Treatment of Metastatic Bone Pain with Rhenium-188 Hydroxyethylidene Diphosphonate

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Key Words

Bone pain control · Skeletal metastases, treatment · ¹⁸⁸Rhenium-hydroxyethylidene diphosphonate (¹⁸⁸Re-HEDP) · Toxicity · Whole body dynamic scans

Abstract

Objective: This study was designed to evaluate the safety and effectiveness of rhenium-188 hydroxyethylidene diphosphonate (¹⁸⁸Re-HEDP) in patients with skeletal metastases. **Methods:** Thirty-two patient volunteers with cancer metastasized to bone were included in this study. All patients underwent bone scanning with technetium-99m methylene diphosphonate 2 days before the administration of ¹⁸⁸Re-HEDP. A dose of 1,110 MBq (30 mCi) of ¹⁸⁸Re-HEDP was injected intravenously and whole body dynamic scans were obtained 1, 2, 3, and 5 days later. Blood and urine samples were collected daily for 5 days and then weekly for 4 weeks. The biokinetic data were obtained and the radiation doses were calculated. The reactions, toxicity and pain relief were corrected. **Results:** No acute reaction or toxicity was evident. Leukopenia was found only in 1 patient with skeletal metastases from prostate cancer. The baseline white blood cell count of $4.3 \times 10^9/l$ (normal range 4.0–10.0) declined to a value of $3.0 \times 10^9/l$ 1 week after receiving 1,110 MBq (30 mCi) of ¹⁸⁸Re-HEDP. The white blood cell count had

returned to the baseline category by 4 weeks after injection. No patient was found to be thrombocytopenic. The hemoglobin concentration remained at the baseline level for 6 weeks. The excretion rate of ¹⁸⁸Re-HEDP in the urine was 62% of the administered activity during the first 2 days. Twenty-eight of the 32 patients (87.5%) were able to reduce their analgesic intake. Twenty of the 32 patients (62.5%) had a significant improvement in the quality of life while 8 patients (25%) had a minor improvement. **Conclusion:** Most of the patients experienced an improvement in the quality of life without induction of serious bone marrow reduction with this treatment regime. It is therefore concluded that the use of ¹⁸⁸Re-HEDP for treatment of skeletal metastasis appears to be feasible.

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Introduction

At least 75% of patients with metastatic cancer of the bone develop pain [1, 2]. The pain leads to decreasing mobility, which may result in generalized weakness, mobilization difficulties, risk of thromboembolism, pneumonia, hypercalcemia and atelectasis. Therefore, the control of pain in patients with cancer is an important clinical challenge. The primary goal of therapy is pain relief with

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an improved quality of life. Three radionuclides are employed for this purpose in clinical practice: phosphorus-32 (^{32}P) [3], strontium-89 (^{89}Sr) [4] and samarium-153 (^{153}Sm) [5]. Recently, we successfully labeled hydroxyethylidene diphosphonate (HEDP) with rhenium-188 (^{188}Re) and analyzed its biodistribution in rats and rabbits. ^{188}Re is an excellent candidate for radiotherapy [6]. It can be easily obtained from a $^{188}\text{W}/^{188}\text{Re}$ generator as a 'no carrier added' radioisotope analogous to the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator. Beta emission with energies of 2.12 MeV (71.6%) and 1.96 MeV (25.1%) are suitable for therapy and the gamma emission of 155 keV (15%) allows for imaging and calculating dosimetry. The half-life of 16.9 h is suitable for treatment and of benefit to minimize toxicity to the whole body [7–12]. This present study was designed to evaluate the safety and effectiveness of ^{188}Re -HEDP in patients with metastases.

Materials and Methods

^{188}Re Production

^{188}Re was obtained from an alumina-based $^{188}\text{W}/^{188}\text{Re}$ generator. The ^{188}W and the ^{188}W -sodium tungstate solution were produced by irradiation of enriched ^{186}W provided by the Oak Ridge National Laboratory (Oak Ridge, Tenn., USA). Carrier-free ^{188}Re sodium perrhenate was extracted from the generator eluted with 0.9% NaCl. The radionuclide purity of ^{188}Re was analyzed by high purity germanium detector and the radiochemical purity of $\text{Na}^{188}\text{ReO}_4$ by paper chromatography developed with 0.9% NaCl as the solvent.

Preparation of ^{188}Re -HEDP

The ^{188}Re -HEDP was prepared from a sterile, lyophilized kit provided by the Institute of Nuclear Research. Each vial of the kit contains 20 mg of HEDP, 10 mg of vitamin C and 10 mg of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$. Four milliliters of the ^{188}Re -perrhenate solution was added to the kit and heated in a boiling water bath for 10 min, which was then passed through a 0.22- μm filter into a nitrogen-purged vial. The final product was assayed by a high purity germanium detector and paper chromatographic analyses using acetone as solvents. Sterility and pyrogen tests were performed.

Patients

Thirty-two patients, 23 men and 9 women, with progressive, painful and extensive skeletal metastases from cancer volunteered for the therapeutic protocol. The mean age was 60.4 ± 8.2 years (range 30–76 years). To participate, the white blood cell count had to be at least $4.0 \times 10^9/\text{l}$ with a total platelet count of at least $100 \times 10^9/\text{l}$.

