Palliation and Survival After Repeated ^{188}Re-HEDP Therapy of Hormone-Refractory Bone Metastases of Prostate Cancer: A Retrospective Analysis

Hans-Jürgen Biersack[1], Holger Palmedo[1], Andrej Andris[1], Stefan Rogenhofer[2], Furn F. Knapp[3], Stefan Guhlke[1], Samer Ezziddin[1], Jan Bucerius[1], and Dirk von Mallek[1]

[1]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [2]Department of Urology, University Hospital Bonn, Bonn, Germany; and [3]Nuclear Medicine Program, Oak Ridge National Laboratory, Oak Ridge, Tennessee

This retrospective study compared the effects of single and multiple administrations of ^{186}Re-hydroxyethylidenediphosphonate (^{186}Re-HEDP) on palliation and survival of prostate cancer patients presenting with more than 5 skeletal metastases. **Methods:** A total of 60 patients were divided into 3 groups. Group A (n = 19) consisted of patients who had received a single injection; group B (n = 19), patients who had 2 injections; and group C (n = 22), patients who had 3 or more successive injections. The ^{188}Re-HEDP was prepared using non–carrier-added ^{188}Re obtained from an in-house ^{188}W/^{188}Re generator after dilution with carrier perrhenate. Patients' data available from the referring physicians—including prostate-specific antigen levels—were entered into a Windows-based matrix and analyzed using a statistical program. The Gleason scores were similar for all 3 groups. **Results:** Mean survival from the start of treatment was 4.50 ± 0.81 mo (95% confidence interval [CI], 2.92–6.08) for group A, 9.98 ± 2.21 mo (95% CI, 5.65–14.31) for group B, and 15.66 ± 3.23 (95% CI, 9.33–22.0) for group C. Although the 3 groups did not differ in Gleason score, the number of lost life-years was significantly lower in group C than in groups A and B. Pain palliation was achieved in 89.5% of group A, 94.7% of group B, and 90.9% of group C. **Conclusion:** Post-treatment overall survival could be improved from 4.50 to 15.66 mo by multiple-injection bone-targeted therapy with ^{188}Re-HEDP, when compared with a single injection. Significant pain palliation was common and independent of administration frequency.

Key Words: ^{188}Re-HEDP; bone metastases; palliation; prostate cancer; survival

J Nucl Med 2011; 52:1721–1726
DOI: 10.2967/jnumed.111.093674

Bone metastases are frequent and encountered by all physicians treating oncologic patients (*1*). About 50% of prostate cancer patients will develop bone metastases, which are predominantly osteoblastic. The osteolytic type has the tendency to develop fractures resulting in serious morbidity. Chronic pain syndrome is the most important complication of bone metastases and has a negative impact on quality of life. Many of these patients are candidates for radionuclide therapy, since as many as 50% of patients are reported to receive only inadequate pain treatment by alternative methods (*2*).

Radionuclide therapy of bone metastases was first used decades ago by administration of ^{32}P (*3*), which is incorporated in the DNA of rapidly proliferating bone marrow cells as well as in the trabecular and cortical bone structures. A relatively low 1:2 ratio of normal bone to metastatic tissue has been estimated (*4*). More recently, a variety of β-emitting radioisotopes has been investigated for therapy of bone metastases. The maximal β-energy of these radioisotopes is in the range of 0.8–2.3 MeV, with an average β-energy between 0.27 and 0.8 MeV (Table 1). ^{89}Sr-chloride and ionic ^{90}Y are both calcium analogs that are sequestered as cations by bone in relation to the intensity of osseous metabolism (*5–9*). ^{89}Sr is excreted renally to 70%–90% and is eliminated from the vascular compartment within the first few hours (*10*). Except for bone uptake and excretion via the urinary system, there is no accumulation in any organ system. Accumulation of ^{89}Sr in metastatic lesions is 5–20 times higher than accumulation in normal bone tissue. In one study, 90 d after administration, 20%–88% of the injected ^{89}Sr activity was found around metastatic bone lesions (*8*). The effective half-life was calculated to be over 50 d, and thus ^{89}Sr delivers low-dose-rate radiation.

