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Palliative analgesic effect of Re-186 HEDP in various cancer patients with bone metastases

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The clinical picture of bone metastases is manifested by pain and loss of mechanical stability. Standard treatment options for bone metastases include external beam radiotherapy and the use of analgesics. Due to a large number of lesions in many patients, the use of radionuclide therapy with beta emitters may be preferable. Re-186 hydroxyethylidene diphosphonate (Re-186 HEDP) is one of the radiopharmaceuticals suitable for palliative treatment of metastatic bone pain. The aim of this study was to investigate palliative and side effects of Re-186 HEDP in patients with different types of cancers. ***Material & Method:*** Thirty one (17 male, 14 female) patients with various cancers (10 prostate, 10 breast, 4 rectum, 5 lung, 2 nasopharynx) and bone metastases were included in the study. Therapy was started with a fixed dose of 1295 MBq of Re-186 HEDP. If necessary, the same dose was repeated at least 3 times after an interval of 10–12 weeks; A total of 40 standard doses were given; 6 patients received repeated doses (3 doses in 3 patients, 2 doses in 3 patients). The patients with bone marrow suppression were excluded from the study. The pain relief was assessed the Eastern Cooperative Oncologic Group (ECOG) and the Karnofsky status index. All patients were evaluated with standard evaluation forms filled in daily for a maximum of 10 weeks. ***Results:*** The mean response rate was 87.5% in patients with breast and prostate cancer, 75% in patients with rectum cancer and 20% in patients with lung cancer. The overall response rate was 67.5%. The palliation period varied between 6 and 10 weeks, with a mean of 8.1 ± 1.3 weeks. The maximal palliation effect was observed between the 3rd and 7th weeks. No serious side effects were seen except mild hematologic toxicity. ***Discussion & Conclusion:*** It is concluded that Re-186 HEDP is a highly effective agent in the palliation of metastatic bone pain in patients with prostate, breast and rectum cancer, but not effective in lung cancer. On the other hand, Re-186 seems to be a good alternative to Sr-89 because of its preferable physical characteristics (such as short half life and gamma energy emission), low side effect profile, early response and repeatability.

Key words: bone metastases, Re-186 HEDP, pain palliation

INTRODUCTION

BONE METASTASES are often the first presentation of distant disease in patients with cancer, especially prostate, breast and lung cancer.[1] The clinical picture of bone metastases is manifested by pain and loss of mechanical stability. The condition is incurable and the only chance is palliative therapy which includes hormonal application, chemotherapy and radiotherapy.[2] Standard treatment options for bone metastases are external beam radiotherapy and use of analgesic drugs.[3–6] Due to the large number of lesions in many patients, radionuclide therapy with specifically localized internal beta emitters may be preferable.[7,8]

The use of radioisotopes in palliative therapy[9] of bone metastases have started with P-32 (Phosphore)[10–13] and continued with Sr-89 (strontium),[14–16] Sm-153 (Samarium) EDTMP,[17–21] Sn-117m (Tin) DTPA,[22,23] Iodine-131 labeled diphosphonate[24] and Re-186 (Rhenium).[25–35] Favorable responses in patients with bone metastases of cancers were obtained with Sr-89. Unfortunately this radionuclide has a relatively long physical half life and

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Table 1 Performance status scales

Karnofsky scale	Karnofsky Scale (%)	ECOG scale
No complaints; no evidence of disease	100	0
Able to carry on normal activity; minor signs or symptoms of disease	90	1
Some signs or symptoms of disease with effort	80	
Cares for self; unable to carry on normal activity or to do active work	70	2
Requires occasional assistance but is able to care for most personal needs	60	
Requires considerable assistance and frequent medical care	50	3
Disabled; requires special care and assistance	40	
Severely disabled; hospitalization indicated, although death not imminent	30	
Very sick; hospitalization necessary; requires active supportive treatment	20	4
Moribund; fatal processes progressing rapidly	10	
Dead	0	

ECOG: Eastern Cooperative Oncologic group

does not emit gamma rays for post therapy quantitative imaging. Recently Re-186 hydroxyethylidene diphosphonate (Re-186 HEDP) has been proposed for pain palliation in patients with metastatic bone lesions.[25, 26] Initial results showed that Re-186 HEDP is able to reduce pain caused by bone metastases. Because of its proper imaging qualities, 1.07 MeV beta radiation and physical half life, it has found wide use in palliative therapy of bone metastases.

