PALLIATIVE EFFECT OF Re-186 HEDP IN DIFFERENT CANCER PATIENTS WITH BONE METASTASES

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Abstract. 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 hydroxyethydilene 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 pts with different type of cancers. **Material&method:** Thirty one (17 male, 14 female) patients with cancer (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 (1295 MBq Re HEDP, Mallinckrodt, Holland) were given; 6 pts received repeated doses (3 doses in 3 pts, 2 doses in 3 pts). The pts with bone marrow suppression were excluded from the study. The pain relief was assessed with ECOG and Karnofsky status index. All pts were evaluated with standard evaluation forms filled daily a maximum of 10 weeks. **Results:** The respond rate was found as 87.5% in pts with breast and prostate Ca, 75% in pts with rectum Ca, 50% in pts with nasopharynx Ca and 20% in pts with lung Ca. The overall response rate was 67.5%. The palliation period varied between 6 to 10 weeks. The mean palliation period was 8.1 ± 1.3 weeks. Maximal palliation effect was observed between the 3rd and the 7th weeks. Any serious side effects were not seen except mild haematologic toxicity. **Discussion & conclusion:** It is concluded that Re-186 HEDP is a highly effective agent in the palliaton of metastatic bone pain in pts with prostate, breast, rectum cancer, mildly effective in pts with nasopharynx 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 charecteristics (as short half life and gamma energy emission), low side effect profile, early response and repeated repeatebility.

1. 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 state is incurable and the only chance is palliative therapy which includes hormon application, chemotherapy and radiotherapy [3]. Standard treatment options for bone metastases are external beam radiotherapy and use of analgesic drugs [7, 8, 45]. Due to large number of lesions in many patients, radionuclide therapy with specifically localized internal beta emitters may be preferable [5, 6, 9].

Use of radioisotopes in palliative therapy [2] of bone metastases have started with P 32 (10B13) and continued with Sr 89 [14, 15, 16] and Re-186 [24–41], Sm 153 EDTMP (17B21), Sn 117m DTPA [22–23]. Favourable responses in patients with bone metastases of cancers were held with Sr 89. Unfortunately this radionuclide has a relatively long physical half life and does not emit gamma rays for post therapy quantitative imaging. Recently Re-186 HEDP has been proposed for pain palliation in Pts with metastatic bone lesions [24, 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.

2. MATERIAL AND METHOD

10 prostate, 10 breast, 4 rectum, 5 lung, 2 nasopharynx carcinoma (17 males, 14 females, mean age:58 ± 5 year, range 38–84 year) patients were given Re-186 reaching a total of 40 standard doses (1295 MBq Re-186 HEDP, Mallinckrodt, Holland). Some of them received repeated doses of the same activity at 3 months intervals. Including criteria were:

1. At least four bone metastases demonstrated in the bone scan,
2. A Karnofsky performance status of maximum 60%,
3. At least 4.0 × 1000 leukocyte and 150 × 1000 platelet count,
4. Normal renal functions (30 mmol/L serum creatinine 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 MDP bone scintigraphy was performed and bone scan indices were evaluated before the treatment. (34,35).

A standard dose of 1295 MBq Re-186 HEDP was given IV. to the patients with slow infusion. The patients were kept in nuclear medicine department for 6 hours after injection. The next day, anterior and posterior whole body scanning was performed. The daily symptomatic status of patients was recorded whereas blood analysis were 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 number and intensity of metastases was made by means of bone scintigraphy to determine the cause of pain increase.

3. RESULTS

3.1. Prostate cancer

10 patients in D3 phase who had multiple metastases and did not respond to hormonal and/or analgesic therapy received Re-186 HEDP. All had chemotherapy (and 5 of them had radiotherapy also) and had elevated PSA (mean 67 ± 13, 28–258) and PAP levels (mean 58 ± 45, 3–100), normal platelet and leukocyte counts, liver and kidney functions before the therapy. A total of 14 doses were applied (2 pts received 2 doses,1 received 3 doses the remaining 7 received 1 dose). 6 showed complete response, 2 had partial remission, 2 did not respond at all. The response was observed at the end of first week and continued up to 8–10 weeks. 4 patients showed flare up phenomenon. All had a decline in platelet and leukocyte counts starting with the end of first week and continued to decline for 4–5 weeks and reached to normal level within 5–6 weeks ($p < 0.05$). Biochemical blood analyses of kidney and liver functions remained normal whereas alkaline phosphatase levels declined within 4 weeks after therapy ($p < 0.05$). PSA levels increased 20% after therapy in 4 weeks ($p<0.001$) and PAP values showed about a 10% decrease ($p < 0.05$).

