9$/l, $50–74\times10^9$/l, $25–49\times10^9$/l and below 25×10^9/l correspond to toxicity grades 1, 2, 3 and 4, respectively. The maximum decrease was calculated by comparison of the pretreatment level of thrombocytes and leucocytes (baseline) with the lowest level during the 8-week follow-up period. Three patients received 1.3 GBq (35 mCi) ^{188}Re-HEDP, five received 2.6 GBq (70 mCi), six received 3.3 GBq (90 mCi) and eight received 4.4 GBq (120 mCi). The body surface area (BSA) of patients was calculated according to the following formula: $0.2025\times BW^{0.425}\times H^{0.725}$, where BW is body weight (in kg) and H is height (in m). The individual dose of every patient was normalized to a standard BSA of 1.73 m^2.

After the injection, patients were hospitalized for 48 h in the nuclear medicine ward. ^{188}Re-HEDP was administered as a bolus injection via a running intravenous saline drip. Subsequently, whole-body scintigraphy was performed.

Blood samples were drawn before and weekly after treatment for the determination of blood counts and clinical chemistry parameters (for at least 8 weeks). For analysis of toxicity, the thrombocyte and leucocyte counts, creatinine, liver enzymes and electrolytes were determined. To assess the extent of metastatic disease, the pretherapy whole-body scintigraphy with ^{99m}Tc-MDP was graded with the help of the bone scan index (BSI) [15]. BSI values were calculated independently by two nuclear medicine physicians.

Pain palliation. The patient had to complete a pain diary during the baseline period and throughout the study. The week before the injection of ^{188}Re-HEDP was considered as the baseline period. During this time no new analgesics were administered. For the assessment of pain palliation, patients had to document the pain situation with the help of pain diaries. The consumption of analgesics was noted daily by the patient. The clinical follow-up was performed for 6 months. If no response to treatment was observed, the follow-up was terminated after one additional month. The diary was controlled by a physician at weeks 1–4 and at months 2, 3 and 6.

The Visual Analog Scale (VAS) [1] served as a basis for pain documentation. On the scale, zero represents no pain and 10, intolerable pain. A multisite VAS was used, recording the patient's pain intensity for each of several body regions (head, upper spine, lower spine, arms, legs, ribs, sternum and claviculae, pelvis). The area under the curve (AUPC) of an overall daily pain score was calculated (according to the method of Donaldson [16]) for the 7-day period before treatment and for each 7-day period thereafter. Referring to the medication index system of Foley [17], a daily pain medication index was calculated.

Statistical tests. Regression analysis was performed to calculate the relation of the percentage decrease in thrombocyte and leucocyte counts with the administered activity standardized to standard BSA. The percentage decreases in thrombocyte and leucocyte counts were also correlated with BSI (Spearman rank order test). Additionally, regression analysis was performed to assess the functional relation between BSI and the BSA-standardized dose as well as the pretherapy thrombocyte count ($p<0.05$ was considered to be statistically significant). For statistical testing of the average thrombocyte and leucocyte counts, Student's *t* test for dependent variables was used, comparing each week with the baseline value (again $p<0.05$ was taken to be statistically significant).

For primary assessment of pain, the change in the baseline area under the pain curve of the VAS (VAS-AUPC) was compared with week 4 VAS-AUPC. A decrease of 40% was considered a significant treatment response if pain medication was stable. If the medication index decreased by 50% or more and the VAS-AUPC did not increase, the patient was also considered a treatment responder.

Results

Clinical results

Within the toxicity follow-up period of 8 weeks one patient who received a dose of 4.4 GBq died 6 weeks after the injection due to acute renal failure. Out of the eight patients in the 4.4 GBq group, three reported a short period of nausea and vomiting some days after the injection. Four patients reported a flare phenomenon.