The aim of this study was to evaluate the benefit of Re-186 HEDP in terms of pain relief as well as benefit from repeated doses and unwanted effects in patients with different types of cancer with bone metastases.

MATERIAL AND METHOD

Thirty-one patients with various cancer including 10 prostate, 10 breast, 4 rectum, 5 lung and 2 nasopharynx carcinoma (17 males, 14 females, mean age: 58 ± 5 years old, range 39–84 years old) were given Re-186 HEDP (Mallinckrodt, Holland), reaching a total of 40 standard doses (1295 MBq). Some of them received repeated doses of the same activity at 3 month intervals. The criteria are shown below.

1. At least four bone metastases demonstrated in the bone scan,
2. A Karnofsky performance status of a maximum 60% (Table 1).
3. At least 4.0 × 1000 leukocyte and 150 × 1000 platelet counts/mm^3,
4. Normal renal functions (30 mmol/lt serum creatinin concentration or less),
5. At least 3 months life expectancy.

The patients with either bone marrow suppression or signs of nerve compression were excluded from the study. Tc-99m Methylene diphosphonate (MDP) bone scintigraphy was performed and bone scan indices (BSI) were evaluated before the treatment. According to Blake et al.[14] BSI is a diagnostic tool to provide an index of metastatic disease. This method divides the skeleton into four anatomical regions: 1. spine and skull, 2. pelvis, 3. shoulder girdle and ribs, 4. extremities. Each region is scored visually on a scale of zero to ten for the apparent proposition of the skeleton involved. Scores for each region are summed and the sum is normalized to a scale of zero to hundred as an index of the extent of metastatic involvement.

The response rate is evaluated with Karnofsky and Eastern Cooperative Oncologic Group (ECOG) status indices (Table 1). 0–1 was defined as complete response, 2 as partial response and 3–4 as poor response on the ECOG scale.

A standard dose of 1295 MBq Re-186 HEDP was given intravenously to the patients by slow infusion. The patients were kept in the nuclear medicine department for 6 hours after the injection. The next day, anterior and posterior whole body scanning was performed. The daily symptomatic status of patients was recorded, whereas blood analysis was performed weekly for 8 weeks after the therapy. A control Tc-99m MDP scintigraphy was performed approximately 30 days after the therapy. Especially for patients who did not have any pain relief despite therapy, a comparison of the number and intensity of metastases was made by means of bone scintigraphy to determine the cause of pain increase.

RESULTS

The overall response rate was 67.5%. The palliation period varied between 6 and 10 weeks, with a mean of 8.1 ± 1.3 weeks. The maximal palliation effect was observed between the 3rd and the 7th weeks. No serious side effects were seen except mild hematologic toxicity.

Prostate cancer

Ten patients, who had multiple metastases and did not respond to hormonal and/or analgesic therapy, received Re-186 HEDP (Table 2). All had chemotherapy (5 of

Table 2 Summary of findings in patients with prostate cancer

	Case	Age	Diagnosis (year)	BSI (%)	Chemo-therapy	Radiation therapy	Response rate (%)	Thrombocyte ($\times 10^3$)		Leucocyte		Alkaline phosphatase	
								Before	After (4w)	Before	After (4w)	Before	After (4w)
1	KV	69	5	50	+	+	100	306	211	5100	5000	140	100
	KV2						100	190	140	8700	5000	180	100
2	CS1	71	6	80	+	+	100	280	200	11100	8000	432	300
	CS2						100	250	150	9700	6500	750	400
	CS3						75	250	90	8500	5000	800	850
3	TB	65	3	80	+	+	100	200	120	5900	4200	1109	1200
4	OK	70	4	80	+	+	75	120	900	9000	7600	600	650
5	ŞC	69	1	70	+	+	75	150	129	6900	5200	118	120
6	İA	75	6	50	+		100	180	126	6100	3300	150	100
7	MD1	84	7	80	+		100	158	145	7000	5200	85	80
	MD2						50	150	38	4400	3800	120	100
8	AD	60	2	50	+	+	80	290	200	6500	4900	280	180
9	MC	64	3	60	+	+	10	235	180	5800	4200	350	245
10	AÖ	64	2	60	+		10	309	273	8100	9800	102	100
Mean		70±6	4±2	70			87.5	212.875 ±74.885	163.250 ±59.830	7400 ±1900	6030 ±2100	347 ±266	325 ±295