A different radiopharmaceutical option is to chemically attach radionuclides to phosphonate carrier molecules that are known to have a high osteoaffinity. Among these radiopharmaceuticals are, for example, ^{153}Sm-ethylenediaminetetramethylenephosphonate (EDTMP) and ^{186}Re-hydroxyethylidenediphosphonate (HEDP) (*11,12*). Like the above-mentioned radionuclides, these agents are also excreted mainly by the kidneys, and they disappear rapidly from the vascular compartment (*13,14*). Twelve hours after administration, 50% of the administered activity of ^{186}Re-HEDP and ^{153}Sm-EDTMP is eliminated renally. Uptake

Received May 23, 2011; revision accepted Aug. 17, 2011.
For correspondence or reprints contact: Hans-Jürgen Biersack, Department of Nuclear Medicine, University of Bonn, Sigmund-Freud-Strasse 25, D-53127 Bonn, Germany.
E-mail: hans-juergen.biersack@ukb.uni-bonn.de
Published online Oct. 5, 2011.

TABLE 1
Comparison of Bone-Seeking Radiopharmaceuticals

Radiopharmaceutical	Standard dose	Half-life (d)	Maximum β-energy (MeV)	γ-energy (keV)	Maximum penetration in tissue (mm)
^{89}Sr-chloride	148 MBq (4 mCi)	50.5	1.46	910 (0.01%)	6 (average, 2.4)
^{153}Sm-lexidronam	37 MBq/kg (1 mCi/kg)	1.9	0.81	103 (28%)	2.5 (average, 0.6)
^{186}Re-HEDP	1,295 MBq (35 mCi)	3.8	1.07	137 (9%)	4.5 (average, 1.1)
^{188}Re-HEDP	1.1–4.4 GBq (30–118 mCi)	0.7	2.12	155 (15%)	10.4 (average, 3.1)

in the skeleton is between 20% and 30% of the injected dose for ^{186}Re-HEDP and between 30% and 50% for ^{153}Sm-EDTMP. Accumulation in metastatic lesions is between 3 and 20 times as high as in normal bone, and the effective half-lives of ^{188}Re-HEDP and ^{153}Sm-EDTMP are between 2 and 3 d. ^{188}Re-HEDP has been used for pain palliation in patients with prostate cancer and bone metastases since the early 1990s (*15,16*). Retrospective results with ^{186}Re-HEDP were published by Schoeneich et al. in 1997 (*17*).

^{188}Re (half-life, 16.9 h) is a more attractive candidate than ^{186}Re since it can be obtained in no-carrier-added form from a ^{188}W/^{188}Re generator and has a long useful shelf-life of several months. In 2003, Palmedo et al. published results obtained from a randomized phase II trial with ^{188}Re-HEDP in patients with hormone-refractory prostate carcinoma (*18*) designed to compare the efficacy of multiple successive injections with that of a single administration of this agent. The effectiveness of ^{188}Re-HEDP for pain palliation was better in the repeated-treatment group, with a response rate and time of response of 92% and 5.66 mo, respectively. In addition, 39% of patients with repeated treatments exhibited a decrease in prostate-specific antigen levels of more than 50% for at least 8 wk. These results were interpreted to indicate that repeated ^{188}Re-HEDP therapy is beneficial in patients with prostate cancer and bone metastases (*18*).

The goal of the present study was to perform a retrospective follow-up analysis of the palliative and survival effects of single versus multiple successive administrations of ^{188}Re-HEDP to prostate cancer patients presenting with multiple skeletal metastases.

