

however, show that the findings of Köhn (12) were consistent with the clinical studies of Alderson et al. (2), which indicated that aerosol studies were adequate to assess whether a lung segment is ventilated or not in the context of a diagnostic evaluation of pulmonary emboli. Aerosol studies, however, were not sufficiently accurate to quantitate local ventilation (e.g., prior to resectional surgery). Finally, our results indicate that, because of turbulent tracheal deposition, ^{99m}Tc -DTPA studies may be inadequate for the assessment of pulmonary emboli in mechanically ventilated patients.

CONCLUSION

The lungs of patients maintained on mechanical ventilation can be imaged after inhalation of ^{99m}Tc -DTPA from commercially available delivery kits, but the correlation between aerosol deposition and regional ventilation is poor. Better definition of ventilated lung segments is obtained when using a gas such as ^{81m}Kr .

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Phase 1 Study of Rhenium-186-HEDP in Patients with Bone Metastases Originating from Breast Cancer

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Rhenium-186-1,1-hydroxyethylidene diphosphonate (^{186}Re -HEDP) has been used for the palliative treatment of metastatic bone pain. A Phase 1 dosage escalation study was performed using ^{186}Re -HEDP in patients with metastatic breast cancer. **Methods:** Twelve patients with metastatic breast cancer were studied. Each patient had at least four bone metastases and adequate hematological function. Groups of three consecutive patients were treated with dosages starting at 1295 MBq (35 mCi) and increasing to 2960 MBq (80 mCi) (escalated in increments of 555 MBq). **Results:** A transient increase in pain ("flare" reaction) was observed in six patients. Two patients who received 2960 MBq ^{186}Re -HEDP showed Grades 3 (platelets $25\text{--}50 \times 10^9/\text{l}$) and 4 (platelets $< 25 \times 10^9/\text{l}$) platelet toxicity, which was defined as unacceptable. Prior to treatment, alkaline phosphatase levels were elevated in seven cases. These patients showed a transient decline in alkaline phosphatase levels during the first 4 wk. **Conclusion:** The maximum tolerated administered activity of ^{186}Re -HEDP in patients with metastatic breast cancer is 2405 MBq (65 mCi). Thrombocytopenia proved to be the dose-limiting toxicity,

which could not be predicted adequately by the administered activity. Changes of alkaline phosphatase levels suggest anti-tumor effects of ^{186}Re -HEDP.

Key Words: breast cancer; bone metastases; rhenium-186-HEDP; dosage escalation; bone marrow toxicity

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Bone is the most common site of metastatic disease in breast cancer patients. The majority of patients with advanced breast cancer have evidence of bone metastases by time of death (1). The most prominent symptom associated with bone metastases is pain, which characteristically develops gradually over weeks or months and becomes progressively more severe (2).

Bone metastases require treatment in order to palliate pain. Localized external-beam radiotherapy is an effective modality in the treatment of bone pain and offers partial or complete relief in 73%–96% of patients treated (3,4). The probability of relief appears slightly better with bone metastases from breast cancer as compared with the instance of carcinoma of the kidney or prostate (2). A common problem in this group of

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TABLE 1
Patient Characteristics

Patient no.	Age (yr)	BSI	Time from diagnosis (yr)	Chemotherapy	Hormonal therapy	Radiotherapy
01B330	46	25	2	—	Ovariectomy	Breast Pelvis
02B330	36	12	2	6 × CMF	—	Breast
03B330	48	32	3	6 × CMF 8 × FAC	Tamoxifen	Breast
04B330	64	35	8	6 × CMF	Tamoxifen Aminoglutethimide	Breast Spine
05B330	61	48	5	—	Tamoxifen Aminoglutethimide	Spine
06B330	55	40	12	6 × CMF	Tamoxifen	Breast Pelvis
07B330	58	8	3	—	Tamoxifen	Breast
08B330	46	43	3	6 × CMF 9 × FAC	Tamoxifen Aminoglutethimide	Pelvis Hip
10B330	43	48	2	6 × CMF mitoxantrone 5FU/MTX	Tamoxifen	Breast Spine
11B330	52	33	7	9 × CMF bleomycine	Tamoxifen Aminoglutethimide	Breast Spine
12B330	46	28	8	6 × CMF mitoxantrone	Tamoxifen Aminoglutethimide	Breast Sternum
13B330	44	23	2	6 × CMF	Tamoxifen	Hip

CMF = cyclofosfamide, methotrexate, fluorouracil; FAC = fluorouracil, doxorubicin, cyclofosfamide.

patients, however, was the development of multiple sites of pain, requiring multiple courses of external-beam radiotherapy.