Haematotoxicity

No significant haematopoietic alterations were observed in any of the patients who received a dose of 1.3 GBq. The mean thrombocyte count levels remained stable around levels of 300×10^9/l: the maximum individual percentage reduction in thrombocyte count ranged from 8% to 17%.

An initial haematological toxicity was noted in the 2.6-GBq group. Of the five patients in this group, a thrombopenia of grade 1 was observed in one case (Table 3). The nadir of thrombopenia was at week 5. In one patient with a leukopenia of grade 1 at baseline, leucocyte counts revealed grade 2 toxicity (Table 4). The maximum individual decreases in thrombocytes and leucocyte counts in comparison with baseline values were 40% and 35%, respectively.

In the 3.3-GBq group, thrombocytopenia of grade 1 was found in one patient, and of grade 2 in another (both patients had normal baseline values). A leukopenia of grade 1 was observed in three patients. The nadir of thrombo- and leukopenia was at weeks 4 and 3, respectively. Blood count values reached baseline levels or at least normal levels at week 8. The percentage reduction in thrombocyte and leucocyte counts ranged from 28% to 60% and from 5% to 48%, respectively.

In the 4.4-GBq group, haematological toxicity was observed in all patients. Thrombocytopenia of grades 3 and 4 was observed in one and two patients, respectively. In this group, three patients had to receive thrombocyte transfusions. Leukopenia of grades 1, 2 and 3 occurred in three, three and one patients, respectively. One patient with increased values at baseline did not show any toxicity. After receiving 4.4 GBq, all patients except one reached baseline levels or normal blood count values at week 8. The maximum individual decrease in thrombocytes and leucocytes in comparison to baseline values was 86% and 67%, respectively.

The mean thrombocyte count of all patients showed a statistically significant decrease at the time of the nadir during week 4 and additionally at week 5 (Fig. 2). At week 8, baseline values had been reached again. The decrease in the mean leucocyte count was less marked, as demonstrated in Fig. 3.

Table 3. Grade of toxicity, maximum percentage decrease, bone scan index and thrombocyte counts before treatment and at week 8 in the different dose groups

Patient	Dose (MBq)	StaDos (MBq)	BSI (%)	BL Thrombo (10^9/l)	Week 8 Thrombo (10^9/l)	Max. decrease (10^9/l)	Grade of toxicity (WHO)
1	1314	1152	30	187	155	155	None
2	1295	1228	65	261	269	240	None
3	1284	1175	10	430	389	357	None
1	2594	2278	35	221	141	132	None
2	2634	2503	60	261	247	195	None
3	2620	2681	67	116	123	78	1
4	2675	2752	70	161	155	125	None
5	2571	2484	40	173	183	156	None
1	3352	3181	65	193	181	123	None
2	3367	3065	42	180	167	128	None
3	3308	3193	27	158	186	79	1
4	3404	3001	75	178	128	71	2
5	3448	3238	37	354	310	220	None
6	3290	3385	80	298	273	215	None
1	4373	4025	35	461	487	83	1
2[a]	4562	4639	15	150	137	37	3
3	4455	4122	60	139	[b]	57	2
4[a]	4466	4680	70	145	40	22	4
5	4421	3712	25	284	230	74	2
6[a]	4518	3616	40	105	190	15	4
7	4536	4755	65	289	255	173	None
8	4510	4337	37	255	230	110	None

[a] Patient with thrombocyte transfusion; [b] Patient died before week 8
StaDos, BSA-standardized dose; BSI, bone scan index; BL Thrombo, baseline thrombocyte count

Table 4. Grade of toxicity, maximum percentage decrease, bone scan index and leucocyte counts before treatment and at week 8 in the different dose groups