MATERIALS AND METHODS

Patients

This retrospective study included 60 hormone-refractory patients. Group A comprised patients who had received only 1 therapy (n = 19); group B, patients who had received 2 therapies (n = 19); and group C, patients who had received 3 or more therapies (n = 22). All patients had bone pain and presented with more than 5 lesions documented by a bone scan. Because ^{188}Re is not commercially available as an approved radiopharmaceutical, informed consent was required and the agent was ordered and compounded by a radiopharmacist (in-house production). We provided the referring physicians with a questionnaire asking if the patient was alive or deceased, and if deceased, whether the death was attributed to prostate carcinoma or other causes. Additionally, the questionnaire asked for the survival time after the last ^{188}Re-HEDP therapy (and if the pain had decreased), the prostate-specific antigen (PSA) level, and the referring physician's objective impression about pain palliation.

Radiopharmaceutical Production

^{188}Re-HEDP was prepared according to the method of Palmedo et al. (*15*), Knapp et al. (*19*), and Guhlke et al. (*20*). Especially important in the formulation of ^{188}Re-HEDP is the use of carrier perrhenate, since the ^{188}Re is obtained essentially carrier-free from a generator system by β-decay of ^{188}W.

In contrast to ^{188}Re is ^{186}Re, which is produced in nuclear reactors through neutron capture of stable ^{185}Re and thus by virtue of its mode of production is carrier-added. The presence of macroscopic amounts of stable rhenium in rhenium-HEDP preparations is decisive with respect to the form of the phosphonate chemical species (*15*). In carrier-added preparations, these species consist of rhenium–rhenium bonds that cannot be formed using carrier-free ^{188}Re. As a consequence, the biodistribution and intravenous stability of carrier-added and no-carrier-added ^{188}Re-HEDP show remarkable differences, and only the carrier-added composition accumulates to a high percentage in bone (*20*).

^{188}Re was obtained from an 18.5-GBq (500-mCi) alumina-based ^{188}W/^{188}Re generator fabricated at the Oak Ridge National Laboratory, using ^{188}W produced in the High Flux Isotope Reactor. Depending on the specific volume of activity required, the generator eluates (typically 20 mL of physiologic saline) were concentrated to a volume of 1.5 mL of physiologic saline using a convenient and useful online concentration method that has been reported elsewhere (*19,20*). For preparation of the ^{188}Re-HEDP, 15 μL of a stable ammonium-perrhenate solution (26 mg of NH_4ReO_4/mL) in physiologic saline were added to the concentrated ^{188}Re solution. This carrier-added ^{188}Re-perrhenate solution was used for the labeling reaction by being added through a 0.22-μm sterile filter to a kit vial containing 8.3 mg of HEDP, 3.0 mg of gentisic acid, and 3.9 mg of stannous chloride dehydrate. The vials were then heated for 20 min at 90°–100°C and cooled to room temperature. For neutralization, 1.5 mL of a sterile solution of 39 mg of sodium acetate trihydrate were added, yielding a final pH of 4.5–5.5. Quality control of carrier-added ^{188}Re-HEDP was performed using instant thin-layer chromatography silica gel strips (*15*).

According to a dose escalation study published earlier by Palmedo et al. in 2000 (*15*), a dose of 2,960–3,330 MBq (80–90 mCi) of ^{188}Re-HEDP was administered to each patient. The interval between successive administrations of ^{188}Re-HEDP was approximately 8 wk, and up to a maximum of 8 successive therapies per patient were applied.

Data Analysis

The data from patient records and the questionnaire were entered into a Windows Excel (Microsoft) data matrix and were

then transferred and evaluated using the SPSS statistics program (version 16.0; IBM). The parameters that were evaluated included the absolute (*n*) and relative (%) frequency. In addition, the mean, SEM, median, minimum, and maximum values were calculated. Because a goal of this study was to compare the 3 therapy groups, nominal and ordinal figures were used to calculate nonparametric tests, using the χ^2 test and the Kruskal–Wallis test. Survival was analyzed according to the Kaplan–Meier procedure and log-rank test, with the significance set to a value of P less than 0.05.