Hemibody irradiation has been advocated as an effective treatment modality in patients with extensive disease. Pain relief appears to occur in up to 85% of patients, but is more toxic than localized external-beam radiotherapy, which is generally associated with minimal side effects (5–8). Virtually all patients receiving lower hemibody irradiation suffer mild acute gastrointestinal toxicity, usually nausea and diarrhea 12–24 hr following treatment, with more severe symptoms in up to 25% of patients. Other acute toxicity includes transient hair loss, taste loss and xerostomia following upper hemibody irradiation. Bone marrow depression is seen in about 10% of patients receiving a single half-body treatment, but in all patients receiving whole-body irradiation. Pulmonary toxicity (radiation pneumonitis), which may be fatal, rarely occurs. Furthermore, in view of potential toxicity of hemibody irradiation, hospital admission and careful patient preparation and subsequent after-care are required in many centers (5,7,9,10).

Bone-seeking radiopharmaceuticals traditionally have been used to image tumors in bone. But, depending on the carrier ligand and the energy of the radioactive label, these agents can also be used to treat metastatic tumors in bone, or as a bone marrow-ablative modality prior to transplantation (11–20). Targeted radionuclide therapy offers several advantages over conventional external-beam radiotherapy, due to systemic administration and preference for metastatic bone lesions. Treatment is tumor-specific, with relative sparing of the surrounding tissue.

Rhenium-186 (^{186}Re) is a beta-emitting radionuclide with a maximum beta emission of 1.07 MeV. It has a 9% abundant gamma emission of 137 keV which allows external imaging. The physical half-life of 89.3 hr makes it a suitable candidate for use in patients with bone metastases and it has been complexed to hydroxyethylidene diphosphonate (HEDP). This

complex localizes in bone by bridging the hydroxyapatite. Initial results showed favorable effects of ^{186}Re -HEDP in patients with metastatic bone pain using dosages on the order of 1300 MBq (21–23). Since bone marrow toxicity was only mild and pain relief only transient, it is important to consider whether more lasting relief of pain can be accomplished with higher dosages of ^{186}Re -HEDP. The goal of this study was to determine a maximum tolerated dosage (MTD) in patients with symptomatic bone metastases originating from breast cancer.

METHODS

Patients

Twelve patients (mean age: 50 yr, range 36–64 yr) were studied (Table 1). All patients had been treated with hormonal and/or chemotherapy. Patients had at least four bone metastases demonstrable on standard bone scintigraphy and radiography. Nine patients were previously treated with external-beam radiotherapy to the bone at limited parts of the skeleton. Each patient had a projected life expectancy of at least 3 mo; a Karnofsky performance status of at least 60%; a total leukocyte count of at least $4.0 \times 10^9/\text{liter}$; a total platelet count of at least $150 \times 10^9/\text{liter}$ and a serum creatinine concentration of 130 $\mu\text{mole/liter}$ or less. Chemotherapy was stopped at least 3 mo prior to treatment with ^{186}Re -HEDP and the agents used in the patients, who were treated with chemotherapy prior to ^{186}Re -HEDP treatment, did not contain cytostatic agents with long lasting or cumulative destruction of bone marrow function.

The study was approved by the hospital review board and all patients gave informed consent.

Treatment and Follow-up

Groups of three successive patients were treated with increasing dosages, starting at 1295 MBq (35 mCi). Escalation of administered activity was implemented in increments of 555 MBq (15 mCi). Escalation was stopped if any patient experienced unaccept-