Patient	Dose (MBq)	StaDos (MBq)	BSI (%)	BL Leuko (10^9/l)	Week 8 Leuko (10^9/l)	Max. decrease (10^9/l)	Grade of toxicity (WHO)
1	1314	1152	30	8.8	8.6	8.6	None
2	1295	1228	65	10.5	9.2	8.9	None
3	1284	1175	10	5.9	7.3	5.8	None
1	2594	2278	35	6.3	6.3	4.1	None
2	2634	2503	60	10.4	6.9	6.8	None
3	2620	2681	67	3.6	5.0	3.6	1
4	2675	2752	70	3.5	4.5	2.9	2
5	2571	2484	40	5.3	7.3	5.3	None
1	3352	3181	65	6.4	5.9	3.5	1
2	3367	3065	42	4.7	5.0	3.9	1
3	3308	3193	27	5.8	5.1	4.5	None
4	3404	3001	75	7.2	6.3	3.9	1
5	3448	3238	37	7.9	6.8	4.1	None
6	3290	3385	80	4.6	4.9	4.4	None
1	4373	4025	35	6.6	8.1	3.1	1
2[a]	4562	4639	15	4.5	5.0	2.4	2
3	4455	4122	60	5.0	[b]	2.8	2
4[a]	4466	4680	70	4.0	2.6	1.5	3
5	4421	3712	25	14.0	7.5	4.6	None
6[a]	4518	3616	40	7.9	5.1	3.6	1
7	4536	4755	65	5.0	4.4	2.9	2
8	4510	4337	37	4.9	4.3	3.2	1

[a] Patient with thrombocyte transfusion; [b] Patient died before week 8; BL, Baseline leucocyte count; other abbreviations as in Table 3

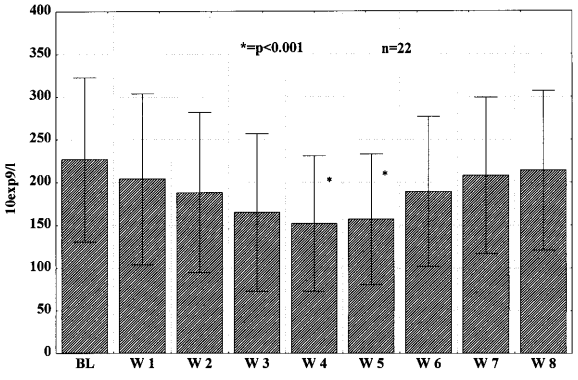

Fig. 2. Mean thrombocyte count with standard deviation after injection of ^{188}Re-HEDP, beginning at pre-therapy baseline and ending at week 8

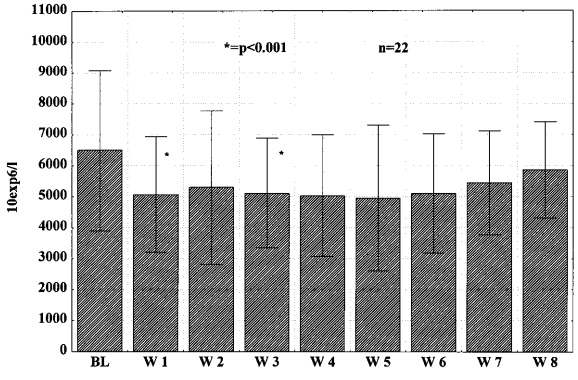

Fig. 3. Mean leucocyte count with standard deviation after injection of ^{188}Re-HEDP, beginning at pre-therapy baseline and ending at week 8

There was a strong correlation between standardized dose and the percentage reductions in thrombocyte (r=0.78, P<0.0001) and leucocyte (r=0.69, P<0.001) counts (Figs. 4, 5). However, there was no functional relation between BSI and the percentage reductions in thrombocyte and leucocyte counts or the baseline thrombocyte count: the correlation coefficients were –0.12 (P<0.58), –0.10 (P<0.64) and –0.2 (P<0.36), respectively. Furthermore, the statistical testing of BSI and BSA-standardized dose of ^{188}Re-HEDP did not show any positive correlation (r=0.06, P<0.76).

