^{186}Re-Etidronate in Breast Cancer Patients with Metastatic Bone Pain

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The aim of this study was to evaluate the efficacy of ^{186}Re-1,1-hydroxyethylidene diphosphonate (etidronate) in breast cancer patients with painful bone metastases. **Methods:** Thirty patients with advanced breast cancer who had metastatic bone pain were treated with ^{186}Re-etidronate using different dosages in a noncomparative, open-label study. Twenty-four patients were evaluated for efficacy (6 patients had incomplete datasets). Dosages varied from 1295 to 2960 MBq (35 to 80 mCi). Efficacy was evaluated according to the multidimensional pain model using a paper-and-pencil diary. The diary was kept twice daily for 8–10 wk (2 wk before through 6–8 wk after ^{186}Re-etidronate treatment). Response was determined with a strict criteria, in which pain intensity (PI), medication index (MI) and daily activities (DA) were core determinants. Response was defined as: (a) Reduced PI ≥ 5% while MI and DA were at least constant; or (b) Reduced PI <25% in combination with improvement of MI or DA ≥25%, without worsening of either factor. Duration of response should always exceed a minimum of 2 wk. **Results:** Fifty-eight percent (n = 14) of all patients reported a response. The maximum follow-up period was 8 wk. Duration of response ranged from 2 to 8 wk (mean 4 wk). Patients (14/24) not only experienced considerable pain reduction, but in 12 patients this was also accompanied by noteworthy reduction in MI (≥25%). No clear dose-response relationship was found. **Conclusion:** With strict pain assessment criteria, ^{186}Re-etidronate showed a response of 58% in the palliative treatment of metastatic bone pain originating from breast cancer.

Key Words: ^{186}Re-1,1-hydroxyethylidene diphosphonate; breast cancer; palliation

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In The Netherlands, as in other western countries, breast cancer is the most common malignancy in women. This diagnosis is made in more than 9000 out of 7.6 million women a year, and more than 3400 women die from this disease annually (*1*). In breast cancer patients, the skeleton is a prime site of metastatic disease, and the majority of patients dying from breast cancer have bone metastases (*2*). Along with endocrine therapy, chemotherapy and analgesics, local external beam radiotherapy is commonly used for treatment. However, metastatic lesions often occur in multiple places, and pain changes place in many of these patients. Therefore, radionuclide therapy with a specifically localizing β-emitter has been used as a promising substitute for or adjunct to external beam radiotherapy.

^{186}Re-1,1-hydroxyethylidene diphosphonate (etidronate) is one of the bone-seeking agents that is used for palliative treatment of metastatic bone pain (*3–7*). Like other pharmacological therapeutics, ^{186}Re-etidronate directly influences the sensoric dimension of pain (*8*). Therefore, initial changes in the sensoric aspects (in particular the intensity of pain) are to be expected. These changes, however, also affect the other dimensions of pain, such as the affective, cognitive and behavioral ones. To determine the overall efficacy of ^{186}Re-etidronate, a clinically relevant instrument should be used that takes into account these reciprocal influences.

This study describes the pain-reducing effects of ^{186}Re-etidronate in patients who are entering a clinical phase I/II study with breast cancer resistant to endocrine therapy and chemotherapy and who also have metastatic bone pain.

MATERIALS AND METHODS

Patients

The study protocols were approved by the Institutional Review Board of the University Hospital Utrecht. Patients gave written informed consent. Two protocols were aimed at the evaluation of the toxicity of ^{186}Re-etidronate: an escalating dosage study (1295–2980 MBq [35–80 mCi]) and a study that used a fixed dose of 1295 MBq (35 mCi) ^{186}Re-etidronate.

A total of 30 patients entered the studies. All patients had histologically proven breast cancer; had been treated with hormonal therapy, chemotherapy or both; and had bone pain that required the use of analgesics. They had at least four scintigraphically and radiologically proven metastatic bone lesions. Adequate platelet count (>150 × 10^9/L), leukocyte count (>4.0 × 10^9/L) and renal function (plasma creatinine levels <130 μmol/L) were required for eligibility. Karnofsky performance status was required to be ≥60% and life expectancy estimated to be at least 3 mo. Although no specific recommendations on alteration of the analgesic treatment were made, the patients were requested to keep the analgesic regimen constant if possible.

