

Rhenium-188-HEDP in the Palliative Treatment of Bone Metastases

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Introduction: Rhenium-188-HEDP (¹⁸⁸Re-HEDP) is a new and attractive radiopharmaceutical for the treatment of bone pain due to metastases. As a product of a ¹⁸⁸W/¹⁸⁸Re generator it is convenient for clinical use. With a short physical half life of 16.9 hours and a maximal β -energy of 2.1 MeV, it is suitable for therapy.

Methods: We investigated the influence of ¹⁸⁸Re-HEDP on pain relief, analgesic intake and impairment of bone marrow function in 15 patients. All patients were interviewed using standardized questions before, and 1, 2, 3, 4, 8, and 12 weeks after therapy. Blood samples were drawn weekly for 12 weeks, and a blood count was performed. Patients underwent gamma camera imaging to determine the radionuclide accumulation 4, 20, and 28 hours after therapy. The patients were treated with 1600 to 3459 MBq of ¹⁸⁸Re-HEDP.

Results: Patients showed an improvement of the Karnofsky performance index from $74 \pm 8\%$ to $84 \pm 11\%$ 12 weeks after therapy. This improvement was statistically significant ($p = 0.001$). Eighty percent of the patients described pain relief and reduction of analgesics. Twenty percent of the patients could discontinue their analgesics. Mean platelet count decreased from $(284 \pm 84) \cdot 10^3/\mu\text{l}$ to $(205 \pm 62) \cdot 10^3/\mu\text{l}$, and mean leukocyte count from $(7.5 \pm 1.5) \cdot 10^3/\mu\text{l}$ to $(5.9 \pm 2.1) \cdot 10^3/\mu\text{l}$ after therapy. The maximal differences between the values of platelets and leukocytes before and after therapy were not statistically significant ($p = 0.021$ and $p = 0.094$). Prostate specific antigen decreased from 95 ± 83 ng/ml to 41 ± 21 ng/ml, the difference was not statistically significant ($p = 0.443$). The bone accumulation 4, 20, and 28 hours after therapy was $1.3 \pm 0.5\%$, $0.6 \pm 0.3\%$, and $0.45 \pm 0.2\%$ of the injected dose of a single metastasis, and $57 \pm 17\%$, $15.5 \pm 2\%$ and $11 \pm 3\%$ in the whole body, respectively. The effective half-life of ¹⁸⁸Re-HEDP was 15.3 ± 3.0 hours in the bone metastases, and 11.4 ± 2.8 hours in the whole body. This corresponds to a residence time of 0.22 ± 0.25 hours in the bone metastases, and of 10.54 ± 2.59 hours in the whole body.

Conclusion: In a small patient population, ¹⁸⁸Re-HEDP therapy for bone pain palliation was effective and was associated with minimal toxicity.

Key Words: Rhenium-188-HEDP, pain palliation, bone metastases

INTRODUCTION

The skeleton is frequently affected by painful metastases from breast and prostate cancer. Metastatic bone pain is a serious problem for the patient influencing quality of life. The major mechanism of pain from small metastases appears to be the stimulation of nerve endings in the endosteum by a variety of chemical mediators. Larger bone metastases produce stretching of the periosteum which leads to pain.¹ Autopsy studies showed that patients with advanced stage prostate cancer have a frequency of bone metastases of 65% to 85%.²

Various radiopharmaceuticals, such as strontium-89, rhenium-186-HEDP (hydroxyethylidene diphosphonate) and samarium-153-EDTMP (ethylenediamine-tetramethylenene), have been used for palliation of bone metastases, Rhenium-188-HEDP (¹⁸⁸Re-HEDP) is a new and attractive radiopharmaceutical for bone pain palliation. As a product of a ¹⁸⁸W/¹⁸⁸Re generator, it is convenient for clinical use, in the sense of an in-house generator system similar to the current ^{99m}Mo/^{99m}Tc-generator. ¹⁸⁸Re-HEDP has a physical half-life of 16.9 hours, but the biological half-life in bone of 60.9 hours is useful for therapy. In contrast, the biological half-life in muscle and blood is short (2.99 hours and 6.21 hours, respectively).³ The maximal energy of the therapeutic β -emission is 2.1 MeV. A 155 keV γ -emission from rhenium-188 allows imaging with a gamma camera to control the tissue distribution of the radionuclide in the patient. The short physical half-life of rhenium-188 allows for higher activity doses compared to longer-lived radionuclides.³

MATERIALS AND METHODS

In this study, we evaluated the influence of ¹⁸⁸Re-HEDP on pain relief, reduction of analgesics, and changes in quality of life. Before, and 1, 2, 3, 4, 8, and 12 weeks after the ¹⁸⁸Re-HEDP therapy, an extended interview with a standardized set of questions concerning pain relief, analgesics, and Karnofsky-Index was conducted. Blood counts were obtained to evaluate the impairment of bone marrow function after therapy and to measure the prostate specific antigen.

