RHENIUM-186-HEDP DOSIMETRY AND MULTIPLE BONE METASTASES PALLIATION THERAPY EFFECTS

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1. Introduction

Skeletal metastases are a most common form of metastatic cancer, appearing in the vast majority of patients with breast and prostate cancer and frequently in patients with lung cancer, renal cancer, thyroid cancer and multiple myeloma. These metastases are a major cause of serious morbidity resulting in severe bone pain, hypercalcemia, loss of function following pathological fractures and neurological symptoms from nerve compression [1]. Since survival of these patients is estimated up to 4 years, more in some cases, improving quality of life by pain palliation is the main goal.

Although bone pain, confined to single sites, usually responds favorably to local external beam radiotherapy, in cases of widespread bone metastases where half – or whole – body irradiation is appropriate, considerable side effects such as bone marrow suppression, gastrointestinal symptoms and radiation pneumonitis are caused by the fact that all irradiated tissues receive similar doses. Therefore delivering high doses to tumor cells while limiting radiation dose to normal tissue, is the key for successful palliation [1,2,3].

Such a combination can be achieved with the application of beta – emitting radionuclides conjugated to bone – seeking pharmaceuticals, such as pyrophosphate analogues. Rhenium – 186(Sn) – 1,1 hydroxyethylidene diphosphonate (^{186}Re – HEDP) is a radiopharmaceutical that combines selective localization in osteoblastic skeletal metastases with favorable radiation characteristics concerning pain palliation as well as dosimetric estimations and scintigraphic imaging . Unavoidable red marrow toxicity is limited to transient and reversible thrombocytopenia while leucopenia plays only a minor role [4], both enabling multiple administrations after appropriate time intervals.

2. Properties of ^{186}Re – HEDP

2.1 Physical Properties of ^{186}Re

Rhenium – 186 is a mainly beta – emitting radionuclide with a physical half – life of $T_{1/2}$ = 89,3 hr (3,78 d). Its main beta – emissions have maximum energies of $E_{max,1}$= 1,077 MeV (71%) and $E_{max,2}$ = 0,939 MeV (22%) respectively. These energies show beta particles with short ranges in tissue, capable of delivering high doses to regions of high Re – concentrations while sparing adjacent regions thus making the irradiation well tolerated for the patient [1–3].

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The relatively short physical half – life combined with the beta emissions allow the delivery of relatively high dose rate for a short period of time in areas of concentration. Furthermore its short half – life not only makes ^{186}Re – HEDP capable of administration on an outpatient basis, but also reduces the problems of radioactive waste handling and storage[5].
Along with the beta – emissions there is a gamma – emission of energy E_γ= 137keV (9%) as well, enabling scintigraphic imaging during therapy and biodistribution assessment for patient – specific dosimetry calculations [1–3,6,7].

2.2 Uptake and Biokinetic Properties of ^{186}Re – HEDP

Rhenium – 186 – HEDP is a radiopharmaceutical designed to concentrate on osteoblastic skeletal metastases by bridging the hydroxyapatite crystals [6]. Therefore the extent of bone uptake and residual retention is the main determinant of both pain relief and radiation damage to bone marrow.
A sensitive and well – established method of bone uptake quantification is measurement of whole – body retention at 24h after injection but since soft – tissue retention of diphosphonates is known to be as high as 30% of whole – body retention, it seems appropriate to measure soft tissue retention and net bone uptake[8].
A study performed on 11 patients (9 males – 2 females) with multiple bone metastases who received a bolus injection of 1295MBq of ^{186}Re – HEDP, using quantification methods of whole – body scintigraphic images, showed mean bone uptake 13,7% ± 8,6% at 3h after injection increasing to 21,8% ± 9,0% at 24h after injection. The corresponding values for soft – tissue retention and urinary excretion were 49,4% ± 16,9% and 36,9% ± 14,4% respectively at 3h after injection, reaching 12,8% ± 5,4% and 65,3% ± 12,8% respectively at 24h after injection [8].
On another study performed on rabbits receiving high doses of 400MBq/kg of body weight utilizing similar quantification methods, the mean bone uptake, soft – tissue retention and urinary excretion were 31,2% ± 1,5%, 16,2% ± 2,7% and 52,6% ± 3,4% respectively at 24h after injection [9].