RESULTS

The 3 patient groups were similar in mean and median age (Table 2). Table 2 summarizes the Gleason score data for the 3 groups. At the time of diagnosis, the Gleason scores were comparable, and by evaluation of the prognostic factor according to Helpap, no differences were found. Table 2 also shows the mean age of the patients at the time of the first ^{188}Re-HEDP therapy. The time span between diagnosis of prostate cancer and first therapy ranged from 5.7 y (group C) to 6 y (group B) to 7.5 y (group A) (Table 3), and this difference was not significant.

Table 3 summarizes the pain palliation results; no significant differences between the 3 groups were observed.

In contrast to Palmedo et al. (*18*), we did not observe any significant differences with respect to the course of PSA (Table 3). Table 4 presents the data on age at death and number of lost life-years, which was significantly lower in group C than in Groups A and B. Table 5 shows the survival results after diagnosis of prostate cancer. Mean survival after the initial therapy improved from 4.5 mo in group A to 9.98 mo in group B and 15.7 mo in group C. The results of survival after the initial rhenium therapy are also presented in Figure 1. As has already been described by Palmedo et al. (*15*), only reversible grade 2 thrombopenia and reversible grade 1 leukopenia were observed.

DISCUSSION

In a comprehensive review of systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain, Paes and Serafini (*21*) have summarized the available literature data on various bone-seeking radiopharmaceuticals labeled with different therapeutic isotopes. For ^{89}Sr-chloride, a response usually occurs within 6 wk, with a mean duration of 6 mo (*22*). A painful flair response is often seen in approximately 10%–20% of patients treated with ^{89}Sr, and these patients experience better pain relief (*23*). A report by Finlay et al. (*25*) showed that 8%–77% of patient had a complete response to ^{89}Sr. In general, 44% of patients had some degree of response to ^{89}Sr treatment.

^{153}Sm-lexidronam (^{153}Sm-EDTMP [Quadramet]; EUSA Pharma) has increasingly been used during the last decade. In general, ^{153}Sm provides effective palliation in 83.8% of patients with painful bone metastases (*25*).

^{186}Re-HEDP, although initially developed at the University of Cincinnati, is not available in the United States for clinical use. This pharmaceutical was also withdrawn from the European market in 2010. Maxon et al. (*27*) concluded that pain improved significantly in 77% of patients after the initial injection. The PLACORHEN (Placebo-Controlled Rhenium) study (*28*) included 111 patients initially, and 79 were evaluated (43 treated, 36 placebo). The total response of patients treated with ^{186}Re-HEDP varied from 0% to 96% (mean, 27%), and in the placebo group, the total

TABLE 2
Patient Data

Parameter	Group A (1 therapy) (n = 19)	Group B (2 therapies) (n = 19)	Group C (≥3 therapies) (n = 22)
Age at diagnosis (y)			
Mean ± SEM	62.3 ± 1.5	61.9 ± 1.8	64.0 ± 1.4
Median	64.1	61.7	62.6
Range	48.1–69.9	46.2–73.1	54.8–78.5
P	0.744		
Age at start of treatment (y)			
Mean ± SEM	69.7 ± 1.8	67.9 ± 1.9	69.6 ± 1.5
Median	70.8	67.7	67.2
Range	49.1–83.9	50.4–86.6	58.3–81.2
P	0.556		
Gleason score			
3	1 (5.9%)	—	—
5	3 (17.6%)	1 (5.2%)	—
6	—	2 (10.5%)	2 (9.5%)
7	4 (23.5%)	6 (31.6%)	8 (38.1%)
8	5 (29.4%)	6 (31.6%)	9 (42.9%)
9	4 (23.5%)	4 (21.1%)	2 (9.5%)
Prognostic factor according to Helpap			
Good (≤7)	8 (47.1%)	9 (47.4%)	10 (47.6%)
Bad (8–10)	9 (52.9%)	10 (52.6%)	11 (52.4%)
P	0.999		