We treated 15 patients (mean age: 67 ± 9 years) with a dose of 1600 to 3459 MBq. One pt

received 1600 MBq, a further pt two doses of 1600 MBq within two days, and 13 patients were treated with doses between 2700 and 3459 MBq.

Patients consisted of one female with breast cancer and 14 males with prostate cancer. Entry criteria into the study were a positive ^{99m}Tc-HMDP bone scan showing at least three metastases, severe bone pain under analgesics and sufficient bone marrow function with a platelet count $\geq 10^5/\mu\text{l}$, leukocyte count $\geq 3.0 \cdot 10^3/\mu\text{l}$ and haemoglobin ≥ 6.0 mmol/l. Chemotherapy and bisphosphonate therapy were discontinued 4 weeks before injection of the radiopharmaceutical. Patients with pathologic bone fractures, spinal cord compression, an unstable spine or soft tissue tumours elsewhere pressing on nerves were excluded from the therapy.

Patients were hospitalized for two days for the ¹⁸⁸Re-HEDP therapy due to regulations in the radiation protection law in Germany. The patients underwent gamma camera imaging 4, 20, and 28 hours following the administration of the radioisotope to determine the radionuclide accumulation in the bone metastases and the effective half life of ¹⁸⁸Re-HEDP. The whole body scans were performed on a double-head camera (Genesys, ADAC Laboratories) equipped with a high-energy collimator to reduce the effect of the bremsstrahlung.

Accumulation of the radionuclide was calculated with software provided by ADAC. With this software, we measured the count rate of the metastases, the whole body and a standard of ¹⁸⁸Re-HEDP. By comparing the count rates to that of the standard, the percent accumulation of ¹⁸⁸Re-HEDP in the whole body and the metastases was calculated.

The effective half-life of the accumulated ¹⁸⁸Re-HEDP in metastases and in remaining areas of the whole body (remainder) was estimated in eight cases. The time-activity curve of the percent uptake of the radiopharmaceutical in a specific ROI was fitted by a least square method with a monoexponential function. From this fit, half-life was derived and, according to MIRDOSE, the residence time,⁴ which equaled the area under the fit.

The patients underwent a ^{99m}Tc-HMDP bone scan within 5 weeks before as well as three weeks after treatment to evaluate a possible decrease of the mass of bone metastases.

Rhenium-188 was obtained from an alumina-based ¹⁸⁸W/¹⁸⁸Re generator as described previ-

ously.⁵ The preparation of ¹⁸⁸Re-HEDP is described elsewhere.³ The significance of improvement of Karnofsky-Index and thrombo- and leukocytopaenia was calculated with a paired t-test with an α -value of 0.01.

RESULTS

The analgesic intake decreased in 80 % of the patients. Twenty percent of patients were able to discontinue analgesics completely. Sixty percent of patients reported considerable and 20 % minor pain relief. No patient with pain relief required an increase of analgesics. The Karnofsky-Index increased from 74 ± 8 % before therapy to 84 ± 11 % at 12 weeks after therapy. This increase was statistically significant ($p = 0.001$). The maximal increase of the Karnofsky-Index was 27 %.

With regards to haematological toxicity, thrombocyto- and leukopaenia were dose-limiting. The decrease in blood counts was reversible within 12 weeks in all patients. No pt. showed a decrease of leukocytes below $3.0 \cdot 10^3/\mu\text{l}$. Only one patient had a decrease of platelets below $100 \cdot 10^3/\mu\text{l}$. Decrease of platelets from $(284 \pm 84) \cdot 10^3/\mu\text{l}$ to $(205 \pm 62) \cdot 10^3/\mu\text{l}$ (maximal decrease: to $86 \cdot 10^3/\mu\text{l}$) was observed within 12 weeks. Leukocytes decreased from $(7.5 \pm 1.5) \cdot 10^3/\mu\text{l}$ to $(5.9 \pm 2.1) \cdot 10^3/\mu\text{l}$ (maximal decrease: to $3.8 \cdot 10^3/\mu\text{l}$) (Fig. 1). The nadir of the platelets was 2.8 \pm 0.7 weeks and of the leukocytes 2.5 \pm 1.0 weeks after therapy.