TABLE I. PROSTATE CA PATIENTS FINDING THE CHAGEMENT OF AFTER TREATMENT.

	Year	Diag (year)	BSI (%)	KT	RT	Resp (%)	Trom 1	trom2	Leuk1	leuk 2	ALP 1	ALP2
KV	69	5	50	+	+	%100	306000	211000	5100	5000	140	100
KV2						%100	190000	140000	8700	5000	180	100
CS1	71	6	80	+	+	%100	280000	200000	11100	8000	432	300
CS2						%100	250000	150000	9700	6500	750	400
CS3						%75	250000	90000	8500	5000	800	850
TB	65	3	80	+	+	%100	200000	120000	5900	4200	1109	1200
OK	70	4	80	+	+	%75	120000	90000	9000	7600	600	650
SC	69	1	70	+	+	%75	150000	129000	6900	5200	118	120
IA	75	6	50	+		%100	180000	126000	6100	3300	150	100
MD1	84	7	80	+		%100	158000	145000	7000	5200	85	80
MD2						%50	150000	38000	4400	3800	120	100
AD	60	2	50	+	+	%80	290000	200000	6500	4900	280	180
MC	64	3	60	+	+	%10	235000	180000	5800	4200	350	245
AÖ	64	2	60	+		%10	309000	273000	8100	9800	102	100
Mean	70±6	4±2	70			%87.5	212875± 74885	163250± 59830	7400± 1900	6030± 2100	347± 266	325± 295

3.2. Breast cancer

10 female patients (9 infiltrative ductal ca, 1 mucinous adenoCA) 38–52 years old (43 ± 5) received 12 standard doses of Re-186 HEDP. Two were considered to be inoperable and the others had modified radical mastectomy and lymph node resection. All of them received chemotherapy and hormone therapy, 8 of which also received radiotherapy. Four patients showed complete response. The other four showed decrease in pain level, but still needed low dose analgesics. The performance status were elevated. 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 thrombocyte counts were decreased slightly higher than leukocytes, but they returned to the original level in 6–7 weeks after treatment (20% fall in thrombocyte and 15% fall in leukocyte). Similar to prostate cancer, alkaline phosphatase showed a decrease within 4 weeks after treatment but returned to the same level at the end of 6–8 weeks (140 ± 48;105 ± 41IU/dl). No change was observed in CA 15–5 or CEA levels except two patients who showed a 10% decrease in Ca 15–5.

TABLE II. BREAST CA PATIENTS

	year	Diag (year)	RT	KT	BSI	Res(%)	trom 1	trom 2	leuk 1	Leuk 2	ALP1	ALP2
FD	42	5	+	+	50	%75	375000	351000	6440	4300	199	104
TC	51	3	+	+	30	%100	327000	127000	5900	3500	112	100
EM1	44	7	+	+	60	%100	328000	220000	8470	5400	166	98
EM2						%100	250000	120000	7000	5800	120	95
EM3						%90	240000	98000	6400	4200	180	120
SI	38	2	+	+	40	%75	274000	140000	5500	3500	67	129
SA	47	2	-	+	60	%100	389000	300000	7890	5500	129	80
ZS	38	4	+	+	70	%50	175000	126000	3600	3000	120	150
ZS	52	2	-	+	60	%20	450000	350000	6300	4100	100	78
MK	46	4	+	+	40	%75	350000	28000	4800	3600	350	220
SA	38	2	-	+	50	%100	256000	195000	6200	3900	37	105
FS1	59	12	+	+	55	% 75	158000	79000	5600	4780	222	200
FS2							120000	70000	8000	760	350	320
Mean	43±5	4±3			50	%87.5	303500±97000	214000±10100	6230±1390	4040±890	140±48	105±41

3.3. Nasopharyngeal cancer

Two patients (48 and 67 years old) received therapy. 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. Haematologic side effects were not observed to be at dangerous levels.