TABLE 3
Results of ^{188}Re-HEDP Therapy

Parameter	Group A (1 therapy) (n = 19)	Group B (2 therapies) (n = 19)	Group C (≥3 therapies) (n = 22)
Time between diagnosis of prostate cancer and initial ^{188}Re-HEDP therapy			
Mean ± SEM	7.5 ± 1.4	6.0 ± 1.0	5.7 ± 0.7
Median	6.4	6.0	5.2
Range	0.9–23.5	0.5–13.5	0.1–12.6
P	0.729		
Pain palliation			
Pronounced	6 (31.6%)	6 (31.6%)	5 (22.7%)
Mild	11 (57.9%)	12 (63.2%)	15 (68.2%)
Not efficient	2 (10.5%)	1 (5.2%)	2 (9.1%)
P	0.926		
Course of PSA			
Decreased	5 (26.3%)	3 (15.8%)	6 (27.3%)
Unchanged	1 (5.3%)	3 (15.8%)	—
Increased	13 (68.4%)	13 (68.4%)	16 (72.7%)
P	0.329		

response varied from 0% to 80% (mean, 13%). The number of patients requesting radiotherapy was higher in the placebo group (67%) than in the ^{186}Re group (44%). Other studies (*28,29*) found response rates of 80% and 92%, respectively. The duration of pain relief ranged from 3 wk to 12 mo.

In a study by Lam et al. (*31*), ^{188}Re-HEDP was combined with gemcitabine in hormone-refractory prostate cancer patients with bone metastases, in a phase 1 safety and toxicity study. It was concluded that capecitabine may safely be used in combination with ^{188}Re-HEDP, in a dose of 2,500 mg/m^2 per day and 37 mg/kg, respectively. The same investigators combined zoledronic acid and ^{153}Sm-EDTMP in hormone-refractory prostate cancer patients and concluded that zoledronic acid treatment does not influence the uptake of the respective radiopharmaceutical (*32*). These and other studies reflect possible benefits of such combined therapeutic strategies.

The potential of long-term pain relief and possible therapeutic effects from these bone-seeking therapeutic radiopharmaceuticals is important. A group led by Sartor (*23*) reported the efficacy of repeated doses of ^{153}Sm-EDTMP patients with metastatic bone pain. The pain scores and side effects were analyzed in 55 patients receiving 2 or more doses. Decreases in pain scores were observed in 70%, 63%, and 80% of patients at 4 wk after the first, second, and third administrations, respectively. Only minor decreases in platelet and white blood cell counts were seen, with a nadir at week 4 and recovery in 90% of patients by week 8. These data prove that repeated treatment with ^{153}Sm-EDTMP is both safe and effective in patients with metastatic bone disease (*33*).

Maxon et al. (*27*) performed an open-label trial using a single intravenous administration of approximately 1,258 MB1 (34 mCi) of ^{186}Re-HEDP. After the second treatment, 50% of patients showed an improvement in pain. After up to 5 treatments, a complete resolution of pain was found. Clinically unimportant decreases in white blood cell and platelet counts were observed, but no other toxicity was apparent.

Palmedo et al. (*18*) found that compared with single-injection therapy, repeated bone-targeted therapy with ^{188}Re-HEDP administered to patients with advanced progressive hormone-refractory prostate carcinoma enhanced pain palliation and improved progression-free and overall

TABLE 4
Age at Death and Lost Years of Life

Parameter	Group A (1 therapy) (n = 15)	Group B (2 therapies) (n = 15)	Group C (≥3 therapies) (n = 18)	*P*
Age at death				0.184
Mean ± SEM	69.0 ± 2.0	67.3 ± 2.2	72.0 ± 1.7	
Median	71.1	65.7	71.2	
Range	49.3–80	50.7–87.1	59.4–81.8	
Lost years of life				0.183
Mean ± SEM	15.1 ± 1.4	16.2 ± 1.4	12.9 ± 1.0	
Median	12.9	16.8	12.8	
Range	8.7–30.0	5.9–28.8	5.7–21.4	