The maximal differences between the values of

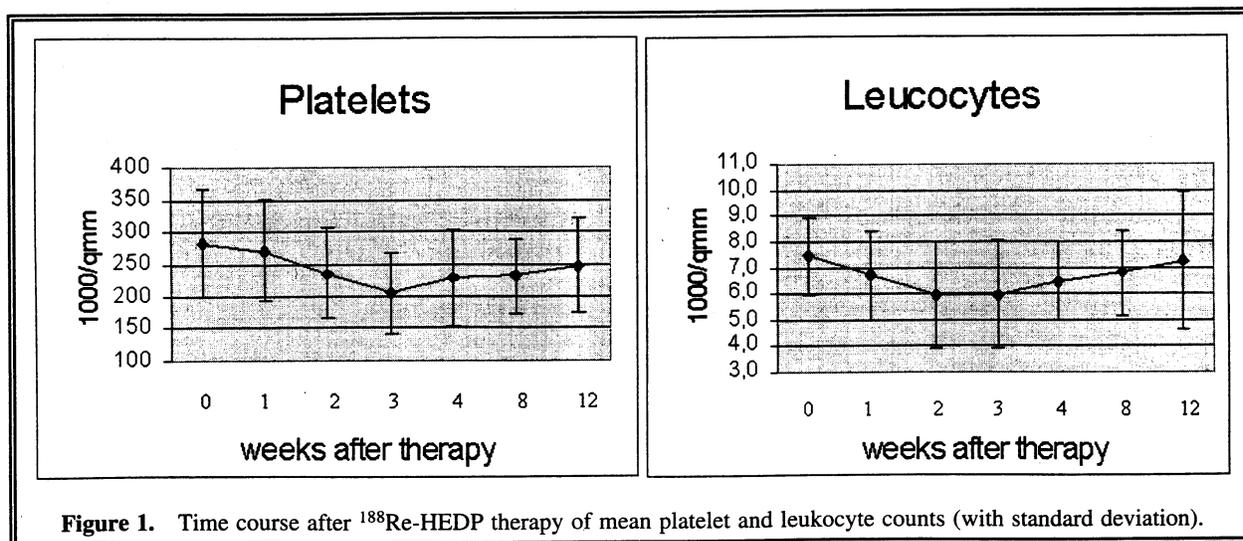
platelets and leukocytes before and after therapy was not statistically significant ($p = 0.021$ and $p = 0.094$).

Only one patient had a decrease of haemoglobin below 6.0 mmol/l with temporary anaemia; in this patient a transfusion was not necessary.

Prostate specific antigen decreased from 95 ± 83 ng/ml to 41 ± 21 ng/ml; this was not statistically significant ($p = 0.443$).

Accumulation of ¹⁸⁸Re-HEDP expressed as percentage of the injected dose at 4 hrs was 57 ± 17 % in the whole body, and 1.3 ± 0.5 % in a single metastasis, at 20 hrs 15.5 ± 2 % in the whole body, and 0.6 ± 0.3 % in a single metastasis, at 28 hrs 11 ± 3 % in the whole body, and 0.45 ± 0.2 % in a single metastasis. Effective half-life was 11.4 ± 2.8 hours in the whole body and 15.3 ± 3.0 hours in 44 metastases of 8 patients. This corresponds to a residence time of 10.54 ± 2.59 hours in the whole body, and of 0.22 ± 0.25 hours in the metastases. In the patient who received two doses of 1600 MBq ¹⁸⁸Re-HEDP within two days. There was an accumulation of 11% of the injected dose in all metastases after the first therapy and of 16% after the second therapy.

The ^{99m}Tc-HMDP bone scan showed no obvious reduction of bone metastases 12 weeks after therapy when compared to the scan before therapy. However, one patient with breast cancer showed a reduction of the number of metastases in the ^{99m}Tc-HMDP bone scan at 7 months after therapy. This pt. discontinued her analgesic intake, developed no pain symptoms for 10 month



and showed an increase of the Karnofsky-Index of 15% within 12 weeks after therapy.

