

Short- and Long-Term Effects of ^{186}Re -1,1-Hydroxyethylidene Diphosphonate in the Treatment of Painful Bone Metastases

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This study evaluates the short- and long-term therapeutic efficacy of ^{186}Re -1,1-hydroxyethylidene diphosphonate (HEDP) in the palliation of painful bone metastases and the influence of variables before therapy in determining the characteristics of pain palliation. **Methods:** Sixty patients with painful bone metastases from different tumor types were treated with 1406 MBq ^{186}Re -HEDP. After treatment, the patients were followed up clinically at weekly intervals for the first month and monthly thereafter up to 1 y, until death or pain relapse. Pain response was graded as complete, partial, minimal, or absent using the Wisconsin test scoring system. Duration of pain relief, performance status, tumor markers, serum alkaline phosphatase levels, hematologic toxicity, and metastatic bone progression were also evaluated. **Results:** Overall, 80% of individuals experienced prompt relief of pain, with 31% complete, 34% partial, and 15% minimal responses. Transient World Health Organization grade 1–2 hematologic toxicity was apparent, with a decrease in the mean platelet (32%) and mean leukocyte (18%) counts at 3 and 4 wk, respectively. The degree of pain response did not correlate with any pretreatment variable. The duration of pain relief ranged from 3 wk to 12 mo and correlated positively with the degree of response ($P = 0.02$) and negatively with pretreatment scintigraphic scores and alkaline phosphatase levels ($P = 0.02$). **Conclusion:** ^{186}Re -HEDP is effective for fast palliation of painful bone metastases from various tumors. The effect tends to last longer if patients are treated early in the course of their disease.

Key Words: ^{186}Re -hydroxyethylidene diphosphonate; radionuclide therapy; bone metastases

J Nucl Med 2000; 41:647–654

Systemic therapy with bone-seeking β -emitting radionuclides has been reported effective for bone pain palliation since the 1940s but has achieved relatively wide clinical acceptance only lately, with most studies performed with ^{89}Sr -chloride (1–4). In the late 1980s ^{186}Re -1,1-hydroxyethylidene diphosphonate (HEDP) was recognized as a potential therapeutic agent, and it is now in phase I and II clinical trials (5–8). ^{186}Re has a sufficiently energetic β emission

(maximum, 1.07 MeV), a γ emission adequate for imaging (137 keV with a 9% abundance), and a short physical half-life of 90 h. Formation of complexes between ^{186}Re and HEDP permits selective localization in bone cancer lesions by bridging the hydroxyapatite crystals (5,9). These characteristics allow relatively high doses to the target with low systemic radiotoxicity, even with repeated treatments, and easy performance of dosimetric studies and scintigraphic imaging (9,10).

Despite favorable physical and biologic characteristics and proven efficacy in pain associated with bone metastases, clinical experience with ^{186}Re -HEDP is limited (6). In fact, available studies involve small groups of patients and lack long-term follow-up (6–8,11,12). In addition, evaluation of the efficacy of any analgesic therapy is complicated by the highly subjective character of pain, so that a simple, reproducible protocol of pain assessment is critical to avoid biased studies (13,14).

This study was an open clinical trial on 60 patients with different types of advanced cancer and was designed to evaluate the short- and long-term therapeutic efficacy of ^{186}Re -HEDP in the palliation of painful bone metastases and the influence of pretherapy variables in determining the characteristics of pain palliation.

MATERIALS AND METHODS

Patients

The study was approved by the local ethics committee, and all patients gave written informed consent before therapy. Sixty patients (10 women, 50 men; age range, 37–82 y; mean age, 67 y) with pain associated with bone metastases entered the study. The primary histologically proven malignancy was prostate carcinoma in 45 patients and breast carcinoma in 10 patients, whereas the remaining 5 patients presented with a variety of other types of cancer (1 leiomyosarcoma, 1 small-cell lung cancer, 1 liver cancer, 1 colon cancer, and 1 lung adenocarcinoma). Forty patients presented with intense and continuous pain even with narcotic medication, and the remaining 20 presented with occasional or continuous mild pain and were receiving nonsteroidal anti-inflammatory drugs.

Fifty-five patients received therapy with ^{186}Re -HEDP once, and 5 patients with prostate cancer were treated twice. A total of 65 therapeutic cycles were performed.

Received Jan. 19, 1999; revision accepted Jun. 21, 1999.

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Fifteen patients had previously been treated by chemotherapy; 10 patients, by local external beam radiotherapy; and 8 patients, by both modalities with no significant response. A minimum 6-mo interval from cessation of previous therapeutic regimens was required before the patients could enter the study. Hormonal therapy had not been altered in the previous 3 mo and was continued without changes during the study.