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Treatment

The preparation of ^{186}Re-etidronate has been described in detail previously (*9*). The injected doses ranged from 1295 to 2960 MBq (35 to 80 mCi). ^{186}Re-etidronate (total volume 2 mL) was injected as a bolus through a running intravenous saline drip.

Patients were hospitalized for 24 h. After ^{186}Re-etidronate administration, patients were seen and examined weekly, usually as outpatients.

Additional Clinical Data

The bone scan index (BSI) previously described for prostatic cancer by Blake et al. (*10*) was determined by using a diagnostic pretherapy whole-body scintigram (400 MBq ^{99m}Tc-hydroxymethylene diphosphonate) to provide an index of metastatic disease.

Pain Assessment

The method for pain assessment has been previously described in detail (*7*). To summarize, a paper-and-pencil diary was used to assess the patient's pain. The diary contained validated questions for 7 d and was kept twice a day (*11–12*).

To determine the efficacy of ^{186}Re-etidronate, strict criteria were formulated, in which pain intensity, medication index and daily activities were included as core determinants. According to these criteria, a clinically relevant response was reached when (a) pain reduction was ≥25% for at least 2 consecutive wk, and when the medication index and daily activities remained at least constant; or (b) pain reduction was <25% for at least 2 consecutive wk, and one of the two other factors showed an improvement ≥25% for at least 2 consecutive wk, while the remaining factor remained at least constant. The studies were open label, so that the patients functioned as their own controls. For each patient, post-treatment data were compared with pretreatment data (baseline). Because scores fluctuated considerably over the week, median scores for the aforementioned dependent variables were calculated: one median score over the 2 wk pretreatment period (baseline), and weekly median scores for the 6 or 8 wk after treatment. After the ^{186}Re-etidronate administration, several patients complained of a transient increase in pain intensity compared with the baseline pain. Typically, this so-called "flare" reaction started within the first week post-therapy and lasted for no longer than a week. In this analysis, a "flare" reaction is defined as an increase in pain intensity of more than 25% of the intensity of pretreatment pain.

The independent *t* test was used to test the influence of age, dosage and BSI on the response ($P < 0.05$ was considered to be statistically significant).

RESULTS

Thirty patients entered the study. Six patients' data were excluded from analysis because of incomplete dataset (n = 5) and no baseline (n = 1). The administered dose of ^{186}Re-etidronate was 1295 MBq (35 mCi) in 6 patients, 1850 MBq (50 mCi) in 6 patients, 2405 MBq (65 mCi) in 9 patients and 2960 MBq (80 mCi) in 3 patients. Patient characteristics are shown in Table 1.

Pain reduction >25% lasting more than 2 consecutive wk was achieved in 17 patients (71%) (Fig. 1). The maximum follow-up period was 8 wk. Duration of response ranged from 2 to 8 wk (mean 4 wk). Response rate of pain reduction was not correlated to treatment dosage. Four patients (67%) in the 1295 MBq (35 mCi) group, 4 patients (67%) in the 1850 MBq (50 mCi) group, 7 patients (78%) in the 2405 MBq (65 mCi) group and 2 patients (67%) in the 2960 MBq (80 mCi) group had responses. Within this group of 17 patients, 2 patients increased their medication indices simultaneously.

TABLE 1
Patient Characteristics

Patient	Age	Administered dose (mCi)	Baseline pain
01b330	47	35	21.5
02b330	36	35	14
03b330	48	35	8.5
05b330	62	50	64
06b330	55	50	34
07b330	58	65	30.5
08b330	46	65	50
10b330	43	65	65
11b330	52	80	58
12b330	46	80	54
13b330	44	80	55
01b341	53	35	12
04b341	47	35	45
05b341	60	35	71.5
PB03	61	50	86
PB06	49	65	60
PB07	51	65	70
PB08	65	69	40.5
PB09	49	50	31.5
PB10	46	50	73
PB11	44	65	61
PB12	66	65	72
PB13	40	65	12
PB14	53	50	25

Improvement in daily activities was noted in 14 patients (58%). In 6 patients, daily activities remained constant. Three patients reported worsening of their daily activities, accompanied by progression of their pain and medication indices or both. One patient reported a worsening of her daily activities, despite a period of >25% pain reduction, lasting 6 wk.