BSI: Bone Scan Index

Table 3 Summary of findings in patients with breast cancer

	Case	Age	Diagnosis (year)	BSI (%)	Chemo-therapy	Radiation therapy	Response rate (%)	Thrombocyte ($\times 10^3$)		Leucocyte		Alkaline phosphatase	
								Before	After (4w)	Before	After (4w)	Before	After (4w)
1	FD	42	5	50	+	+	75	375	351	6440	4300	199	104
2	TC	51	3	30	+	+	100	327	127	5900	3500	112	100
3	EM1	44	7	60	+	+	100	328	220	8470	5400	166	98
	EM2						100	250	120	7000	5800	120	95
	EM3						90	240	98	6400	4200	180	120
4	ŞI	38	2	40	+	+	75	274	140	5500	3500	67	129
5	ŞA	47	2	60	+	−	100	389	300	7890	5500	129	80
6	ZŞ	38	4	70	+	+	50	175	126	3600	3000	120	150
7	ZŞ	52	2	60	+	−	20	450	35	6300	4100	100	78
8	MK	46	4	40	+	+	75	350	28	4800	3600	350	220
9	ŞA	38	2	50	+	−	100	256	195	6200	3900	37	105
10	FŞ1	59	12	55	+	+	75	158	79	5600	4780	222	200
	FŞ2							120	70	8000	760	350	320
Mean		43±5	4±3	50			87.5	303.5 ±97	214 ±10.1	6230 ±1390	4040 ±890	140 ±48	105 ±41

them had radiotherapy) and high prostate specific antigen (PSA) (mean 67 ± 13 IU/m*l*, 28–258 IU/m*l*) and prostatic acid phosphatase (PAP) levels (mean 58 ± 45 IU/m*l*, 3–100 IU/m*l*) before the therapy. Platelet and leukocyte counts and liver and kidney functions were within normal limits. A total of 14 doses were applied (2 patients received 2 doses, 1 received 3 doses and the remaining 7 received 1 dose). Six patients showed complete remission, 2 had partial remission, 2 did not respond at all. The response was observed at the end of the first week and continued up to 8–10 weeks. Four patients showed signs of the flare up phenomen. All had a decline in platelet and leukocyte counts starting at the end of the first week and it continued to decline for 4–5 weeks and reached the normal level within 5–6 weeks. Biochemical blood analyses of kidney and liver functions remained normal whereas the alkaline phosphatase levels declined within 4 weeks after therapy. PSA levels increased 20% after therapy in 4 weeks and PAP values showed about a 10% decrease after therapy.

Breast cancer

Ten female patients (9 infiltrative ductal carcinoma, 1 mucinous adenocarcinoma) received 12 standard doses of Re-186 HEDP (Table 3). Two were considered to be inoperable and the others had modified radical mastec-

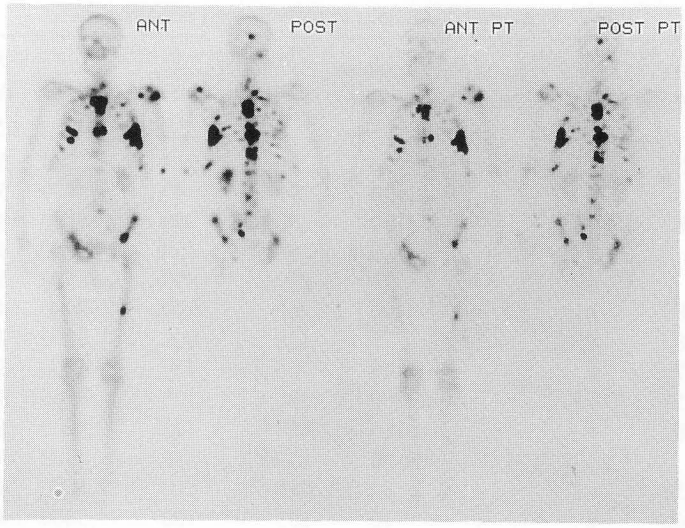

Fig. 1 Anterior and posterior views of Tc-99m MDP whole body scan of a breast cancer patient before therapy (left). Anterior and posterior views of Re-186 HEDP whole body scan 24 hours after administration (right).