TABLE 5
Survival Data

Parameter	Group A (1 therapy)	Group B (2 therapies)	Group C (≥3 therapies)	*P*
Mean survival (y)	9.35 ± 1.74 (5.94–12.75)	7.60 ± 1.12 (5.40–9.80)	7.54 ± 0.82 (5.93–9.16)	0.696 (LR = 0.72)
Median survival (y)	9.01 ± 1.73 (5.61–12.40)	8.99 ± 1.79 (5.48–12.51)	6.59 ± 1.51 (3.63–9.54)	
Survival after 1 therapy (mo)				
Mean	4.50 ± 0.81 (2.92–6.08)	9.98 ± 2.21 (5.65–14.31)	15.66 ± 3.23 (9.33–22.0)	<0.001 (LR = 21.52)
Median	3.37 ± 0.67 (2.05–4.68)	6.90 ± 0.66 (5.61–8.19)	12.03 ± 1.47 (9.14–14.92)	

LR = likelihood ratio.
Data are mean ± SEM, with 95% confidence interval in parentheses.

survival. In the current study with ^{188}Re-HEDP, we extended our data by adding a group of patients receiving 3 or more successive therapies. According to age and Gleason score, patients in the multiple-therapy group did not differ from those patients undergoing only 1 or 2 therapies. Mean survival after the first therapy could be improved from 4.50 to 9.98 mo and up to 15.66 mo. The data from groups A and B are comparable to the previously published results by Palmedo et al. (*18*), with median overall survival after 1 therapy of 7.0 mo, which could be extended to 12.7 mo after 2 therapies. Our study showed that the mean survival could be extended to up to 15.66 mo using 3 or more therapies. However, no significance was found in mean and median survival after diagnosis of the prostate cancer. Unexpectedly, group A showed the longest overall survival, compared with the other 2 groups. Although the 3 groups did not differ in Gleason score, at least at the time of the diagnosis of prostate cancer, no differences for the other 2 groups were found. In contradiction to this, the number of lost life-years was significantly lower in group C (3 or more therapies) than in groups A and B. One other explanation would be that patients with a better prognosis would survive long enough to undergo repeated treatment. The only possibility of evaluating this observation would be in a study in which all patients with painful bone metastases have the initial ^{188}Re-HEDP treatment at the same time, as is of course not possible because of ethical considerations. Thus, large randomized and prospective studies would be needed to clearly define the benefits of repeated radionuclide therapy with ^{188}Re.

We did not observe an antitumor effect (PSA) to the extent observed by Palmedo et al. (*18*), probably because all patients in their series had a fixed follow-up. In our patients, PSA had been determined only at relatively long intervals. Therefore, in our patients with longer survival, the PSA decreases were not as pronounced as in patients who had regular follow-up, including PSA determinations, for at least 3 mo. Because ^{188}Re-HEDP is not commercially available, in-house production is required, which is cost-effective because of the multiple-month useful shelf-life of the ^{188}W/^{188}Re generator system. But even without clarification of the situation with respect to survival, patients receiving ^{188}Re-HEDP treatment will benefit from bone pain palliation. The group of patients treated had therapy-refractory bone metastases for which no other treatment modality is available.