To enter the study, patients had to have pain arising from bone metastases and resistant to chronic analgesic intake, increased ^{99m}Tc -methylene diphosphate (MDP) uptake in multiple skeletal foci, adequate hematologic function (a baseline total platelet count $> 100 \times 10^9/\text{L}$ and a baseline total white blood cell count $> 4.0 \times 10^9/\text{L}$), no severe renal failure (serum creatinine < 0.15 mmol/L), and an estimated life expectancy > 3 mo. Patients were considered eligible for repeated ^{186}Re -HEDP administration if they had responded well to the first treatment.

Evaluation Before Therapy

Before ^{186}Re -HEDP treatment, all patients underwent standard physical and neurologic examinations; bone scintigraphy; evaluation of hematologic and renal function, serum alkaline phosphatase, and tumor markers (prostate-specific antigen [PSA], cancer antigen [Ca] 15.3, neuron-specific enolase [NSE], or carcinoembryonic antigen [CEA], as appropriate); and conventional radiography or CT. Symptoms were evaluated to determine whether the patients' pain was caused by metastatic bone disease rather than osteoarthritis, musculoskeletal diseases, or nerve root compression. The pain was scored using a modified Wisconsin test consisting of a 5-point pain-rating scale (0–4) recording pain severity, pain frequency, analgesic intake, and change in sleep patterns (Table 1) (14,15). Baseline scores were assigned on the basis of the median score during the 2 wk before treatment. Daily activity, mobility, and performance status were assessed according to the Karnofsky index. A radionuclide bone scan with ^{99m}Tc -MDP was performed on all patients within 2 wk before radionuclide therapy, and a scintigraphic score was assigned on the basis of the number or

TABLE 2
Scintigraphic Score According to Soloway Grades

Score	Scintigraphic findings
0	Normal findings or benign bone disease
1	Less than 6 bone metastases, each of which is less than 50% the size of a vertebral body (1 lesion approximately the size of a vertebral body is counted as 2 lesions)
2	Between 6 and 20 bone metastases
3	More than 20 bone metastases
4	Superscan, or more than 75% involvement of the ribs, vertebrae, and pelvic bones

extent of metastases (Table 2) according to the criteria of Soloway et al. (16).

Treatment Protocol

Patients were hospitalized in an isolated room in the nuclear medicine department for 48 h, according to local safety regulations. ^{186}Re -HEDP (Osteopal; Byk-Gulden, Milan, Italy), delivered in the form of a single-dose prelabeled kit, was injected as a bolus through a running intravenous saline drip. The mean administered activity was 1406 MBq with an SE of $\pm 1.3\%$.

A whole-body scan was obtained 3–6 h after injection to evaluate uptake of the radiotracer into the bone lesions. Five patients underwent a second ^{186}Re -HEDP administration at the same dosage from 3 to 12 mo after the first treatment.

Follow-Up

After the treatment, the patients were followed up clinically at weekly intervals for the first month and monthly thereafter. Each patient used a pain diary during the whole follow-up period, and the efficacy of the therapy was scored according to the combined evaluation of the written and oral story about the patient's pain. A routine laboratory investigation, including a full blood count and evaluation of tumor marker levels (PSA, Ca 15.3, NSE, or CEA, as appropriate), was also obtained weekly for 1 mo and monthly thereafter. In 32 patients, the bone scan was repeated 3–6 mo after therapy, thus producing a post-therapy bone scan index. The end point of follow-up was either death or pain relapse.

Data Analysis

Short- and long-term ^{186}Re -HEDP therapy outcomes, i.e., within the first month or extending over the first month, were evaluated separately.

Short-Term Outcome. Short-term outcome was assessed primarily in terms of pain score improvement. Because of score fluctuations during the week, median scores were calculated. Accordingly, on the basis of changes in the Wisconsin test score that persisted at least 3 wk after therapy, the patients were divided into 2 classes: responders with an improved Wisconsin test score and nonresponders with no variations in the Wisconsin test score. Responders were further divided into 3 subgroups according to the degree of pain relief: complete pain response (with complete disappearance of pain and discontinuation of all analgesics; Wisconsin test score = 0), partial pain response (with $>50\%$ improvement in pain and $\geq 50\%$ decrease in analgesic dosage), and minimal response (with less relief of pain and less decrease in analgesic dosage). Performance score improvement, evaluated on the basis of Karnofsky index variations, tumor markers, and changes in alkaline phosphatase serum levels, were considered secondary treatment

TABLE 1
Modified Wisconsin Test

Score	Day	Night	Daily analgesic intake
0	No pain	Normal sleep	None
1	Occasional pain	Occasionally awakened by pain	Occasional or ≤ 2 times; not narcotic*
2	Mild continuous pain	Usually awakened by pain	Usual (≥ 3 times); not narcotic*
3	Moderate continuous pain	Awakened by pain	Usual; not narcotic* + narcotic†
4	Severe continuous pain	Sleepless night because of pain	Resistant to pharmacologic treatment with strong narcotic‡

*Nonopiate analgesics (aspirin and other nonsteroidal anti-inflammatory drugs).