Among 12 patients with baseline thrombocyte counts below 200×10^9/l, haematological toxicity was observed in seven; by contrast, only two of ten patients with higher thrombocyte counts (>200×10^9/l) showed haematological toxicity, assessed by reference to WHO criteria (Table 5).

Pain palliation

A palliative effect was obtained in 12 of the 22 patients, resulting in an overall response rate of 64% (Table 6).

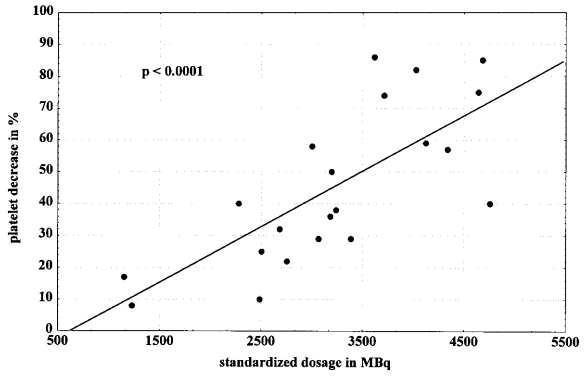

Fig. 4. Influence of standardized dose of ^{188}Re-HEDP on percentage decrease in thrombocyte count

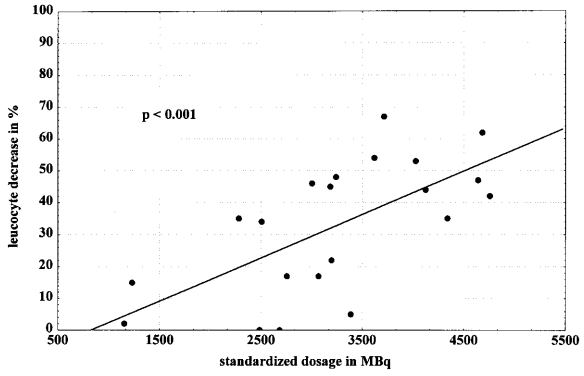

Fig. 5. Influence of standardized dose of ^{188}Re-HEDP on percentage decrease in leucocyte count

Table 5. Number of patients with different grades of platelet toxicity, divided into groups with thrombocyte counts of more or less than 200×10^9/l thrombocytes

Toxicity grade	Thrombocyte count (×10^9/l)	
	<200 (*n*=12)	>200 (*n*=10)
1	2	1
2	2	1
3	1	–
4	2	–

The mean duration of response was 7.5 weeks and the beginning of treatment effects was documented after 12.5 days. In the 1.3-GBq, 2.6 GBq, 3.3-GBq and 4.4-GBq groups the response rate was 33%, 60%, 66% and 75%, respectively.

Other parameters

In three patients, an increase in creatinine values was documented owing to ureteral obstruction by a local recurrence. In two additional patients without evidence of recurrent disease who received 3.3 GBq and 4.4 GBq, respectively, a transient and borderline increase in creatinine (maximum 1.6 mg/dl) was observed. At weeks 5 and 6 the values had returned to normal levels.

Discussion

Rhenium-188 is a potential new isotope for palliative therapy of bone metastases. One of the major advantages of using ^{188}Re is its on-demand availability from a ^{188}W/^{188}Re generator [8]. HEDP can be readily radiolabelled with ^{188}Re (as it can with ^{186}Re), and gamma camera imaging is possible for dosimetry estimates.

Maxon et al. recently reported the results of an initial feasibility study on the use of ^{188}Re-HEDP in animals and humans [9], which showed that about 50% of the patients reported pain relief at maximum doses of 1.8 GBq (50 mCi). Maxon et al. also found that decay-corrected biological uptake of ^{188}Re-HEDP in bone was 15%–18% lower than that of ^{186}Re-HEDP and that renal uptake of ^{188}Re-HEDP was 26%–48% higher than that of ^{186}Re-HEDP. Our own observations in animal studies comparing no-carrier-added ^{188}Re-HEDP with carrier-added ^{188}Re-HEDP also revealed high kidney and soft tissue uptake and indicated the importance of stable rhenium in the preparation of the substance [11, 12].

