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 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 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 palliation 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 characteristics (as short half life and gamma energy emission), low side effect profile, early response and repeated repeateability.

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 hormone 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).
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
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

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<th>Diagnose</th>
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<th>KT</th>
<th>BSI</th>
<th>Response</th>
<th>Trom 1</th>
<th>Trom 2</th>
<th>Leuk 1</th>
<th>Leuk 2</th>
<th>ALP</th>
<th>ALP</th>
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<td>-</td>
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<td>-</td>
<td>3700</td>
<td>300</td>
</tr>
<tr>
<td>KS</td>
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<td>381000</td>
<td>245000</td>
<td>11800</td>
<td>7100</td>
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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

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<th>KT</th>
<th>BSI</th>
<th>Response</th>
<th>Trom 1</th>
<th>Trom 2</th>
<th>Leuk 1</th>
<th>Leuk 2</th>
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<td>+</td>
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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

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<th>KT</th>
<th>Response</th>
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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 repeatability 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 4th 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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