TABLE III. NASOPHARYNGEAL CA

	years	Diagnose	RT	KT	BSI	Response	Trom 1	Trom 2	leuk 1	leuk 2	ALP1	ALP2
MU	47	2	+	+	%40	-	60000	-	3700	-	300	-
KS	67	1	+	-	%20	% 85	381000	245000	11800	7100	1570	1280

3.4. Lung cancer

Five male patients (58 ± 6 years old) were treated with Re-186 HEDP. None of them were operated on and all of them received chemotherapy and radiotherapy. Only two patients experienced pain relief and decrease use of analgesics. Others did not seem to respond. No important side effects were observed.

TABLE IV. LUNG CA

	year	Diagnose	RT	KT	BSI	Response	Trom 1	Trom 2	Leuk 1	Leuk 2	ALP 1	ALP2
KU	85	1	+	+	10	0	356000	276000	12600	10900	238	100
HC	62	2	+	+	40	75	280000	190000	4600	3500	140	120
CM	59	1	+	+	20	0	360000	250000	3900	2500	280	190
MB	59	2	+	+	25	20	240000	200000	4200	3500	180	220
CD	64	1	+	+	30	0	363000	250000	11100	12000	180	200

3.5. Rectal cancer

Two females and 2 males with mean age of 49 ± 14 received Re-186 HEDP. Two patients showed complete response, one partial response and one no answer. The one with complete response, 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 haematological effects increased after the second and third doses. The haematological toxicity was 30–40% decrease (grade 3) after the third dose. The duration of painless period decreased slowly after the third treatment.

TABLE V. RECTAL CA

	year	Diag (year)	RT	KT	Response	BSI (%)	Trom 1	Trom 2	Leuk 1	Leuk 2	ALP 1	ALP 2
FK	39	1	-	+	%5	50	70000	-	3200	-	250	-
ZA1	70	2	-	-	%100	20	400000	350000	6800	6000	465	300
ZA2					%90		250000	150000	7000	5400	480	400
MÖ	39	1	-	+	%75	60	200000	150000	11000	5200	1047	699
TA	51	1	+	+	%100	40	540000	480000	7060	4060	750	800
mean	49± 14	1.5			%75	30	380000± 170000	326000± 166000	8200± 2300	5000± 1000	754± 291	599± 166

4. DISCUSSION

Bone metastases are important indicators of distant spread in patients with cancer and they are clinically manifested by excessive pain. In the presence of bone metastases, therapy is palliative more than curative.

Since 1930s, radio-isotopes have been used with the purpose of palliation of the pain due to bone metastases [2, 5]. P32 was the first radio-isotope which has been used and Friedell and Straash [46] reported 90% palliation rate in bone metastases of breast cancer. Similar results have been reported in prostate cancer [10, 11, 12]. But this agent couldn't have been used widely because of bone marrow toxicity [13]. Later, Pecher et al. have used Sr89 and reported high palliative effect in breast and prostate cancer [47]. In 1979, Maxon used Re186 HEDP as an alternative to Sr89 and concluded it to have less side effects, the chance of repeatability and higher palliative rates [25, 26, 27, 35]. Nowadays Sm153 EDTMP, Sn117m DTPA are used widely in pain palliation because of advantages like less side effects, gamma rays and repeatibility in short periods. High palliation rates were reported with Sm153, also [20, 19].