According to the criteria for determination of the overall efficacy of ^{186}Re-etidronate, in 58% (n = 14) of the patients in the total group, clinically relevant responses were reached. No responders were found with pain reduction of less than 25% in combination with ≥25% improvement of daily activity or demand for pain medication (Fig. 2). Ten of 14 responders showed increases in daily activity combined with reductions of the medication index.

All patients had received chemotherapy and/or hormonal therapy before rhenium therapy, but responses were not related to previous chemotherapy and/or hormonal therapy.

Transient worsening of bone pain, the so-called "flare" phenomenon, occurred in about 29% of patients. The incidence was similar for responders and nonresponders.

The mean BSI (range) of all patients was 37 (8–68). The BSI was not correlated to the chance of response, indicating that there was no relationship between the scintigraphic metastatic load and the response. The BSI was not correlated to the chance of flare.

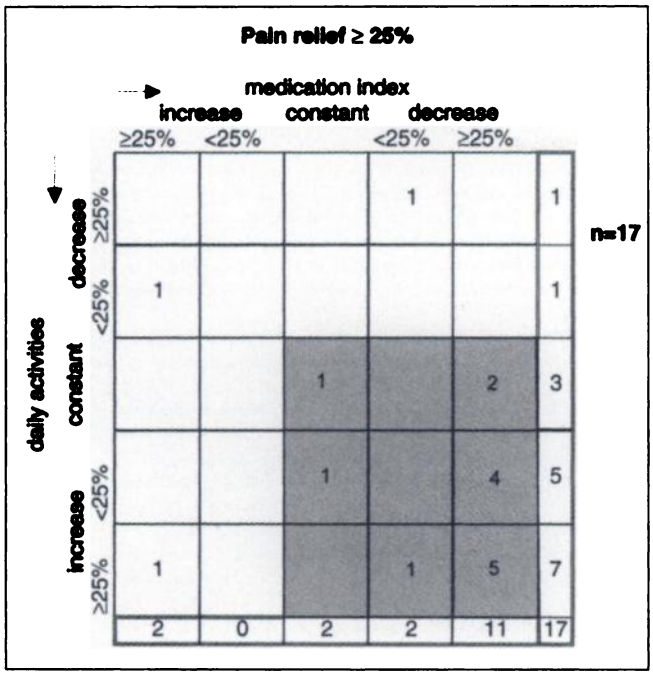

FIGURE 1. Number of patients with at least 25% pain relief in combination with changes in medication index and daily activities. Shaded area indicates patients fulfilling response criteria.

DISCUSSION

Pain control in patients with bone metastasis is of prime importance in improving the quality of life. Although local external beam radiotherapy is very effective in patients with only a minimal area involvement, radionuclide therapy that uses bone-seeking agents has the advantage of treating multiple bone metastases simultaneously (*13*). Various radiopharmaceuticals have been effective in the palliative treatment of bone metastases in breast or prostate cancer (*3–7,14–15*). Response rate was often impossible to compare, due to the complexity and diversity of pain analysis (*15–18*). Various methods have been used previously, but the multidimensional pain model is one of the most complete, objective and standardized methods to assess the treatment response in cancer-related pain (*8,11,19*).

We previously reported a 54% response rate of ^{186}Re-etidronate in prostatic cancer patients with painful bone metastases (*7*). This study reports the efficacy of ^{186}Re-etidronate in breast cancer patients with metastatic bone pain. We observed a response rate of 58%, according to our strict response criteria. These efficacy data indicate a similar response rate. Even with a minimum of >50% pain reduction as the criteria for response, 10 responders were noted. This would result in a 42% response rate instead of a 58% response rate.

This study group previously reported that the toxicity of ^{186}Re-etidronate in breast cancer patients was higher (*20*). This may be explained by previous treatment regimens. Patients who were referred to our department for painful bone metastases often had previously received several courses of chemotherapy, reflecting end-stage breast cancer. It is possible that pretreatment with severe bone marrow-toxic agents would make these patients more susceptible to hematologic toxicity, as their hematopoietic reserves would have been compromised by prior chemotherapy or radiotherapy, compared with patients with prostate cancer.

In this study, the response rate of pain reduction was not correlated to the treatment doses. Therefore, we were not able to assess the optimal dose of ^{186}Re-etidronate for treatment of painful metastases in breast cancer patients, because of the small subgroups.