With respect to dosimetry, we assumed that the biokinetics and biodistribution of carrier-added ^{188}Re-HEDP would be the same as those of the commercially available ^{186}Re-HEDP, for which dosimetry data were known. Further, we assumed that only the different S-factors of the two radionuclides would need to be taken into con-

Table 6. Effect of ^{188}Re-HEDP on pain palliation, according to the applied dose

	Total	Dose (GBq)			
		1.3	2.6	3.3	4.4
No. of patients	22	3	5	6	8
Pain palliation	64%	33%	60%	66%	75%
Duration of response (weeks)	7.5	3	7	10.5	7.2
Start of response p.i. (days)	12.5	14	14	11	12

sideration in order to estimate the dose of ^{188}Re-HEDP to a given organ using the dosimetry data for ^{186}Re-HEDP. For this comparison we calculated the ^{188}Re/^{186}Re ratio of the products of S-factors and effective half-life (t_{eff}) to be 0.61. This theoretical consideration means that, for example, a dose of 100 MBq ^{188}Re would correspond to a dose of 61 MBq ^{186}Re. This is confirmed by the dosimetric data for red marrow published by Maxon et al. [9], who obtained an average value of 3.5 cGy/37 MBq in five patients; as would be expected, this is much lower than the radiation dose for red marrow resulting from ^{186}Re-HEDP, calculated to be 5.4 cGy/37 MBq. Therefore, it was expected, and confirmed by the haematological data obtained, that the maximum tolerated dose of ^{188}Re-HEDP would be significantly higher than that of ^{186}Re-HEDP.

In this study, the most important limitation of the dose escalation of ^{188}Re-HEDP treatment was the observed haematological toxicity. There was a clear correlation between dose standardized to BSA and percentage decrease in thrombocytes and leucocytes. We found thrombocytes to be the most radiation-sensitive blood cells. The nadir of total platelet count occurred 4 weeks after injection. In the 4.4-GBq group, three patients demonstrated a decrease in the thrombocyte count to below 30×10^9/l 2 weeks after injection, necessitating transfusion therapy. This is in agreement with the observation that the higher the dose to the bone marrow, the sooner there is a decrease in thrombocytes, the interval approximating to the platelet life span of 9 days [18].

The maximum tolerated dose, as defined in this study, was 3.3 GBq (90 mCi) of ^{188}Re-HEDP. In this patient group, reversible thrombopenia of grade 2 toxicity was observed in one patient. Reversible leukopenia of grade 1 toxicity was found in three patients.

However, the toxicity is certainly influenced by the baseline blood count. In patients with thrombocyte counts over 200×10^9/l, no toxicity of grade 3 or 4 was observed. It can be speculated that for patients with the aforementioned thrombocyte count, the dose of ^{188}Re-HEDP that will cause grade 3 or 4 toxicity will be 370–1110 MBq over the 4.4-GBq level. The tumour burden also can influence the baseline platelet count. De Klerk et al. have developed a formula to calculate the expected reduction in thrombocyte count after treatment with ^{186}Re-HEDP [18], based on baseline count, BSA and BSI. Like De Klerk et al., we were able to demonstrate an impact of baseline count and BSA on the extent of the reduction in the thrombocyte count; however, we did not find a correlation between BSI and baseline thrombocyte count or percentage decrease in the count. Therefore, prediction of the reduction in the platelet count by means of pretherapy bone scintigraphy seems not to be possible for therapy with ^{188}Re-HEDP. It may be of interest to note that the functional relation between BSI and decrease in platelet count found by De Klerk et al. [18] did not apply for the higher range of BSI. This might explain the different results in comparison to our study, which included more cases with a BSI over 50%.