†Moderate narcotics including codeine at doses between 0.5 and 1 g.

‡Morphine or comparable opiates.

Final pain score was assigned considering highest value reached.

end points. Hematologic toxicity and side effects were reported in accordance with World Health Organization (WHO) guidelines (17).

A second type of analysis was retrospectively performed on the short-term data according to the decision rule formulated by the Utrecht workers (13). According to these criteria, a positive response was defined either as $\geq 25\%$ pain reduction during at least 2 consecutive weeks and medication index and daily activities at least constant or as $< 25\%$ pain reduction during at least 2 consecutive weeks and $> 25\%$ improvement in 1 of the 2 other factors (medication index and daily activities) during at least 2 consecutive weeks, while the remaining factor remained constant.

Long-Term Outcome. Long-term outcome was judged from the duration of pain relief. A worsening of the Wisconsin test score was taken as an index of the end of the analgesic effect of ^{186}Re -HEDP. Performance score, tumor markers, alkaline phosphatase modifications, and metastatic bone progression on bone scans were also evaluated during the follow-up period.

Statistical Analysis

The study was designed as an open-label trial, so patients functioned as their own controls. Statistical analysis was performed only on the data from patients treated once to avoid any confounding effect caused by disease progression or previous treatment carryover.

Differences between serum chemical, hematologic, and tumor marker values before and after treatment were analyzed by a *t* test with Bonferroni adjustment. Differences in Wisconsin test, Karnofsky index, and scintigraphic scores before and after therapy were evaluated by a Wilcoxon signed rank test. The correlation between variables before therapy (i.e., age, sex, height, weight, histologic type, bone scan score, pain score, performance status, tumor markers, alkaline phosphatase level, platelet and white blood cell counts, and creatinine level) and response to treatment were evaluated by the Spearman rank correlation. Differences in variables before therapy among all 4 patient groups (3 groups of responders and nonresponders) were assessed by 1-way ANOVA and by the χ^2 test, as appropriate. Differences in the degree of response in prostate cancer versus breast cancer and versus other cancer histologic types were evaluated by the χ^2 test. Pain relief duration was evaluated by the Kaplan-Meier method, including confidence intervals (CIs) at each month, and the differences between pain relief duration and all the variables before therapy were evaluated by the log-rank test. Differences between the prevalence of responses as evaluated with different criteria (i.e., Wisconsin test versus Utrecht score) were analyzed by examining the CIs of the differences of proportions. Values of $P < 0.05$ were considered significant, and values of P just slightly greater than the α value of 0.05 were considered marginally significant (18).

RESULTS

Short-Term Treatment Outcome

Overall prompt relief of pain occurred in 52 of 65 total treatments (80%) and in 49 of 60 first treatments. A complete response was observed in 20 instances (31%), a partial response in 22 (34%), and a minimal response in 10 (15%). Clinically evident pain relief occurred within 1 wk, with a median time to onset of 3 d. In 13 instances no response was apparent (20%). None of the 5 retreated patients became

completely free of pain after the second injection, and 3 of them had only a partial or minimal response. Three of these 5 retreated patients had previously experienced a complete response, and the other 2 a partial response, after the first treatment. Overall, the percentage of responders declined from 80% to 68% when the Utrecht criteria were used for data analysis (Fig. 1).

A good correlation was found between the $^{99\text{m}}\text{Tc}$ -MDP images before therapy and the ^{186}Re -HEDP images after therapy (Fig. 2). No patient showed any appreciable change in vital

