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*review*

# Palliation of painful osseous metastases in patients with prostate cancer using Re-186-HEDP

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*The skeleton is the second most common site of metastases in patients with prostate cancer. While curative means are strongly limited in these patients their life expectancy may be still several years. Therefore, it is essential to improve quality of life of these patients. Sufficient therapy of painful osseous metastases is the main goal in patients with advanced prostate cancer. The primary approach to relieve bone pain is the application of peripheral or central analgesics. In case of bone pain due to a single metastatic site local external beam radiation may provide pain relief in a reasonable amount of patients. In case of painful multilocular metastases systemic application of radiopharmaceuticals may irradiate bone metastases while normal tissue is spared from β-irradiation. Due to their physical characteristics Re-186 and Sm-153 have been developed for palliative treatment of metastatic bone pain. The response rate amounts to about 70-80% of all patients treated. Pain relief may last for 1-6 months. Due to its low grade toxicity which is mainly dominated by a transient thrombocytopenia therapy can be repeated. However, Re-186-HEDP therapy does not alter life expectancy.*

*Key words: prostatic neoplasms; bone neoplasms-secondary; pain-therapy; rhenium, radioisotopes, Re-186-HEDP*

## Introduction

Prostate cancer is the second most common malignancy in men in Western Europe. The incidence is 15-16 per 100000 habitants per year with increasing tendency. As much as 80% of patients with prostate cancer will develop bone metastases.[1] In about one third of all patients osseous metastases are detected at primary staging. Moreover, the skeleton is the only single site of metastases in a reasonable amount of patients.[2] In case of multilocular osseous metastases a complete remission of prostate cancer is nearly impossible.

Since osseous metastases are often associated with bone pain effective pain relief is the primary goal when caring for patients with prostate cancer and multiple osseous metastases.[3] Traditional therapeutic approach is the application of central or peripheral analgesics in combination with neuroleptics.[4]

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Moreover, steroid medication, diphosphonates, and hormonal drugs may complete analgesics effects. However, therapy with opioids is limited in many patients due to side-effects, i.e. nausea, vomitus and gastrointestinal symptoms[5] and thus, often associated with a loss of patient's quality of life.[6]

Skeletal pain confined to single site metastases usually responds to external beam radiotherapy in 70-80 %.[4,7,8] In case of multilocular osseous metastases external beam radiation is helpful to avoid pathologic fractures or compression of the spinal cord.[9,10] However, hemibody or whole-body irradiation for pain relief is often limited by bone marrow suppression, gastrointestinal symptoms and a radiation pneumonitis.[11,12] Therefore, an effective relief of pain with low side-effects and an improvement in patient's quality of life is warranted in these patients.

## Osteotropic radionuclides

The application of β-emitting osteotropic radionuclides is a promising method to selectively irradiate osseous metastases by sparing normal tissue from short-range irradiation.[13] Due to the osteoblastic character of osseous metastases the radionuclide is predominantly accumulated in malignant transformed cells which leads to a selective irradiation of bone metastases. The first agent used for this purpose, P-32-orthophosphate, was replaced by Sr-89-chloride due to its severe bone marrow toxicity. Up to now Sr-89 is still the most commonly used agent for osteotropic radionuclide therapy.[14] Sr-89 has a long physical half-life of 50,5 days with a maximum β-energy of 1,49 MeV (Table 1). Pain relief may occur 2-3 weeks after systemic application of 1,5-2,0 MBq/kg bodyweight. However, Sr-89 has no γ-emission and thus, posttherapeutic scintigraphy imaging is not feasible. Therefore, the aim of research was to develop alternative radionuclides for palliative treatment of painful osseous metastases.

## Rhenium-186-HEDP

Re-186-hydroxyethylidendiphosphonate as well as Sm-153 (Table 1) have recently been developed for the palliative treatment of painful osseous metastases.[15] Re-186 has a therapeutic β-emission of 1,07 MeV associated with a γ-emission of 137 keV. Moreover, Re-186-HEDP and Tc-99m-HDP, that is commonly used for diagnostic bone scintigraphy, have an almost exactly similar bone distribution since both sorts of diphosphonates bridge to the hydroxyapatite of bone substance. Therefore, pretherapeutic and posttherapeutic scintigraphy is possible which allows a control of Re-186 distribution as shown in Figure 1. Re-186 has a short physical half-life of 3,8 days when compared to Sr-89. This allows a single application of activities of 1110 to 1850 MBq[16,17] with high tumor doses as well as an easy handling of radioactive waste, i.e. urine.

About 50 % of the activity injected are excreted via the kidneys into the urine within the first 6 hours post application. Nearly 70 % of the activity are urinary eliminated within the first 24 hours post application. Apart from the distribution in osseous structures Re-186-HEDP is not accumulated in any other structures of the body.

Pain relief is attained within two weeks after application of Re-186-HEDP and lasts for about 1-6 months. Response rates of Re-186-HEDP therapy of 70-80 % have been reported.[2,17,18] Especially in patients with oral medication of non-opioids analgesics rhenium-therapy led either to a reduction or to a stop of taking oral drug medication. Thus, the requirement for central analgesics may be delayed. Moreover, it is known that the clinical response is influenced by the size of osseous metastases. Pain relief mainly occurs

**Table 1.** Characters of different radionuclides used for treatment of painful osseous metases

| | P-32 | Sr-89 | Re-186 | Sm-153 |
|---|---|---|---|---|
| Physical half-life [d} | 14.3 | 50.5 | 3.8 | 1.9 |
| β-emission [keV] | 1710 | 1490 | 1070 | 810 |
| γ-emission [keV] | ø | ø | 137 | 103 |
| Tracer | phosphate | chloride | HEDP | EDTMP |
| Scintigraphic imaging | ø | ø | possible | possible |