Therapeutic Protocol

All patients underwent bone scanning with technetium-99m methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) 2 days before the administration of ^{188}Re -HEDP. A dose of 1,110 MBq (30 mCi) of ^{188}Re -HEDP was injected intravenously and whole body scans were obtained 1, 2, 3, and 5 days later. The ratio of tumor to normal bone

of the contralateral side (T/NT ratio) was calculated. The biokinetic data were obtained and the radiation doses were calculated. The reactions, toxicity and the extent of the pain relief were corrected. For investigation of the toxicity of the radiopharmaceutical, hemoglobin concentration, leukocyte count, platelet count and renal function (plasma creatinine) were studied. Blood and urine samples were collected daily for 5 days, then weekly for 4 weeks and the volume was recorded. The radioactivity in 1 ml of each urine sample was counted in a counter.

The method for pain assessment previously discussed in detail by Turk and Okifuji [13] and other authors [14, 15] was used. Briefly, a box intensity scale was used to assess the patient's pain. A diary containing validated self-reports of rating scales of pain intensity was maintained for more than 30 days.

Results and Discussion

The average radionuclidic and radiochemical purities were 99 and 98%, respectively. No acute reaction or toxicity was evident.

Leukocytes. Leukopenia was found only in 1 patient with skeletal metastasis from prostate cancer. The baseline white blood cell count of $4.33 \times 10^9/\text{l}$ (normal range $4.0\text{--}10.0 \times 10^9/\text{l}$) declined to a value of $3.0 \times 10^9/\text{l}$ 1 week after receiving 1,110 MBq (30 mCi) of ^{188}Re -HEDP. The white blood cell count had returned to the baseline level 4 weeks after injection.

Platelets. All of the patients' platelet counts remained at the baseline value. No patient was found to be thrombocytopenic.

Hematopoietic Toxicity. In all of the 32 patients, the hemoglobin concentration remained at the baseline level during the 6 weeks. Based on these results, hematopoietic toxicity of ^{188}Re -HEDP after injection of 1,110 MBq (30 mCi) seems to be limited.

Renal Function. Only 1 patient experienced mild renal toxicity with serum creatinine concentrations greater than $140 \mu\text{mol/l}$ (1.6 mg/dl) at 1 week post injection of ^{188}Re -HEDP. The serum creatinine returned to normal baseline level at 3 weeks after injection. Results of urinalyses in the other subjects were variable, but none developed elevated serum creatinine levels.

Biodistribution

Urine. The excretion rate of ^{188}Re -HEDP in the urine was 62% of the administered activity within the first 2 days (fig. 1). Figure 2 is the bone scan of ^{188}Re -HEDP taken about 24 h after injection in a patient with skeletal metastasis from prostate cancer. For comparison, the whole body bone scan of $^{99\text{m}}\text{Tc}$ -MDP in the same patient is also shown. These images, obtained 1, 2, 3, and 5 days

Fig. 1. The urine excretion of ¹⁸⁸Re-HEDP.

after injection, revealed low soft-tissue activity and high bone accumulation of ¹⁸⁸Re-HEDP. The accumulation in lesions that had metastasized was higher than that in normal bone.

Pain Relief

Three of the 32 patients (9.4%) experienced a transient increase in pain shortly after the injection of ¹⁸⁸Re-HEDP. No other acute reactions occurred. Twenty of the 32 patients (62.5%) experienced marked pain relief. The pain relief continued during the final 5-week follow-up visit. Eight of the 32 patients (25%) who responded also had a reduction in pain medication of at least 50%. The other 4 patients (12.5%) had no response to these treatments. They did not obtain pain relief. In this group, 28 of 32 patients were able to reduce their analgesic intake. Twenty of 23 patients had a significant improvement in the quality of life whereas 8 patients had a minor improvement. Therefore, a positive response, as indicated by at least a 50% reduction in pain and/or analgesic usage, was seen in 28 out of 32 (87.5%) patients.

Fig. 2. The bone scan of ¹⁸⁸Re-HEDP about 24 h after injection in a patient with skeletal metastases from prostate cancer and for comparison a bone scan using ^{99m}Tc-MDP.

The findings of this study may broaden the use of radiopharmaceuticals for treatment of metastatic bone pain. Compared to the other agents, such as ^{153}Sm -ethylenediaminetetramethylene phosphoric acid, ^{188}Re -HEDP has a number of advantages: ^{188}Re can be produced from a radionuclide generator and hence be readily available and offer the opportunity of being widely used; ^{188}Re has a reasonably short half-life (17 h) suitable for treatment and causes less radiotoxicity than ^{153}Sm ($t_{1/2}$ 1.95 days), ^{186}Re ($t_{1/2}$ 3.7 days) and ^{89}Sr ($t_{1/2}$ 53 days). The maximum penetration range of ^{188}Re is longer than that of ^{89}Sr , ^{153}Sm or ^{186}Re . ^{188}Re has gamma ray (E_γ 155 keV) suit-

able for imaging and therefore does not require the administration of another radiopharmaceutical for radionuclide imaging to monitor the efficacy of treatment.

Conclusion

Most of the patients experienced an improvement in the quality of life without induction of serious bone marrow reduction with this treatment regime. Therefore, it is concluded that the use of ^{188}Re -HEDP for treatment of skeletal metastasis appears to be feasible.

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