We calculated a lower BSI in our breast cancer patients compared with patients with prostate cancer (37% ± 17% and 54% ± 23%, respectively) (*21*). BSI reflects the scintigraphic evidence of the metastatic bone load, although purely lytic lesions, seen in bone metastases of breast cancer, are not shown by scintigraphy. Our data indicate that low BSI values in breast cancer patients will give rise to an underestimation of their metastatic load, whereas the toxicity is even higher when compared with prostate cancer patients. As in prostate cancer patients, the BSI could not predict the response. This suggests that factors other than the total amount of ^{186}Re-etidronate uptake in the metastatic lesions will also play a role in pain relief. This is in agreement with data showing that a variety of mechanisms may be involved in the cause of pain (*22*).

Very little data are currently available that describe the efficacy of systemic radionuclide therapy of bone metastases in breast cancer patients. Berna et al. (*14*) reported pain relief and reduction in analgesic requirements in 47% of ^{89}Sr-treated breast cancer patients. They evaluated pain perception at each metastatic site and dependency on

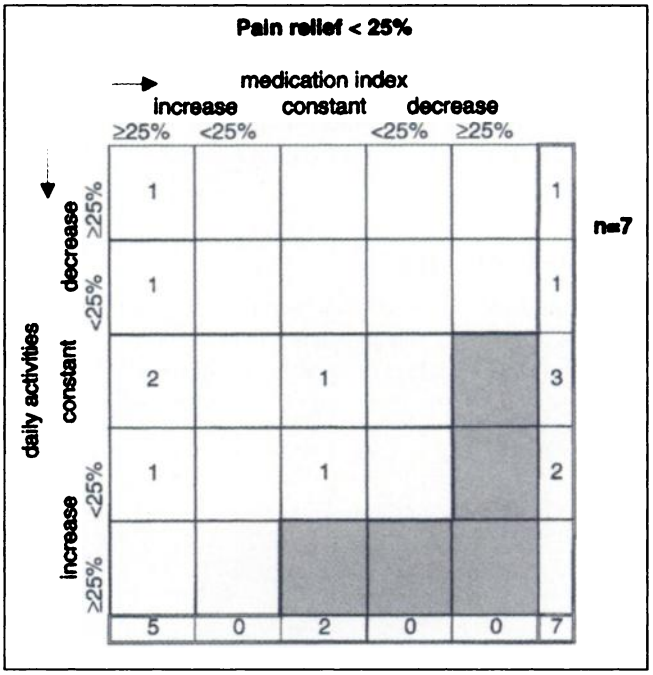

FIGURE 2. Number of patients with <25% pain relief in combination with changes in medication index and daily activities. Shaded area indicates patients fulfilling response criteria.

analgesics at each visit in 15 patients. Although their 47% response rate was similar to this study, little information was provided regarding alteration of medication index, daily activities and minimum duration of response. In a review, Silberstein et al. (*15*) reported pain reduction in up to 84% of patients with breast cancer who used ^{32}P for the treatment of painful osseous metastases. But they also warned that tabulating and analyzing these favorable results had several flaws: Pain scales were rarely spelled out clearly and therefore not reproducible; pretreatment conditions of the patient were rarely clear and most investigators did not state that, during the period of radiophosphorus evaluation, no other therapy was given. Furthermore, in the majority of the patients androgen was added to phosphorus to stimulate an increase in phosphorus uptake in new bone.

Efficacy of treatment in patients with painful bone metastases may also be evaluated, using the so called "physician's pain model." This model only measures the sensoric component of pain. If pain reduction was considered to be the only parameter of response, we would have scored a 71% response rate instead of the 58%, according to our more stringent criteria of response.

We prefer the "multidimensional pain model" and used a scoring system to standardize pain assessment. This will certainly make clinical studies more comparable. Most investigators determined efficacy by using some measurement of pain, analgesic use and quality of life. However, they often failed to delineate the construction, validity or reliability of resulting measurements in their published reports.

CONCLUSION

With the strict pain assessment criteria, ^{186}Re-etidronate showed a 58% response rate in the palliative treatment of metastatic bone pain originating from breast cancer. Comparison of our results with other studies were difficult, as standardized response criteria for pain assessment still have to be defined.

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