TABLE 2
Dosages and Toxicity Grade

Patient no.	Dosage (MBq)	ADN (MBq)	Baseline platelet count (10 ⁹ /liter)	Grade of platelet toxicity	Platelet count at the end of follow-up (10 ⁹ /liter)	Baseline leukocyte count (10 ⁹ /l)	Grade of leukocyte toxicity
01B330	1300	1136	218	—	213	5.6	1
02B330	1308	1330	312	—	296	6	1
03B330	1281	1095	263	1	187	6.2	—
04B330	1804	1706	349	—	362	7	1
05B330	1805	1669	192	1	164	7.7	—
06B330	1804	1970	209	1	170	4.0	1
07B330	2320	2176	172	1	174	4.4	2
08B330	2385	2598	388	—	313	6.9	—
10B330	2295	2213	190	2	112	5.6	—
11B330	2661	2711	247	3	36	6.6	1
12B330	2898	2584	240	1	92	4.0	1
13B330	2962	2936	159	4	85	7.6	2

able toxicity, defined as Grades 3 or 4 toxicity at any point, or Grade 2 toxicity which did not resolve by 8 wk postinjection. In either case, three more patients were injected at the same activity level. If any one of these additional three patients, or two of the original group experienced unacceptable toxicity, the MTD was defined as given to the previous group. For this study, patients were hospitalized in an isolated room at the nuclear medicine ward for 24 hr. Previously, we reported the preparation of ¹⁸⁶Re-HEDP in detail (24,25). The radiopharmaceutical was administered as a bolus injection (total volume 2 ml) through a running intravenous saline drip. Patients were seen and examined weekly as outpatients. Blood samples were drawn weekly for hematology and clinical chemistry. The follow-up period was intended to be 8 wk.

Analysis of Toxicity and Pharmacological Effects

Pre- and postinjection hematologic profiles (white cell, red cell and platelet counts), serum chemistry (BUN, creatinine, liver enzymes, LDH, alkaline phosphatase and carcinoembryonic antigen) were determined. For the assessment of toxicity, the 1988 National Cancer Institute Common Toxicity Scale Criteria were used (26). Vital signs (blood pressure, pulse rate and respiratory rate) were recorded prior to and 5 and 60 min after the administration of ¹⁸⁶Re-HEDP. Body surface area (BSA) was calculated according to Boer (27): $BSA (m^2) = 0.2025 \times BW^{0.425} \times H^{0.725}$ in which BW is body weight (in kg) and H is height (in m).

Percentage of decrease in peripheral platelet count (%DEC) was defined as $(1 - \text{nadir of peripheral platelet count} / \text{baseline peripheral platelet count}) \times 100$.

Bone Scan Index

At 2 wk prior to therapy, a diagnostic whole-body scintigram was performed using ^{99m}Tc-hydroxymethylene diphosphonate (HDP). From these scintigrams, the bone scan index (BSI) was determined to provide an index of the extent of metastatic disease as described by Blake et al. (28). Briefly, this method divides the skeleton into four anatomical regions: spine and skull, pelvis, shoulder girdle and ribs and the extremities. Each region is scored visually on a scale of 0–10 for the apparent proportion of skeleton involved. Scores for each region are summed, and the sum is renormalized to a scale of 0–100 as an index for the extent of skeletal involvement. BSI values were calculated independently by two nuclear medicine physicians.

Statistical Analysis

Data were analyzed using the SYSTAT 5.1.2 program (SYSTAT, Inc., Evanston, IL). The Student's t-test was used to detect statistical significance at $p < 0.05$ to verify the decline in leukocyte count, platelet count and alkaline phosphatase levels.

RESULTS

Side Effects

No acute side effects were noted in the first hour postinjection in terms of changes in blood pressure, pulse rate or respiration rate. Six patients experienced a transient increase in pain after the administration of ¹⁸⁶Re-HEDP ("flare" reaction). This flare reaction started within the 24 hr postinjection and lasted one to three days in most cases. The pain intensity caused by this flare reaction was relatively mild and required no additional analgesics. No other subjective side effects were noted.

Hematological Toxicity

Hematological toxicity was limited to thrombocytopenia and leukopenia. Baseline platelet and leukocyte counts, grade of toxicity and platelet counts at the end of the follow-up period for each individual patient are shown in Table 2. The declines in peripheral platelet and leukocyte counts were reversible and returned to the normal ranges (platelet counts $> 150 \times 10^9/\text{liter}$, leukocyte counts $> 4.0 \times 10^9/\text{liter}$) in most patients. One patient (10B330), who received a 2295 MBq dosage of ¹⁸⁶Re-HEDP did not return to normal platelet count at 6 wk. Because of liver metastases progression, this patient was taken out of the study and received additional chemotherapy. Although the follow-up period was not completed, the initial Grade 2 platelet toxicity was already improving but there was no time available to determine the complete recovery of peripheral platelet count. In the three patients who received the highest dosage of ¹⁸⁶Re-HEDP, no return to normal platelet count ranges was observed.