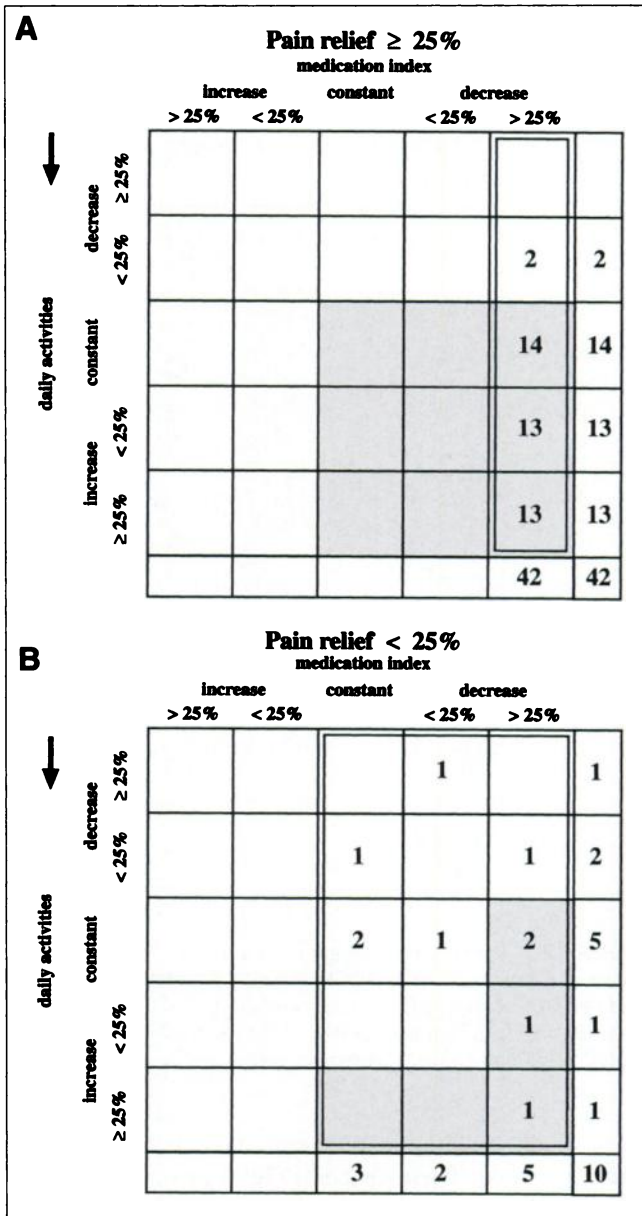


FIGURE 1. Representation of responses to 65 treatments using both sets of analysis criteria (Wisconsin and Utrecht). Shaded areas indicate responses fulfilling Utrecht criteria ($n = 44$, with 40/42 in A and 4/10 in B). Areas within double lines indicate responses fulfilling Wisconsin criteria ($n = 52$, with 42/42, representing complete and partial responses, in A and 10, representing minimal response, in B).