Table 4 Summary of findings in patients with nasopharynx cancer

	Case	Age	Diagnosis (year)	BSI (%)	Chemo-therapy	Radiation therapy	Response rate (%)	Thrombocyte ($\times 10^3$)		Leucocyte		Alkaline phosphatase	
								Before	After (4w)	Before	After (4w)	Before	After (4w)
1	MU	47	2	40	+	+	–	60	–	3700	–	300	–
2	KS	67	1	20	–	+	85	381	245	11800	7100	1570	1280

tomy and lymph node resection. All patients received chemotherapy and hormonotherapy and 8 of them also received radiotherapy. Four patients showed signs of complete response (Fig. 1). The other four had a decrease in the pain level, but still needed low dose analgesics. The performance status was high in all 4 patients. Only 2 patients did not experience any decrease in pain. The flare up phenomenon was observed in two patients who had complete response. No neurologic effects were observed. The decrease in thrombocyte counts was slightly greater than that of leucocytes, but they returned to the original level in 6–7 weeks after treatment (20% fall in thrombocytes and 15% fall in leucocytes). Similarly to prostate cancer, alkaline phosphatase showed a decrease within 4 weeks after treatment (105 ± 41 IU/d*l*) but returned to the same level at the end of 6–8 weeks. No change was observed in carcinogenic antigen (CA) 15-5 or carcinoembriogenic antigen (CEA) levels except in two patients who showed a 10% decrease in CA 15-5.

Nasopharynx cancer

Two patients received Re-186 therapy (Table 4). One did not show any response and died in the fifth week. The other patient, who refused chemotherapy and volunteered for Re-186 HEDP therapy, responded well. The response started at the end of the first week but this patient died in the sixth week. We could not evaluate the duration of palliation. Hematologic side effects were not observed to be at dangerous levels.

Lung cancer

Five male patients were treated with Re-186 HEDP (Table 5). None of them was operated on and all of them received chemotherapy and radiotherapy. Only two patients experienced pain relief and decrease in use of analgesics. Others did not seem to respond. No important side effects were observed.

Rectal cancer

Two female and 2 male patients received Re-186 HEDP (Table 6). Two patients showed complete response, one partial response and one poor response. The one with complete response (case 2), had pain again at the end of 8 weeks and received a second dose. The response of the second dose was complete and treatment was repeated 8 weeks after the second dose. The thrombocyte and leucocyte levels were decreased slightly after the first treatment and the degree of hematological effects increased after the second and third doses. The hematological toxicity decreased 30–40% after the third dose. The length of the painless period decreased slowly after the third treatment.

Table 5 Summary of findings in patients with lung cancer

	Case	Age	Diagnosis (year)	BSI (%)	Chemo-therapy	Radiation therapy	Response rate (%)	Thrombocyte ($\times 10^3$)		Leucocyte		Alkaline phosphatase	
								Before	After (4w)	Before	After (4w)	Before	After (4w)
1	KU	85	1	10	+	+	0	356	276	12600	10900	238	100
2	HC	62	2	40	+	+	75	280	190	4600	3500	140	120
3	CM	59	1	20	+	+	0	360	250	3900	2500	280	190
4	MB	59	2	25	+	+	20	240	200	4200	3500	180	220
5	CD	64	1	30	+	+	0	363	250	11100	12000	180	200
Mean		58±6		25			20	319.8 ±41.5	233.2 ±31.1	7100 ±54	6480 ±260	190 ±23	150 ±22

Table 6 Summary of findings in patients with rectum cancer

	Case	Age	Diagnosis (year)	BSI (%)	Chemo-therapy	Radiation therapy	Response rate (%)	Thrombocyte ($\times 10^3$)		Leucocyte		Alkaline phosphatase	
								Before	After (4w)	Before	After (4w)	Before	After (4w)
1	FK	39	1	50	+	–	5	70	–	3200	–	250	–
2	ZA1	70	2	20	–	–	100	400	350	6800	6000	465	300
	ZA2						90	250	150	7000	5400	480	400
	ZA3												
3	MÖ	39	1	60	+	–	75	200	150	11000	5200	1047	699
4	TA	51	1	40	+	+	100	540	480	7060	4060	750	800
Mean		49±14	1.5	30			75	380 ±170	326 ±166	8200 ±2300	5000 ±1000	754 ±291	599 ±291