The mean platelet and leukocyte count values are shown in Figures 1 and 2. Nadir in platelet count occurred at Week 4 ($p < 0.01$) and at Week 5 in leukocyte count ($p < 0.05$). With dosages up to 2385 MBq, platelet and leukocyte toxicity was limited to Grade 2. Patients 11B330 and 13B330 experienced Grade 3 and 4 platelet toxicity, respectively. Leukocyte toxicity was confined to Grades 1 or 2 in these patients. They received dosages of the 2960 MBq (80 mCi) group. This meant that, according to our protocol, the MTD was defined as 2405 MBq (65 mCi). Thrombocytopenia was found to be the dose-limiting toxicity. The influence of the administered activity normalized to standard body surface area of $1.73 m^2$ (ADN) on the percentage of decrease in peripheral platelet count relative to baseline level (%DEC) is shown in Figure 3. This figure demonstrates that ADN alone could not adequately predict the %DEC.

The values of the BSI ranged from 8 to 48 (mean 31 ± 13). The reproducibility of its calculation between two independent

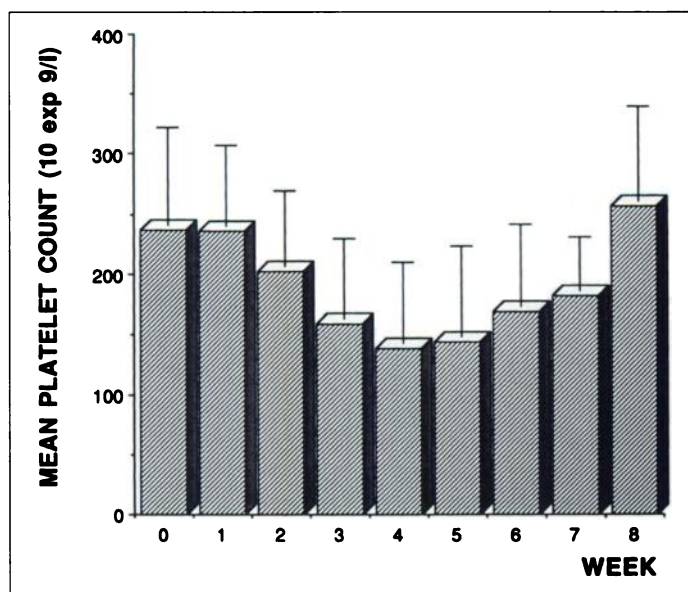


FIGURE 1. Mean platelet count with standard deviation following ^{186}Re -HEDP administration.

observers was good ($r = 0.94$) and of the same order as the reproducibility of the BSI calculation in prostate cancer patients (28). Unlike our previous report on patients with metastatic prostate cancer (28), multiple regression analysis showed no improvement of the prediction of %DEC, when the BSI as an index of metastatic bone involvement was taken into account.

Renal and Hepatic Toxicity

None of the patients showed changes in creatinine levels after treatment. In one case, however, liver enzymes (ASAT, ALAT and γ -GT) showed no change after treatment during the 8-wk follow-up period. This particular patient (03B330) showed a progressive elevation of the ASAT, ALAT and gamma-GT values, which was probably caused by multiple liver metastases proven by ultrasound. She died rather soon after the follow-up period due to extensive metastases in the parenchymal organs.

Biochemical Changes

Prior to treatment, alkaline phosphatase levels were in the normal range (35–95 U/liter) in five patients. The other seven

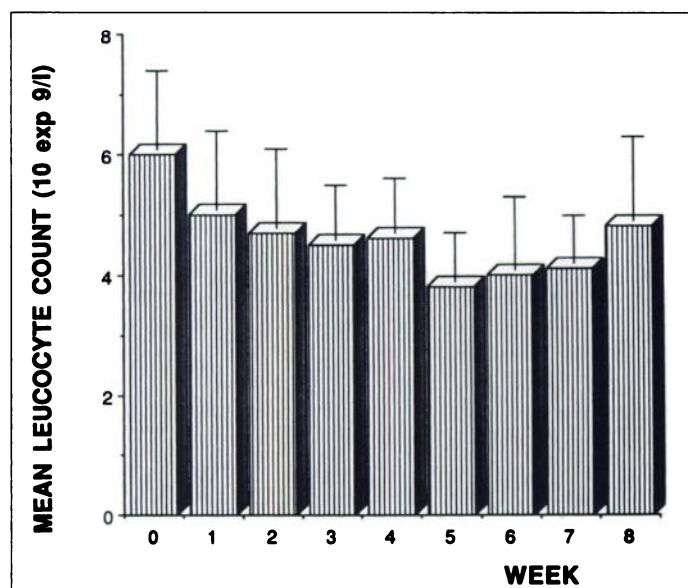


FIGURE 2. Mean leukocyte count with standard deviation following ^{186}Re -HEDP administration.