3. Dosimetry Estimations

Radiation dose estimation from bone – seeking radiopharmaceuticals is a difficult problem with various patient – specific parameters. Soft tissue and bone intermixture geometry is quite complex itself without taking into account the fact that in patients with bone metastases, normal bone marrow distribution is disturbed by the metastases [1]. Furthermore biodistribution parameters such as skeletal uptake, soft tissue retention, cumulated activity etc often vary from one patient to another, making patient – specific measurements necessary for accurate dose estimations [7,8].
Gamma – camera images (whole – body scintigrams and SPECT) of radiopharmaceutical distribution in patients injected with Re – 186 HEDP, Re – 188 HEDP, Sm – 153 EDTMP, Sr – 89 Chloride and Sn – 117m DTPA were analyzed to measure activity in

specifically selected normal and metastatic regions of interest [7]. Calculations based on the MIRD schema, gave values of absorbed dose per unit volume (voxel) for metastatic and normal bone tissue, for all the radiopharmaceuticals studied. Further analysis of these values lead to calculations of 2 important parameters: *metastatic/normal bone absorbed dose ratio* (M/B ratio) and *bone/red marrow mean absorbed dose ratio* (B/RM ratio). M/B ratio provides valuable information in assessing tumor – control probability, normal tissue toxicity and radiopharmaceuticals' qualification and superiority whereas B/RM ratio displays the red marrow toxicity induced by the radiopharmaceutical, a key issue for the success of the radiopharmaceuticals' therapeutic use. All calculated values are presented in the following table (Table 1)

Table 1. Absorbed dose calculated values for 5 different bone - seeking radiopharmaceuticals

Radiopharmaceutical	Normal bone absorbed dose (mGy/MBq/Voxel)	Metastatic lesion absorbed dose (mGy/MBq/Voxel	M/B[1] Ratio	B/RM[2] Ratio
Re – 186 HEDP	**3,12**	**16,2**	**5,2**	**3,4**
Re – 188 HEDP	**1,80**	**9,0**	**5,0**	**1,9**
Sm – 153 EDTMP	**3,80**	**22,8**	**6,0**	**5,5**
Sr – 89 Chloride	**1,20**	**10,8**	**9,0**	**1,1**
Sn – 117m DTPA	**11,60**	**57,1**	**4,9**	**3,1**

[1]*Metastatic/Normal bone tissue absorbed dose ratio*
[2]*Bone tissue/Red marrow absorbed dose ratio*

In another study red marrow absorbed dose estimations were performed in 10 patients with scintigraphic and radiological evidence of at least 4 bone metastases. From this group of patients 80% had histologically confirmed prostate cancer and entered a Re – 186 – HEDP dosage escalation subgroup, while the rest 20% received fixed activities of 1295MBq [1].

Estimations were based on the MIRD schema after S – values and cumulated activities were calculated independently. Calculation of S – value from trabecular bone to red marrow was based on previously reported data while S – values for cortical bone, red bone marrow and the remainder of the body to the red marrow were tabulated from MIRDOSE2 computer program after appropriate modifications were made on the source code and decay files to account for Re – 186 photon emissions and 1,5kg red marrow mass. Cumulated activities were calculated from measurements of activity excreted in the urine and application of 2 different methods: the noninvasive and the pharmacokinetic method. According to the noninvasive method total body cumulated activity ($\tilde{A}_{TB}$) is the difference between injected activity and excreted activity, while trabecular ($\tilde{A}_{TrB}$) and cortical bone ($\tilde{A}_{CrB}$) cumulated activities are equal to each other and:

$$\tilde{A}_{TrB} = \tilde{A}_{CrB} = 0{,}5 * \tilde{A}_{TB}$$

According to the pharmacokinetic method the cumulated activity calculated using the previous method is corrected for blood cumulated activity ($\tilde{A}_{Bl}$) and red bone marrow cumulated activity ($\tilde{A}_{RM}$) so that:

$$\tilde{A}_{TrB} = 0{,}5 * (\tilde{A}_{TB} - \tilde{A}_{Bl} - \tilde{A}_{RM})$$
$$\tilde{A}_{RM} = 0{,}3 * 1{,}5 * \tilde{A}_{Bl}/6$$

Red marrow absorbed doses (D_{RM}) derived from these calculations for each patient along with the percentage of decrease in peripheral platelet count (**%DEC**) are listed in the following table (Table 2). In the same table administered activity ($\mathbf{A_{adm}}$) for each patient and mean red marrow absorbed dose per unit of administered activity ($\mathbf{D_{RM}/A_{adm}}$) are listed as well.

Table 2. Administered activities and calculated red marrow absorbed doses using a noninvasive and a pharmacokinetic approach. Percentage of platelet decrease for each patient is also listed.

Patient No.	A_{adm} (MBq)	$D_{RM,noninvasive}$ [1] (Gy)	$D_{RM,pharmacokinetic}$ [2] (Gy)	%DEC
03P330	1252	1,11	1,06	33
05P330	1834	2,61	2,53	61
07P330	1865	2,08	2,01	69
11P330	2353	2,09	1,93	34
12P330	2339	1,86	1,80	64
14P330	2373	2,38	2,19	64
15P330	2914	3,08	2,95	68
16P330	2911	3,55	3,41	46
03P341	1310	1,49	1,43	22
04P341	1163	1,35	1,29	28
D_{RM}/A_{adm} (mGy/MBq)		**1,07 ± 0,19**	**1,02 ± 0,19**	--

[1] *Red marrow absorbed doses from calculations using the noninvasive approach*
[2] *Red marrow absorbed doses from calculations using the pharmacokinetic approach*

This study went a step further by determining the 50% effective red marrow absorbed dose (ED_{RM50}) to be 2,09 Gy, i.e. absorbed dose of 2,09 Gy by the red marrow will lead to 50% decrease of peripheral platelet count. In the same study adjusting the bone marrow mass for each patient gives a value of 1,95 Gy for ED_{RM50}.
On another study performed in 20 male patients with advanced prostate cancer, who received a mean administered activity of 1225MBq i.v., absorbed doses by tumor and bone marrow were calculated. The mean values for tumor and marrow absorbed dose were 40,4Gy (32,98mGy/MBq) and 1,81Gy (1,48mGy/MBq) respectively [10].

Other studies calculated mean bone marrow absorbed dose to be 0,92mGy/MBq, 0,75Gy/1295MBq and 2Gy/3515MBq of administered activity [1,2,11].