**Table 2.** Inclusion criteria of patients for Re-186-HEDP therapy [20]

| |
|---|
| Four or more osseous metastatic sites (at last one single site presents with bone pain) |
| No diphosphonate therapy within 12 weeks |
| No irradiation within 3 weeks |
| No chemotherapy within 6 weeks |
| No change of dosis of hormone therapy within 8 weeks |
| Thrombocytes > 150000/µl |
| Leukocytes > 4000/µl |
| Creatinine < 1,3 mg/dl |
| No clinical sign of cerebral involvement |
| No heart insufficiency NYHA IV |
| Karnofsky-Index > 70 % |
| Life expectancy > 12 weeks |
| No level III oder level IV toxicity of previous rhenium-therapy (only in case of re-treatment) |

in patients with small or medium-sized metastases, whereas large metastases with soft tissue infiltration often do not respond to radionuclide therapy.[2] Therefore, the application of bone-seeking radiopharmaceuticals is a treatment option to early complete oral drug therapy. Due to the short physical half-life of Re-186 the treatment can be repeated after 4-6 months.

## Side-effects

The main radiobiological side-effect of bone seeking radionuclides is their potential bone marrow toxicity. In contrast to Sr-89 which is associated with a prolonged bone marrow suppression, Re-186 has a relatively mild hematological toxicity. Thrombocytopenia plays the major role in its bone marrow suppressing effect. The decline of thrombocytes presents with a nadir about 3 weeks post application. Prior to treatment the decrease of platelet count can be estimated for an individual patient presenting for rhenium-therapy.[19] Thus, severe hematological side-effects can successfully be avoided. In general, a control of platelet counts in a two-week interval for the duration of two months is sufficient in posttherapeutic follow-up.

## Patient management

Several days before the therapeutic administration of Re-186-HEDP the patients undergo conventional bone scintigraphy with labeled diphosphonates, e.g. 600 MBq Tc-99m-HDP. In case of multilocular, osseous metastases with at least four metastatic sites and at least one single painful lesion rhenium-therapy is indicated if the patient fulfills inclusion criteria[20] as given in Table 2. Due to its potential bone marrow suppression

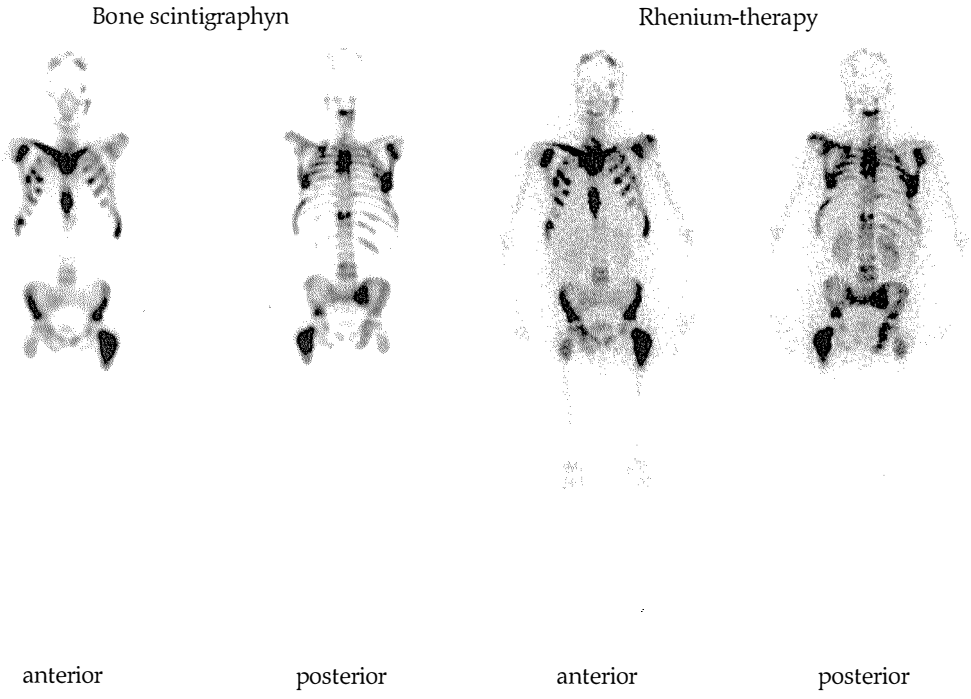


**Figure 1.** 64-year-old patient with multilocular bone metastases of a primary prostate cancer. The patient claimed about pain of the left femur and both scapulas. Left scintigram: Pretherapeutic conventional whole-body bone scintigraphy 3 hrs after application of 600 MBq Tc-99m-HDP i.v. Note tracer accumlations of the skull, the ribs, the sternum, the bassin, both proximal femurs, and the spinal column corresponding to sites of osseous metastases. Right scintigram: Posttherapeutic whole-body scintigraphy 48 hrs after application of 1.3GBq Re-186-HEDP i.v. Note distribution of Re-186-HEDP corresponds to osseous metastatic sites.

patients with thrombocytes below 150000/µl have to be excluded from therapy. In clinical routine, the blood count is defined directly prior to rhenium-application. If there are no contraindications, 1.3 GBq Re-186-HEDP with a total volume of about 2 ml are administered via an intravenous line. 48 hrs post application a whole-body scintigraphy with a scan-speed of 6 cm/min is obtained in order to evaluate the distribution of the bone-seeking Re-186-HEDP.

## Conclusion

Palliative Re-186-HEDP therapy of multilocular, painful osseous metastases in patients with prostate cancer is a sufficient therapeutic modality for pain alleviation with low toxicity, thereby increasing patient's quality of life. However, life expectancy will not be affected.

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