De Klerk et al. investigated ^{186}Re-HEDP in prostate cancer patients and observed a maximum tolerated dose of 2.96 GBq (80 mCi), with thrombocytopenia (grade 1) being the dose-limiting toxicity [19]. It seems that, in spite of the above-mentioned dosimetric data, the appropriate dose of ^{188}Re-HEDP cannot be estimated by simply doubling the dose of ^{186}Re-HEDP. However, the experimentally obtained data show that the first haematological effects of ^{188}Re-HEDP occurred at a dose of 2.6 GBq, whereas with ^{186}Re-HEDP the first haematological toxicity was detected at a dose of 1.3 GBq [19]. From these data it is obvious that the difference between ^{188}Re- and ^{186}Re-HEDP with regard to the absorbed dose is not such a major issue as has been suspected. One explanation for the aforementioned discrepancy in haematological toxicity may be that in comparison to ^{186}Re-HEDP, the radiation dose from ^{188}Re-HEDP to the bone marrow is delivered to a significant extent by blood perfusion through the marrow and not only by local irradiation from activity localized at the metastases. Another possibility is that the differences in the β-energy (see Table 1), and thus the depth of penetration of the β-particles into the bone marrow, may play a major role in this observation.

All patients entering this study were treated because of multiple sites of bone pain. There were no severe clinical side-effects which could have been directly correlated to the application of ^{188}Re-HEDP. In particular, we did not observe any neurological side-effects, which have previously been reported to be a rare complication of ^{186}Re-HEDP treatment [20]. In two patients without evidence of recurrent disease we were able to document a slight increase in creatinine levels which was, however, reversible. These borderline changes in creatinine values cannot be interpreted as a sign of renal toxicity of ^{188}Re-HEDP.

The overall response rate in this study was 64% and the average period of response was 7.5 weeks. The response rate is similar to that found for the treatment of bone metastases with ^{186}Re-HEDP [5–7]; however, the duration of pain relief seems to be longer. In a previous study in which 44 patients were treated with ^{186}Re-HEDP, we found an overall response rate of 60% and a duration of response averaging 5.5 weeks [7]. When the response rate of ^{188}Re-HEDP is correlated to the applied dose and the duration of response, it seems that the minimum dose that will achieve effective pain palliation is 2.6 GBq. In this study, the response rate could be improved from 33% to 75% with increasing doses. However, these results are not statistically significant due to the limited number of patients in each dose escalation group, and therefore this study could not prove a dose response for ^{188}Re-HEDP.

The ^{188}W/^{188}Re generator is available from Oak Ridge National Laboratories (ORNL) in the United

States. The cost-effectiveness of ^{188}Re-HEDP therapy depends on the number of patients treated with activity delivered from one generator. If at least two or three patients are treated every month, therapy with ^{188}Re-HEDP is as cost-effective as the standard radiopharmaceuticals which are currently approved for routine use. The generator can be eluted every 2–3 days to obtain sufficiently high radioactivity. The radiolabelling procedure, including quality control, requires about 1 h and can be performed by a specially trained technician.

Conclusion

Carrier-added ^{188}Re-HEDP can be easily prepared on demand using a ^{188}W/^{188}Re generator. ^{188}Re has attractive nuclear properties for radionuclide therapy of bone pain and results in a safe radiopharmaceutical which can be administered in prostate cancer patients with osseous metastases. Thrombopenia and leukopenia represent the most important side-effects. In this study, the maximum tolerated dose of ^{188}Re-HEDP was 3.3 GBq. However, patients with thrombocyte counts over 200×10^9/l might be considered for high-dose treatment with 4.4 GBq of ^{188}Re-HEDP.

With a dose above 2.6 GBq of ^{188}Re-HEDP, pain palliation can be achieved in 60%–70% of prostate cancer patients. The mean duration of palliation (for doses above 2.6 GBq) in this study was 8 weeks. Further investigations have been initiated to study the palliative effect of ^{188}Re-HEDP in a larger patient group.

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