DISCUSSION

Radioisotopes have been used with the purpose of palliation of pain due to bone metastases. High pain palliation rates were obtained; 60–90% with Sr-89,[14–16] 80–90% with Re-186 HEDP,[25] and 70–80% with Sm-153[19–21] in cases of prostate cancer. In our study, complete or partial response was found in 8 of 10 patients with prostate cancer and in 8 of 10 patients with breast cancer. This result was consistent with the literature. Re-186 HEDP was given to 2 patients with nasopharynx cancer; response to therapy has been observed in one of them, but the other died before any kind of evaluation. The number of patients in this group was too small for discussion. There was no evidence of palliation in patients with lung cancer. Only two of 5 patients experienced pain relief and decrease in the use of analgesics. Possible mechanisms were thought to be high cellular turnover rates and/or pleural and/or neural invasions in the early stages. There are no results in the literature on patients with rectal cancer. Despite the limitation in the number, we found a 75% palliation rate in this group. We concluded that further investigation with more patients is needed.

The duration of palliation was reported to be 3–6 months for Sr-89,[16] 6–10 weeks for Re-186 HEDP,[26–28] and 4–8 weeks for Sm-153[17,21] in the literature. Despite the relatively long palliation period with Sr-89,[14] it is not widely used because of retardation of therapeutic response and more side effects. The long palliation period of up to 8–10 weeks observed in our study can be accepted as a satisfactory level when repeatability of the therapy is taken into account.

In an early stage after radionuclide palliative therapy, an increase in the pain level (flare up) is observed. Later, a major consequence is bone marrow toxicity. Flare up was observed in 10% of cases with Sr-89[15] and similar results have been reported with Re-186 HEDP.[30] This observation has been thought to be due to cellular necrosis in the early stage and/or secreted mediators during this process. The flare up phenomenon is reported to be seen more often in cases of multiple metastases and patients with this phenomenon respond better to the therapy than those without. We observed flare up phenomenon in 6 of 31 cases in our series. BSI rates and responsiveness to therapy were higher in these cases. Flare up phenomenon was thought to be a possible early indicator of responsiveness to therapy. No distinct data were obtained with either Sm-153 or Sn-117m.

Bone marrow toxicity is the most important side effect of the therapy and it is more prominent with P-32,[13] but can be seen with Sr-89 also.[15] It is the major limitation in the use of P-32. It is observed with Sr-89 after the 4th week at the rate of 20–30%.[15] This effect has been reported to be seen at a lower rate and for a shorter period with Re-186 HEDP.[31] Sm-153[18] and Sn-117m[22,23] are today's choices because of lower side effect profiles. In our study we

observed bone marrow suppression an average of 4 weeks after the therapy in 15–20% of our cases. Repeated therapy caused an increase in side effects but none of the patients needed a blood transfusion and no permanent bone marrow suppression was observed.

A temporary decrease in alkaline phosphatase levels was observed and these observation were correlated with other pharmaceutical studies.[36] Temporary decreases in PSA levels in patients with prostate cancer have been reported.[37] No change in other tumor markers has been observed. Changes in PSA levels have been observed with Re-186 HEDP.[35] In our study, changes in PSA levels were observed in patients with prostate cancer; these changes were thought to be due to PSA subtypes and necrosis in bone lesions was concluded to cause a rise in the blood PSA level.

Neurological side effects have been reported after radionuclide therapy, especially in patients with parietal and temporal metastases. Re-186 HEDP therapy has been found to cause symptoms of neurological compression.[29,30] We did not observe any neurological symptoms in our patients. Sites of metastases and the possible relationship with nerves were thought to be responsible for neurological side effects.

CONCLUSION

It is concluded that Re-186 HEDP is a highly effective agent in the palliation of metastatic bone pain in patients with prostate, breast and rectum cancer, but not effective in lung cancer. On the other hand, Re-186 seems to be a good alternative to Sr-89 because of its preferable physical characteristics (short half life and gamma energy emission), low side effect profile, early response and repeatability.

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