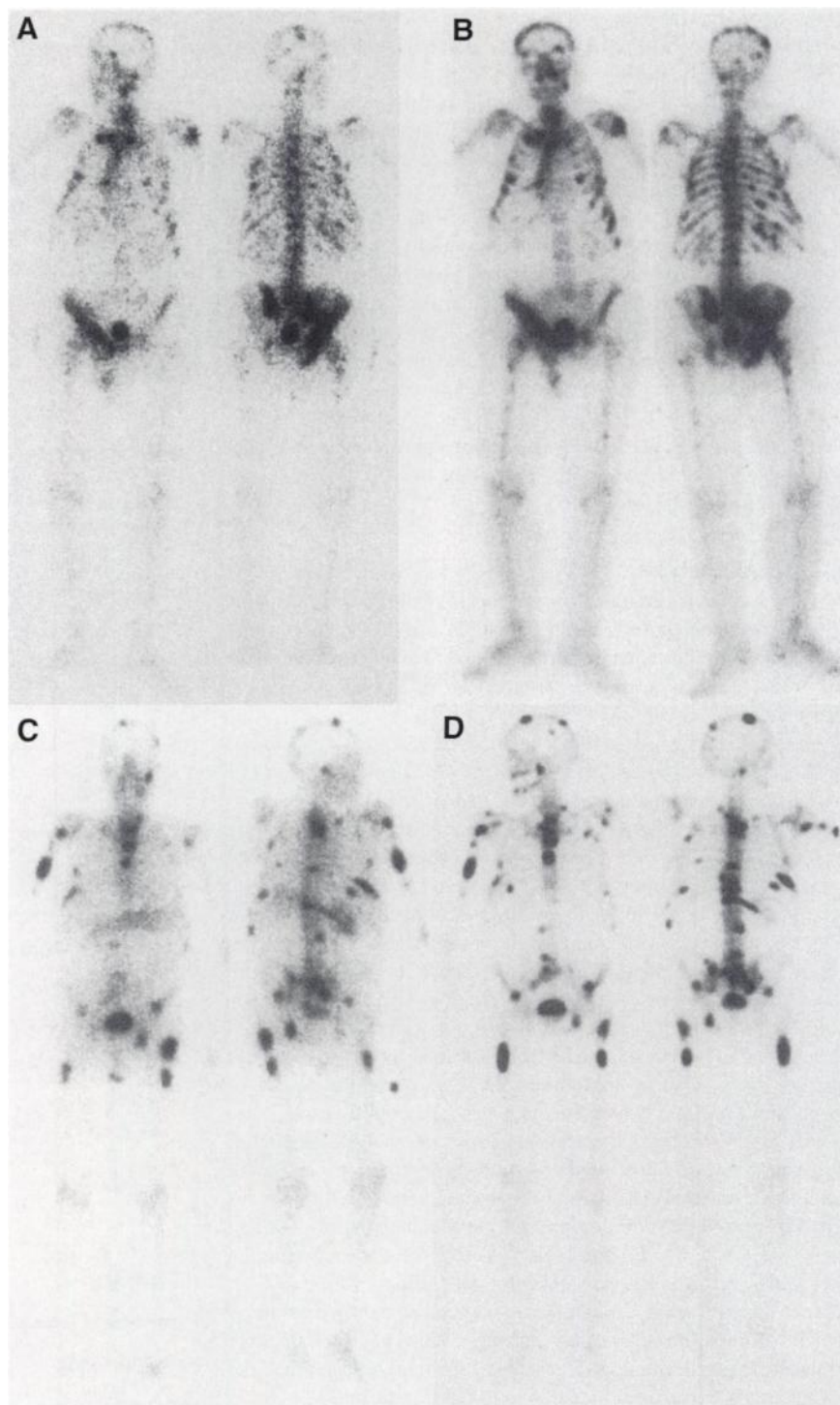


FIGURE 2. Scintigraphic images of 2 patients who received ^{186}Re -HEDP (A and C) and $^{99\text{m}}\text{Tc}$ -MDP (B and D). Good correlation is evident despite inferior quality of ^{186}Re -HEDP because of lower γ emission yield.

signs or any clinically evident acute side effects after ^{186}Re -HEDP injection. Twenty patients (36%) experienced a mild transient increase in pain, i.e., a flare response, within 48 h of ^{186}Re -HEDP injection that resolved within 24–48 h. No patients showed neurologic signs from nerve compression.

Significant short-term effects of ^{186}Re -HEDP treatment are shown in Figure 3. Starting the third week after therapy, a significant improvement versus pretherapy values was

observed for the Wisconsin test ($P < 0.001$), for the Karnofsky index ($P < 0.001$), and for serum alkaline phosphatase levels ($P = 0.01$). A WHO grade 1–2 hematologic toxicity was apparent, with a decrease in the mean platelet (32%) and mean leukocyte (18%) counts at 3 and 4 wk, respectively. The mean (\pm SD) baseline platelet count was $261 \times 10^9/\text{L} \pm 98 \times 10^9/\text{L}$ and decreased to $178 \times 10^9/\text{L} \pm 79 \times 10^9/\text{L}$ at 3 wk ($P < 0.05$). The mean (\pm SD)