DISCUSSION

From a theoretical point of view, ^{188}Re -HEDP is a new and attractive radiopharmaceutical for the treatment of painful bone metastases. As a generator product it has an excellent availability which permits on-site labelling as with a routinely used $^{99\text{m}}\text{Tc}$ -generator resulting in low costs.

In the literature there are few reports about the therapeutic effect of ^{188}Re -HEDP in bone pain palliation and no biokinetic data in bone metastases have yet been published. Maxon et al.⁶ described a radiation dose of 3.2 ± 0.5 rad/mCi to the normal skeleton of five male patients with prostate cancer given ^{188}Re -HEDP, but he had no data for radiation dose in bone metastases. In the same report Maxon published a projected radiation dose from ^{188}Re -HEDP based on prior human experience with rhenium-186-HEDP of 0.4 ± 0.1 rad/mCi in the total body. Data for the effective half life or the residence time were not published.

In a dose escalation study Palmedo et al.⁷ found a maximal tolerated dose of 3,300 MBq of ^{188}Re -HEDP. They reported pain palliation in 60-75 % of the patients receiving at least 2,600 MBq of ^{188}Re -HEDP. We found bone pain palliation in 80% of the patients after a dose of 3,300 MBq. One patient after a dose of 1,600 MBq described pain palliation and reduction of analgesics. This patient was treated before the results of the dose escalation study from Palmedo were published. From then on we used a dose of 3,300 MBq of ^{188}Re -HEDP, if possible. In some cases we could give only doses between 2,700 to 3,300 MBq, when we were near the end of the useful life-span of the generator and the activity of the eluted rhenium-188 was down. In this situation it is possible to give the activity of ^{188}Re -HEDP in two separate doses within two days. We showed in a single case with two doses within two days the same accumulation of the radiopharmaceutical in the metastases on the first and the second therapy with good therapeutic effect.

The results from other groups⁸⁻¹² and ours¹³ for strontium-89 and rhenium-186-HEDP therapy showed pain palliation in 70 % to 85 % of the patients comparable to our results in patients who received ^{188}Re -HEDP therapy.

Quilty et al.¹² described a reduction of analgesic intake following strontium-89 therapy in 70 % of patients. Robinson et al.¹¹ showed a reduction of analgesics and pain palliation in 80 % of 137 patients. In our patients we found a reduction of analgesics in 80 % of the patients and 20 % of the patients could discontinue medication completely.

Our patients showed an increase of the Karnofsky-Index from 74 ± 8 % before ^{188}Re -HEDP therapy to 84 ± 11 % after therapy, slightly higher than that obtained with rhenium-186 or strontium-89 therapy,¹⁴ but this difference was not statistically significant ($p = 0.299$). Porter et al. (15) showed a comparable increase of the Karnofsky-Index from 72 to 78 % after strontium-89 therapy.

Thrombocytopenia is the dose-limiting factor for the treatment. Leukopenia is of lesser significance in this respect.¹⁶ We observed a decrease of platelets from $(284 \pm 84) \cdot 10^3/\mu\text{l}$ to $(205 \pm 62) \cdot 10^3/\mu\text{l}$ within 12 weeks after therapy. The leukocytes decreased from $(7.5 \pm 1.5) \cdot 10^3/\mu\text{l}$ to $(5.9 \pm 2.1) \cdot 10^3/\mu\text{l}$. A decrease of platelets below $100 \cdot 10^3/\mu\text{l}$ and a decrease of leukocytes below $4.0 \cdot 10^3/\mu\text{l}$ was observed in a single case only. This decrease is comparable to a Grade I bone marrow toxicity according to WHO. We conclude that ^{188}Re -HEDP therapy causes only mild bone marrow toxicity, comparable to rhenium-186-HEDP and strontium-89.^{10,14} This is supported by a mean dose to the red marrow of 0.2 Gy for rhenium-186-HEDP¹⁷ and of 0.3 Gy for ^{188}Re -HEDP.⁶

^{188}Re -HEDP had a significant difference between the effective half-life in the metastases (15.3 ± 3.0 hours) and the whole body (11.4 ± 2.8 hours) ($p = 0.003$).

We observed good accumulation of ^{188}Re -HEDP in the metastases (1.29 ± 0.45 % of injected dose after 4 hours).

The therapy with ^{188}Re -HEDP showed good palliative effect and minimal side effects.

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