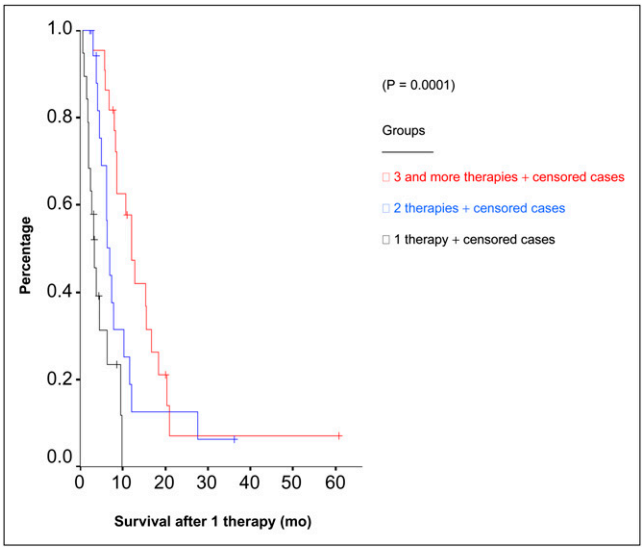

FIGURE 1. Survival of the 3 groups after first rhenium therapy (mo). Statistics are from Table 5.

RGB

CONCLUSION

Compared with single-injection bone-targeted therapy, repeated bone-targeted treatment with ^{188}Re-HEDP improved posttreatment overall survival from 4.50 to 15.66 mo in patients with progressive hormone-refractory prostate cancer. Significant pain palliation was achieved in about 90% of the study cohort. With respect to the unpredictable course of the disease, randomized, prospective studies are needed to achieve a comparable data basis in these patients and to define the benefits of repeated therapy.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