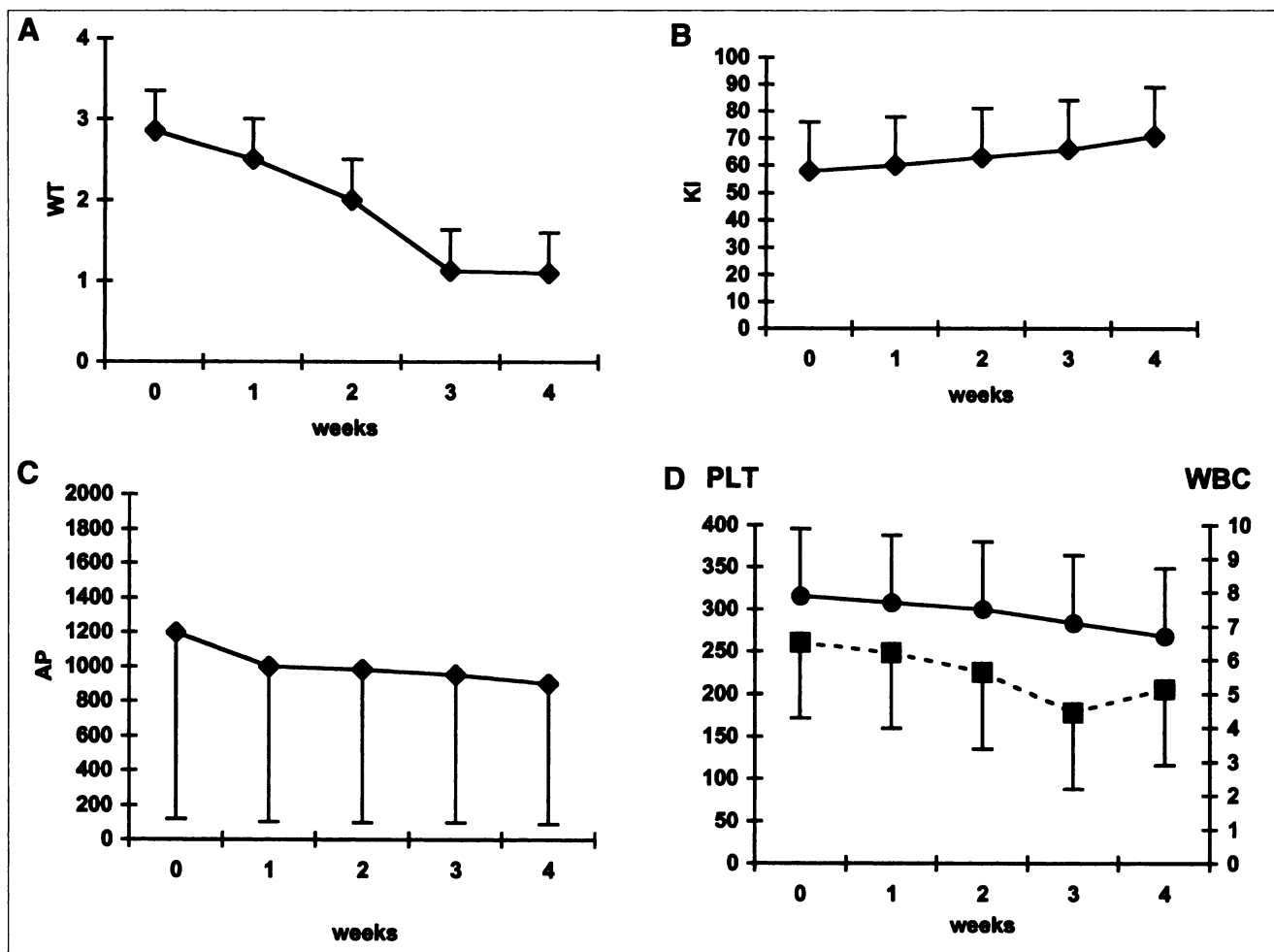


FIGURE 3. Short-term ^{186}Re -HEDP treatment effects, shown as mean \pm SD, on Wisconsin test pain score (WT) (A), Karnofsky index (KI) (B), alkaline phosphatase levels (AP) (C), and white blood cell (WBC) $\bullet = 10^9/\text{L}$ and platelet (PLT) $\blacksquare = 10^9/\text{L}$ counts (D). Normal alkaline phosphatase values were 99–279 U/L.

baseline total white blood cell was $7.9 \times 10^9/\text{L} \pm 2.4 \times 10^9/\text{L}$ and decreased to $6.7 \times 10^9/\text{L} \pm 2.3 \times 10^9/\text{L}$ at 4 wk ($P < 0.05$). In all patients, platelet and white blood cell counts returned to baseline levels within 8 wk after ^{186}Re -HEDP administration.

Relatively wide variations in tumor marker levels (i.e., PSA, Ca 15.3, NSE, or CEA, as appropriate) were observed at different intervals without reaching statistical significance ($P = 0.3$ at 3 wk). Within the first month, tumor markers (PSA and Ca 15.3) decreased dramatically in more than 45% of cases, were unmodified in about 15% of cases, and progressively increased in the remaining cases. Renal function, liver function, and serum calcium and phosphorus levels showed no significant variations before and after therapy. Response rates in different tumor histologic types, together with 95% CIs, are reported in Table 3. Global pain relief occurred in 78% of prostate cancer, in 90% of breast cancer, and in 80% of other tumors grouped together. Differences in prevalence of pain relief in the 3 groups did not reach statistical significance ($P = 0.77$). In fact, no

pretreatment variable correlated with the degree of pain response to therapy.

Long-Term Treatment Outcome

The duration of pain relief ranged from 3 wk to 12 mo (mean duration, approximately 72 d; median duration, 60 d) (Fig. 4). Significant log-rank test correlations were observed between duration of pain relief and pretherapy variables: a

TABLE 3
Response Rates in Different Tumor Histotypes

Response	Prostate	Breast	Others
Global	78 (64–88)	90 (55–99)	80 (28–99)
Complete	30 (17–44)	20 (2–55)	60 (14–19)
Partial	32 (19–46)	50 (18–81)	20 (0.5–7)
Minimal	16 (7–29)	20 (2–55)	0
None	22 (11–36)	10 (0.2–44)	20 (0.5–7)

Values are percentages; 95% CIs are in parentheses.