Pain palliation rates were found to be 60–90% with Sr89 [14, 15, 16], 80–90% with Re186 HEDP [34, 44], and 70–80% with Sm153 (19, 20, 21) in cases with prostate cancer. In our study, palliative rate was found to be 87.5% in 10 patients with prostate cancer and this result was consistent with the literature. Pain palliation rates were found to be 70–80% with Sr89, 75–90% with Re186, and 60–70% with Sm153 [18, 19] in patients with breast cancer. In our study, Re186 HEDP was given to 10 patients with breast cancer and palliation rate was found to be 87,5%. There was complete pain relief in 4 patients and only in 2 patients no significant change in pain level could be observed. These findings are consistent with the literature. There isn't any distinct data concerning nasopharyngeal cancers. Presence of response to therapy has been reported in patients with multiple metastases. In our study, Re186 HEDP was given to 2 patients with nasopharynx cancer; response to therapy has been observed in one of them, but the other one died before any kind of evaluation. There is no evidence of palliation in patients with lung cancer. In a few cases, no effect on pain could be observed with Re186. Our study revealed the same results. Possible mechanisms were thought to be high cellular turnover rates and/or pleural and/or neural invasions in early stages. There are no result in the literature in patients with rectal cancers. Despite the limitation of the number, we found 75% palliation rate in this group. We concluded that further investigations with more patients were needed.

The durations of palliation were reported 3–6 months for Sr89 [16], 6–10 weeks for Re186 HEDP [28, 36], and 4–8 weeks for Sm153 [17, 21] in the literature. Despite the relatively long palliation period with Sr89 [14], it is not widely used because of retardation of therapeutic response and more side effects. The 8–10 weeks' long palliation period we observed in our study can be accepted as a satisfactory level when repeatability of the therapy was taken into account.

In earlier stages after radionuclide palliative therapy, increase in pain level (flare up) is observed. Later, major consequence is bone marrow toxicity. Flare up was observed in 10% of cases with Sr89 [15] and similar results have been reported with Re186 HEDP [29]. This observation has been thought to be due to cellular necrosis in early stages and/or secreted mediators during this process. Flare up phenomenon is reported to be seen more often in cases with multiple metastases and respond better to therapy. We observed flare up phenomenon in 6 of our 31 cases. BSI (bone scan index) 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 was observed with neither Sm153 nor Sn117m.

Bone marrow toxicity is the most important side effect of the therapy and it is more prominent with P32 [13], but can be seen with Sr89 also [15]. It is the major limitation in the use of P32. It is observed with Sr89 after the 4^{th} week in the rate of 20–30% [15]. This effect has been reported to be seen in a lower rate and for a shorter period with Re186 HEDP [33]. Sm153 [18] and Sn117m [22, 23]

are today's choices because of lower side effect profiles. In our study we observed bone marrow suppression after an average of 4 weeks in 15–20% of our cases. Repeated therapy courses caused increases in side effects but no none of the patients needed blood transfusions and no permanent bone marrow suppression was observed.

Temporary decreases in alkaline phosphatase levels were observed and these observations were correlated with other pharmaceutical studies [42]. Temporary decreases in PSA levels in patients with prostate cancer have been reported [43]. No change in other tumour markers has been observed. Changes in PSA levels have been observed with Re186 HEDP [40, 44]. 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 increases in blood PSA levels.

Neurological side effects have been reported after radionuclide therapy. Especially, in patients with parietal and temporal metastases. Re186 HEDP therapy has been found to cause symptoms of neurological compression [30, 31, 32].We did not observe any neurological symptoms in our patients. Site of the metastases and the possible relation with nerves were thought to be responsible from neurological side effects.

6. CONCLUSION

Palliation rate was found to be 87,5% in prostate and breast cancers and this finding is consistent with the literature. High palliation rates are reported in patients with rectal cancers (75%) and it is planned to control this result with more patients. The results of patients with nasopharyngeal cancer are hopeful (75% palliation rate), but further investigations are needed. A number of studies are being performed in this group of patients. There is not enough palliation in patients with lung cancer, and this finding is thought to be due to fast turnover rate of tumour cells and/or neural or pleural invasion in early stages.

The overall palliation rate has been calculated as 67,5% and this result is consistent with the literature.

It is concluded that Re-186 HEDP is a highly effective agent in the palliation of metastatic bone pain in patients with prostate, breast, rectum cancer, mildly effective in patients with nasopharyngeal 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 (as short half life and gamma energy emission), low side effect profile, early response and repeatability.

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