ACKNOWLEDGMENTS

This study was in part supported by the Alexander von Humboldt Foundation, and one of the authors is a former von Humboldt fellow. Research at the Oak Ridge National Laboratory (ORNL) is supported by the U.S. Department of Energy (DOE) under contract DE-AC05-00OR22725 with UT-Battelle, LLC. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Cserháti P. Metastatic disease in breast cancer. *J Clin Oncol.* 1987;21:1235–1241.
2. Strumpf M. Krebbsschmerz. In: Zenz J, Jurna I, eds. *Lehrbuch der Schmerztherapie*. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft; 1993:427–436.
3. Kaplan E, Fels IG, Kotlowski BR. Therapy of carcinoma of the prostate metastatic to bone with P-32 labeled condensed phosphate. *J Nucl Med.* 1960;1:1–13.
4. Lewington VJ. Targeted radionuclide therapy for bone metastases. *Eur J Nucl Med.* 1993;20:66–74.
5. Kutzner J, Dähnert W, Schreyer T, Grimm W, Brod KH, Becker M. Treatment of pain from bone metastases with ^{90}Y [in German]. *Nuklearmedizin.* 1981;20:229–235.
6. Poner A, Mertens W. Strontium 89 in the treatment of metastatic prostate cancer. *Can J Oncol.* 1991;1:11–18.
7. Blake GM, Wood JF, Wood PJ, Zivanovic MA, Lewington VJ. ^{89}Sr therapy: strontium plasma clearance in disseminated prostatic carcinoma. *Eur J Nucl Med.* 1989;15:49–54.
8. Blake GM, Zivanovic MA, McEwan AJ, Ackery DM. Sr-89 therapy: strontium kinetics in disseminated carcinoma of the prostate. *Eur J Nucl Med.* 1986;12:447–454.
9. Blake GM, Zivanovic MA, Lewington VJ. Measurements of the strontium plasma clearance rate in patients receiving Sr-89 radionuclide therapy. *Eur J Nucl Med.* 1989;15:780–783.
10. Blake GM, Zivanovic MA, McEwan AJ, Batty VB, Ackery DM. ^{89}Sr radionuclide therapy: dosimetry and haematological toxicity in two patients with metastasising prostatic carcinoma. *Eur J Nucl Med.* 1987;13:41–46.
11. Holmes RA. [^{153}Sm] EDTMP: a potential therapy for bone cancer pain. *Semin Nucl Med.* 1992;22:41–45.
12. Ketring AR. ^{153}Sm-EDTMP and ^{186}Re-HEDP as bone therapeutic radiopharmaceuticals. *Int J Rad Appl Instrum B.* 1987;14:223–232.
13. Singh A, Holmes RA, Farhangi M. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *J Nucl Med.* 1989;30:1814–1818.
14. de Klerk JMH, van Dijk A, van het Schip AD, Zonnenberg BA, van Rijk PP. Pharmacokinetics of rhenium-186 after administration of rhenium-186-HEDP to patients with bone metastases. *J Nucl Med.* 1992;33:646–651.
15. Palmedo H, Guhlke S, Bender H, et al. Dose escalation study with rhenium-188 HEDP in prostate cancer patients with osseous metastases. *Eur J Nucl Med.* 2000;27:123–130.
16. Maxon HR III, Schroder LE, Washburn LC, et al. Rhenium-188(Sn)HEDP for treatment of osseous metastases. *J Nucl Med.* 1998;39:659–663.
17. Schoeneich G, Palmedo H, Dierke-Dzierzon C, Müller SC, Biersack HJ. Rhenium-186 HEDP: palliative radionuclide therapy of painful bone metastases: preliminary results. *Scand J Urol Nephrol.* 1997;31:445–448.
18. Palmedo H, Manka-Waluch A, Albers P, et al. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: tandomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. *J Clin Oncol.* 2003;21:2869–2875.
19. Knapp FF Jr, Mirzadeh S, Beets AL, et al. Reactor-produced radioisotopes from ORNL for bone pain palliation. *Appl Radiat Isot.* 1998;49:309–315.
20. Guhlke S, Beets AL, Oetjen K, et al. Convenient concentration of [^{188}Re] perrhenate or [^{99m}Tc]pertechnetate eluates from tungsten-188/rhenium-188 or (n,γ) produced molybdenum-99/technetium-99m generators to high specific volumes (12th International Symposium on Radiopharmaceutical Chemistry). *J Labelled Comp Radiopharm.* 1997:294–297.
21. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med.* 2010;40:89–104.
22. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol.* 1991;64:816–822.
23. Sartor O, Reid RH, Bushnell DL, Quick DP, Ell PJ. Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. *Cancer.* 2007;109:637–643.
24. Lee CK, Aeppli DM, Unger J, Boudreau RJ, Levitt SH. Strontium-89 chloride (Metastron) for palliative treatment of bony metastases. The University of Minnesota experience. *Am J Clin Oncol.* 1996;19:102–107.
25. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. *Lancet Oncol.* 2005;6:392–400.
26. Tian JH, Zhang JM, Hou QT, et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. *Eur J Nucl Med.* 1999;26:2–7.
27. Maxon HR III, Schroder LE, Hertzberg VS, et al. Rhenium-186(Sn)HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo. *J Nucl Med.* 1991;32:1877–1881.
28. Han SH, de Klerk JM, Tan S, et al. The PLACORHEN study: a double-blind, placebo-controlled, randomized radionuclide study with ^{186}Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study. *J Nucl Med.* 2002;43:1150–1156.
29. Sciuto R, Tofani A, Festa A, Giannarelli D, Pasqualoni R, Maini CL. Short- and long-term effects of ^{186}Re-1,1-hydroxyethylidene diphosphonate in the treatment of painful bone metastases. *J Nucl Med.* 2000;41:647–654.
30. Sciuto R, Festa A, Pasqualoni R, et al. Metastatic bone pain palliation with ^{89}Sr and ^{186}Re-HEDP in breast cancer patients. *Breast Cancer Res Treat.* 2001; 66:101–109.
31. Lam MG, Bosma TB, van Rijk PP, Zonnenberg BA. ^{188}Re-HEDP combined with capecitabine in hormone-refractory prostate cancer patients with bone metastases: a phase I safety and toxicity study. *Eur J Nucl Med Mol Imaging.* 2009; 36:1425–1433.
32. Lam MG, Dahmane A, Stevens WH, van Rijk PP, de Klerk JM, Zonnenberg BA. Combined use of zoledronic acid and ^{153}Sm-EDTMP in hormone-refractory prostate cancer patients with bone metastases. *Eur J Nucl Med Mol Imaging.* 2008;35:756–765.