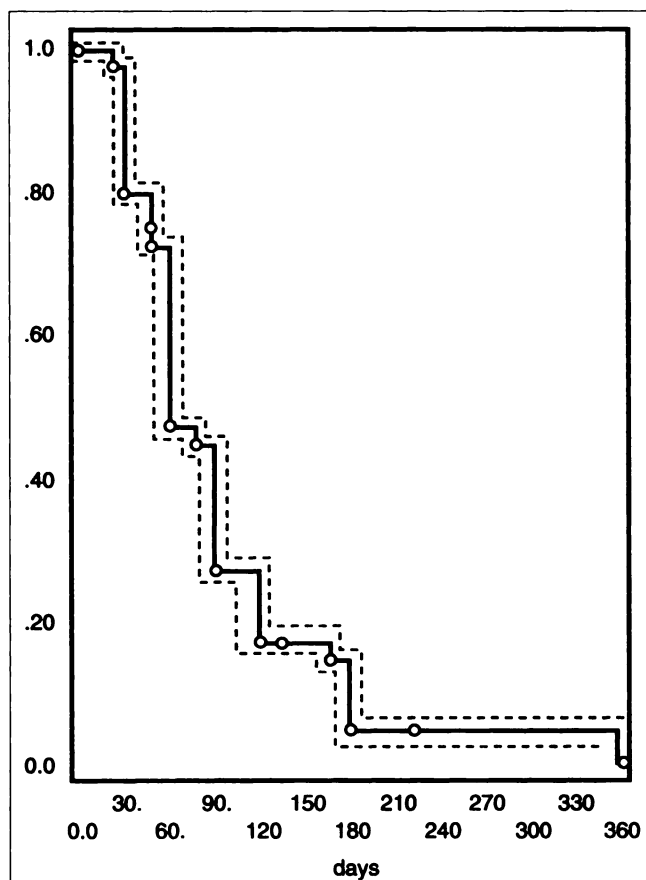


FIGURE 4. Kaplan-Meier curve for duration of pain relief (solid line), with 95% CI (broken lines).

positive correlation between duration and degree of response ($P = 0.02$) and a negative correlation between duration and both scintigraphic score ($P = 0.02$) and alkaline phosphatase level ($P = 0.02$). A marginally significant positive correlation between duration and Karnofsky index was also observed ($P = 0.06$).

The performance score improved in 32 patients, was not modified in 20 patients, and worsened in 8 patients. The scintigraphic score was not substantially modified in 28 patients (22 of whom had no new metastatic sites) and worsened in 4 patients. Alkaline phosphatase levels remained significantly decreased for 2 mo and increased progressively afterward. Tumor marker serum levels showed wide variations throughout follow-up, with an ambiguous pattern. Only 10 patients showed a marked decrease in PSA levels persisting more than 3 mo.

On a subsequent analysis performed only on the first treatments, patients with pain relief persisting beyond the median value, i.e., 2 months, were referred to as longer-time responders, whereas the others were referred to as shorter-time responders. Of 49 responders, 26 were shorter-time and 23 were longer-time when second treatments were excluded from the analysis. Significant differences between shorter- and longer-time responders were shown by log-rank test findings in relation to pretreatment scintigraphic scores ($P =$

0.02) and alkaline phosphatase levels ($P = 0.006$). Correlation coefficients between the degree of response and the Wisconsin test or Karnofsky index were 0.34 and -0.36 , respectively, for shorter-time responders and -0.18 and 0.29, respectively, for longer-time responders, with $0.08 < P < 0.05$.

DISCUSSION

Several radiopharmaceuticals have been proposed for therapy of painful bone metastases, including ^{32}P , ^{89}Sr , and ^{153}Sm (19). Although quite effective, these radiopharmaceuticals have limitations such as severe hematologic toxicity for ^{32}P and ^{153}Sm and physical characteristics unsuitable for imaging and dosimetry for ^{32}P and ^{89}Sr (3,20,21–26).

^{186}Re -HEDP provides an alternative promising treatment for pain associated with bone metastases because of its suitable physical and pharmacokinetic characteristics (27). Surprisingly enough, only limited data are available on the clinical efficacy of ^{186}Re -HEDP and most of them are not readily comparable. Several phase I clinical trials have focused on ^{186}Re -HEDP pharmacokinetics, dosimetry, and toxicity (7–10). In fact, evaluation of clinical effects was only a secondary end point in 2 studies primarily aimed at toxicity evaluation (6,12). Early studies by Maxon et al. (6,11) with a standard dose of 1110–1295 MBq ^{186}Re -HEDP revealed a pain response in 77%–80% of the patients, with a mean duration of 7 wk. In these studies the primary end point was considered a decline in pain intensity of at least 25% from baseline; the other pain components, such as analgesic intake, sleep patterns, and pain persistence, were considered only secondary end points for response evaluation. Recently, Quirijnen et al. (13) suggested the importance of a more complete pain component evaluation and used a multidimensional pain evaluation model to objectify the effects of escalating doses of ^{186}Re -HEDP, reporting an overall response of 54%. Evaluation of the response to radionuclide therapy and the reproducibility of results evidently is critically affected by different approaches to pain assessment and different study designs.

This study was designed to investigate the short- and long-term results of using a standard dose of ^{186}Re -HEDP on a relatively large series of patients. An overall high response rate was observed (80%, with a 95% CI of 68%–88%), characterized by a very short onset of pain relief (<7 d). About one third of patients became completely free of pain without drug intake, and quality of life (considering both complete and partial pain response and performance status) dramatically improved in more than 65%. These results compare well with those of Maxon et al. (6), who reported a 77% response (95% CI, 61%–88%) but differ from those of Quirijnen et al. (13) (54%, with a 95% CI of 39%–70%). The discrepancy is, however, only an apparent one and is caused by bias in study design. In fact, using the decisional rule of the Utrecht workers, our response rate dropped to 68%, which is not statistically different from the 54% reported by the Utrecht group (a 14% difference between proportions,

with a 95% CI of -6% to 33%). Most of the differences observed between the 2 evaluation methods appear related to the group of patients whom we named as minimal responders. In fact, only 4/10 of these were considered responders by the Utrecht criteria, whereas all complete responders and 30/32 partial responders fulfilled the Utrecht criteria (Fig. 1). The use of either set of criteria leads to 2 different situations. In fact, with the Utrecht criteria, only 2 groups of patients (i.e., responders and nonresponders) can be selected without grading pain response. Use of the Wisconsin test evaluation criteria leads to a higher relative probability of spotting a positive response to treatment (ratio of proportion, 1.48, with a 95% CI of 1.07–2.04).