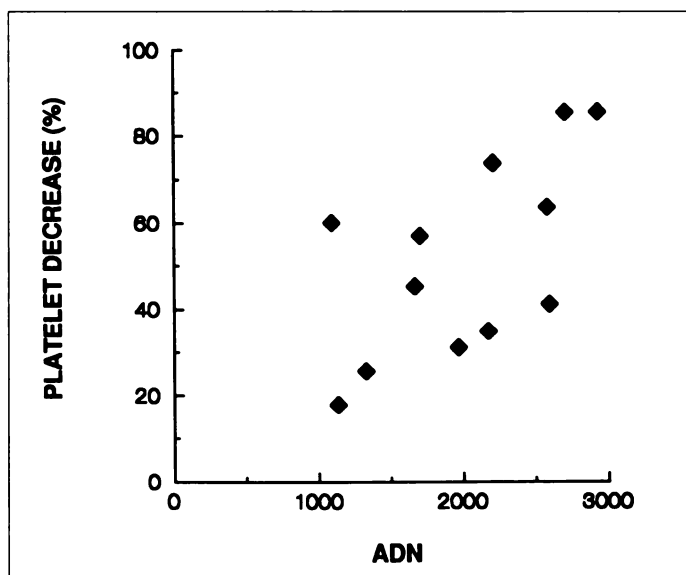


FIGURE 3. Influence of the administered activity normalized to standard body surface area (ADN) on the percentage of decrease in peripheral platelet count (%DEC).

patients, who had elevated alkaline phosphatase levels prior to therapy, showed a transient decline from the first to the fifth week after treatment ($p < 0.05$). This is illustrated in Figure 4. It must be noted that the alkaline phosphatase levels in three patients in the last weeks were not taken into account in this figure due to missing data.

Four patients had normal carcinoembryonic antigen (CEA) (<10 ng/ml). These values remained stable during the follow-up period. Three out of eight patients with elevated CEA values showed no change after treatment, while four of these eight patients showed a gradual increase of the CEA values during follow-up. Only one patient (08B330) showed a transient increase during 3 wk, followed by a decrease (Fig. 5). This patient also experienced prolonged flare reaction pain, which lasted at least 7 days. Subsequently, the pain decreased and the patient improved clinically.

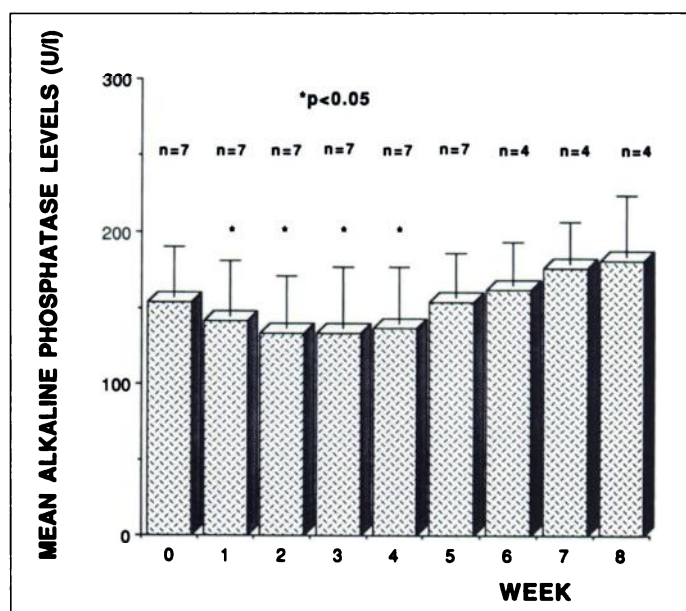


FIGURE 4. Mean alkaline phosphatase level (U/liter) with standard deviation following ^{186}Re -HEDP administration.