^{186}Re -HEDP proved safe and effective for palliation of pain from symptomatic bone metastases of various tumors without causing significant differences in response rates. Only preliminary data have been reported on the toxicity and efficacy of ^{186}Re -HEDP in breast cancer (28,29). To our knowledge, no experience has been published on the effects of ^{186}Re -HEDP in other tumors. The present data show that tumors other than prostate carcinoma have very good global response rates (90% for breast carcinoma and 80% for other histologic types as a group). Lack of correlation between response rate and histologic type in the 5 patients with different histologic types may likely be caused by weakening of the test because of the small number of observations. The mean duration of pain relief in this series was 112 d for breast carcinoma—a value that is not significantly different from the 92 d observed for prostate carcinoma. For other histologic types, pain relief lasted from 50–90 d. Hematologic toxicity was similar for all histologic types.

A second ^{186}Re -HEDP treatment was performed on 5 patients: in all 5, pain relief was less evident than after the first treatment. This issue could be related to the marked progression of disease evident in these patients.

No pretreatment variable correlated significantly with short-term treatment outcome. ^{186}Re -HEDP therapy was effective, with a comparable response both in patients with advanced bone scan involvement and poor performance status and in patients with a less compromised general condition.

Long-term outcomes of ^{186}Re -HEDP treatment have not been reported. In fact, all reported data are censored after 8 wk of follow-up, and data on long-term follow-up (i.e., more than 2 mo) are completely lacking. This lack probably stems from poor patient compliance. In this study, the end points of follow-up were either death (3 patients, 2 of whom were pain free at the end point) or evident disease progression with cessation of ^{186}Re -HEDP effects (57 patients, 2 of whom reached the end point at 12 mo). The reported follow-up period ranged from 60 to 360 d. Prolonged pain relief (>60 d) was observed in more than 45% of patients, and 2 patients (1 with prostate cancer and 1 with breast cancer) remained completely free of pain for almost 1 y.

Unlike the degree of short-term response, which did not appear to correlate with any pretreatment variable, the

duration of response showed an interesting negative correlation with scintigraphic bone involvement and alkaline phosphatase levels. In addition, the duration of pain relief correlated positively with the degree of response. No correlation was observed for tumor markers, which showed a completely independent pattern. These findings suggest that although short-term response is not influenced by baseline patient conditions, the duration of pain relief may be longer in patients with a less compromised bone status.

All patients also showed a moderate decline in alkaline phosphatase levels. The decline was statistically significant during the first 3 wk and persisted for 2 mo. Ten prostate cancer patients showed a marked decrease in PSA levels persisting over 3 months, and in 22 of 32 patients new sites of metastasis were not observed on the bone scan obtained 3–6 mo after therapy. These findings may be consistent with a possible weak tumoricidal effect and agree with preliminary data from an animal model exploring ^{186}Re -HEDP effects on tumor progression (30). In addition, the more prolonged and intense pain relief evidenced by our data on patients with an earlier phase of bone disease also suggests a possible therapeutic effect on micrometastases and on disease progression.

Hematologic toxicity from ^{186}Re -HEDP did not differ from previous reports (7,8). A transient decrease in platelets occurred by 3 wk after injection, with complete recovery by 8 wk, whereas leukocytes manifested a late but insignificant decrease.

CONCLUSION

Three conclusions can be drawn. First, ^{186}Re -HEDP treatment offers safe, effective, and fast palliation of painful bone metastases from various tumors. Second, ^{186}Re -HEDP treatment is indicated for both advanced and relatively early stages of disease, even when the predicted duration of the effect varies. Patients with severe pain, a poor general condition, and diffuse involvement seen on bone scans are likely to experience rapid and effective pain relief leading to a great, although short (<60 d), improvement in quality of life. Patients with early stages of metastatic bone involvement and moderate pain but in whom performance is not yet compromised are likely to experience longer and complete pain relief. Third, ^{186}Re -HEDP treatment may affect the progression of metastatic bone disease, but this possibility requires confirmation through carefully designed prospective studies.

ACKNOWLEDGMENT

This study was supported in part by Ministry of Health grant 96/01/R/40.

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