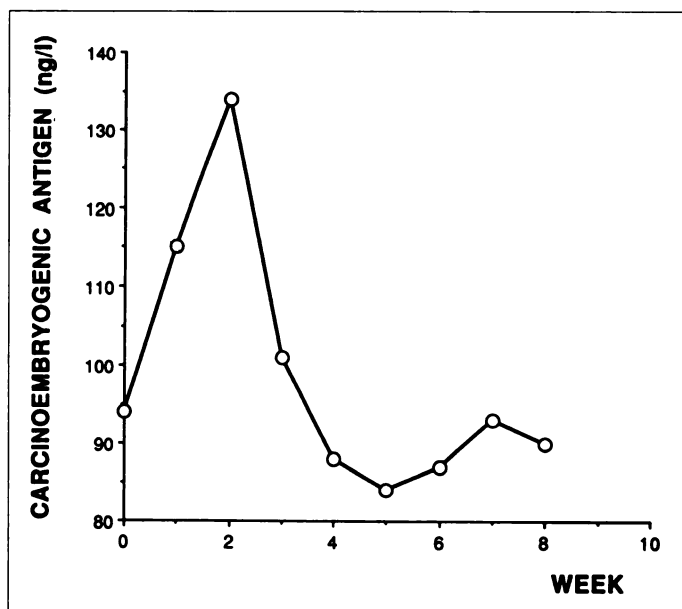


FIGURE 5. The course of CEA values (ng/ml) after ^{186}Re -HEDP therapy in Patient 08B330.

DISCUSSION

Recently, treatment of metastatic bone pain with bone-seeking radiopharmaceuticals has gained new interest. These agents are now widely used for patients with hormone-resistant metastatic prostate cancer, but there is still little clinical data on their use for patients with metastatic breast cancer (30).

When bone-seeking radiopharmaceuticals are used as a palliative therapeutic agent for bone metastases, it is important to know the MTD. We previously reported our experiences with ^{186}Re -HEDP in escalating dosages in prostatic cancer patients (31). The present study reports the use of ^{186}Re -HEDP in patients suffering from metastatic bone pain originating from breast cancer. Similar to the toxicity of other bone-seeking radiopharmaceuticals (16), hematological toxicity proved to be the dose-limiting factor. In patients receiving the highest dosage, thrombocytopenia was more severe than leukopenia. Thrombocytopenia, as well as leukopenia, were reversible in most patients. The peripheral platelet count returned to normal ranges in all but one patient (10B330) with a dosage of 2405 MBq. Above this dosage level the peripheral platelet count did not return to normal ranges. Englaro et al. (32) reported a sustained decrease in both pain and analgesic intake in two patients treated with repeated sequential administrations of ^{186}Re -HEDP. Therefore, not only the grade of toxicity is an important factor for the clinical use of ^{186}Re -HEDP, but in view of the possibility to do repeated administrations of ^{186}Re -HEDP the pattern of peripheral platelet count recovery is also very important.

This study indicates that the MTD as defined in the study protocol is 2405 MBq ^{186}Re -HEDP. This value seems to be lower for breast cancer patients than for prostate cancer patients (2960 MBq) (31). When the administered activity is normalized to a body surface area of 1.73 m^2 (ADN), however, the ADN of the 2405 MBq group in breast cancer patients (ADN mean: $2329 \pm 234 \text{ MBq}$, range: 2176–2598 MBq, $n = 3$) and the 2960 MBq group in prostate cancer patients (ADN mean: $2509 \pm 194 \text{ MBq}$, range: 2253–2720 MBq, $n = 6$) are of the same order.

Patients 11B330 and 13B330 received the highest ADN (2711 and 2936 MBq, respectively), while the ADN of patient 12B330 was 2584 MBq. These particular patients (11B330 and 13B330) showed considerable toxicity, leading to termination of the dosage escalation.

In our patients, chemotherapy was stopped at least 3 mo prior

to treatment with ^{186}Re -HEDP and the agents did not contain cytostatic agents with long-lasting or cumulative destruction of bone marrow function such as mitomycin C or nitroureas. In cases of recent chemotherapy with myelotoxic agents or after treatment with long lasting or cumulative bone marrow depressive agents, care must be taken with the use of bone-seeking radiopharmaceuticals.

As with ^{89}Sr (33), in patients with metastatic prostate cancer, external-beam radiotherapy to limited parts of the skeleton does not influence the percentage decrease in peripheral platelet counts (29). In this study, the most important factor influencing toxicity is the total skeletal metastatic load.

Since it is difficult to assess the degree to which hematopoietic reserve has been compromised by metastatic bone marrow involvement, it is of paramount importance to be able to assess marrow status prior to treatment to avoid serious myelotoxic sequelae.

This study showed that the percentage of decrease in peripheral platelet count (%DEC) cannot be predicted adequately by the ADN alone, just as with prostate cancer patients (29). In contrast to prostate cancer patients, the prediction of %DEC did not improve when scintigraphic evidence of the metastatic load in the bone (BSI) is taken into account. In prostatic cancer patients, the BSI proved to be a good predictor of the amount of ^{186}Re -HEDP taken up by the skeleton (24), which explains the impact of the BSI as a parameter of the prediction of platelet toxicity (29). Apparently, the BSI is not a good indicator for the amount of ^{186}Re -HEDP taken up by the skeleton in breast cancer patients. This might be due to the fact that bone metastases of breast cancer are frequently of a lytic or mixed cell type—osteoblastic plus osteolytic lesions—and rarely purely osteoblastic like bone metastases originating from prostatic cancer (34). Despite the fact that the radiograph shows a lytic lesion, there may be enough osteoblastic activity at the periphery to result in increased uptake of $^{99\text{m}}\text{Tc}$ -HDP (35–37). Some of the lytic lesions, however, fail to induce an osteoblastic response (38). This might lead to lower BSI values in breast cancer patients and an underestimation of their metastatic load when in fact the toxicity is of the same order as in prostate cancer patients.

Patients with elevated alkaline phosphatase levels showed a transient decline over 4 wk. Bone alkaline phosphatase is a marker of the activity of osteoblasts (39). The transient decline could indicate a direct radiation effect of ^{186}Re -HEDP on proliferating osteoblasts or an anti-tumor effect. Tumor kill will lead to a decrease of osteoblastic activity and, consequently, to a decrease of serum alkaline phosphatase levels. In prostate cancer patients with more elevated alkaline phosphatase levels, ^{186}Re -HEDP induced a similar decrease (not of a greater magnitude) of even shorter duration. This suggests that the effect of ^{186}Re -HEDP on alkaline phosphatase levels is not due predominantly to a direct anti-osteoblastic activity.

One patient showed a transient increase of CEA levels, which might be also an indication of anti-tumor effect. After treatment with ^{186}Re -HEDP, a similar pattern was seen in patients with metastatic prostatic cancer, using prostate-specific antigen as a tumor marker (18,31). These findings are in agreement with data from investigators using ^{89}Sr for treatment of patients with metastatic prostate cancer (40,41). The reason that other patients with raised CEA levels did not show this change is probably due to the presence of soft-tissue metastasis.

CONCLUSION

The MTD of ^{186}Re -HEDP in patients with metastatic breast cancer is defined as 2405 MBq (65 mCi). When normalized to a standard body surface area of 1.73 m^2 , this dosage is in the

same range as for prostate cancer patients. Thrombocytopenia is the dose-limiting factor. Further studies to evaluate the efficacy of ^{186}Re -HEDP in patients with painful bone metastases due to breast cancer by placebo controlled studies are warranted.

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EDITORIAL

Dosage and Response in Radiopharmaceutical Therapy of Painful Osseous Metastases

The treatment of pain caused by bone metastases has been a most rewarding aspect of the practice of nuclear medicine for over four decades. The first radiopharmaceutical utilized for this pur-

pose was ^{32}P as sodium phosphate, given intravenously or, occasionally, orally (1).

Strontium-89 (as the chloride) was re-discovered in the mid-1970s and used in several North American medical centers beginning about 1980 (2,3). During the 1980s, other radiopharmaceuticals were identified that could reduce or relieve the pain of osteoblastic metastases. To be effective in reducing pain from tumor in bone, such radiopharmaceuticals must have a relatively high affinity for reactive

bone, a beta or electron emission of sufficient energy to reach the cells responsible for the pain and sufficiently long physical and biological half lives to deposit damaging or lethal radiation doses in these cells, whether they be the cancer itself or one of several cytokine-secreting cell types which may mediate the production of bone pain. Inherent in this form of internal radiotherapy is some radiation damage to adjacent functioning marrow cells. The relevant radiopharma-

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