4. Effects from Re – 186 HEDP Use in Bone Pain Palliation

4.1 Palliative effects of Re – 186 HEDP

Although external radiation therapy can provide significant palliation in about 80% of patients with osseous metastases the amount of body that can be subjected to such radiation is limited, even with regional or hemi – body fields. Nausea, vomiting or diarrhea, occur in about half of patients and hematopoietic toxicity in about one – third of patients treated with hemi – body irradiation [3,12,13].
Therefore application of bone – seeking radiopharmaceuticals emitting medium – to high – energy beta particles is a promising substitute for hemi – or whole – body external radiotherapy due to the fact that internal irradiation from such a radiopharmaceutical can deliver high doses to metastatic lesions providing pain relief while relatively sparing normal tissues [1,2]. Initial trials indicated that there were prompt, significant improvements in the quality of life in 80% of patients treated with a single intravenous injection of Re – 186 HEDP. Response times as well as response rates were similar to those reported after hemi – body external irradiation [3,10,14].
Human studies suggested that a 1120 – 1295MBq administration of Re–186 HEDP would result in relief of pain without significant bone marrow toxicity and with tumor/marrow dose ratios that were higher than those achieved with Sr – 89 Chloride [3].
In a study already mentioned, from a group of 20 patients injected with 1225MBq of Re – 186 HEDP resulting in a mean tumor dose of 40,4Gy, 25% of them had complete pain relief, 55% of them had partial pain relief and the remaining 20% showed no improvement of pain [10].
A double – blind crossover comparison of Re–186 HEDP with Tc–99m MDP as placebo, in 13 patients (6 patients receiving Re–186 HEDP initially and then placebo and 7 patients vice versa), demonstrated that the average percent overall decline in the pain index for all patients was 40% following the Re–186 HEDP injection while there was no essential change following placebo [3]. The same study showed also greater decrease in analgesic index after Re–186 HEDP in comparison with placebo.
In another study of 60 patients with painful bone metastases from different tumor types were treated with 1406MBq Re–186 HEDP and after treatment they were followed up clinically at weekly intervals for the first month and monthly thereafter up to 1 year, until death or full response. Fifty-five patients received a single injection and 5 patients with prostate cancer were treated twice, resulting in a total of 65 therapeutic cycles [6]. A minimum interval of 6 months from cessation of previous therapeutic regimens, such as chemotherapy or external radiotherapy, was required before patients could enter the study. The aim of the study was to evaluate short – and long – term effects of Re–186 HEDP in pain relief, tumor markers, alkaline phosphatase level, platelet and white blood cell counts.
Overall prompt relief of pain occurred in 52 of 65 (80%) total treatments and in 49 of 60 (82%) first treatments. More detailed results concerning response rates in different tumor

histotypes are listed in the following table (Table 3). Clinically evident pain relief occurred within 1 week, with a median time to onset of 3 days. Significant improvement versus pre – therapy values was observed for a modified Wisconsin test and for Karnofsky index (pain relief markers) at the start of the third week. Twenty patients (36%) experienced a mild transient increase in pain, i.e. a flare response, within 48 hours of injection that resolved within 24 – 48 hours. No patients showed neurologic signs of nerve compression. Duration of pain relief ranged from 3 weeks to 12 months (mean 72 days, median 60 days).

Table 3. Response rates in different tumor histotypes after treatment of 60 patients with 1406MBq Re - 186 HEDP

Response	Prostate	Breast	Others
Global	78 (64 – 88)	90 (55 – 99)	80 (28 – 99)
Complete	30 (17 – 44)	20 (2 – 55)	60 (14 – 19)
Partial	32 (19 – 46)	50 (18 – 81)	20 (0,5 – 7)
Minimal	16 (7 – 29)	20 (2 – 55)	0
None	22 (11 – 36)	10 (0,2 – 44)	20 (0,5 – 7)

Values are percentages
Values in parentheses represent 95% Confidence Intervals

Within the first month tumor markers (PSA and Ca 15.3) decreased in more than 45% of cases, remained unmodified in about 15% of cases and progressively increased in the remaining cases. Alkaline phosphatase levels decreased as well during the first month.
After the first month performance score improved in 32 patients, remained steady in 20 patients and worsened in 8 patients. In 23 of 49 responders pain relief persisted beyond 2 months. Alkaline phosphatase levels remained significantly decreased for 2 months and increased progressively afterwards. Tumor markers showed wide variations with an ambiguous pattern. Only 10 patients showed a marked decrease in PSA levels persisting for more than 3 months. In 22 patients no new sites of metastases were observed on their bone scan obtained 3 – 6 months after therapy. These findings may be consistent with a possible weak tumorcidal effect and agree with preliminary data from an animal model exploring Re–186 HEDP on tumor progression. In addition to that the fact that the more prolonged and intense pain relief was observed in patients with an earlier phase of the disease, indicates a possible therapeutic effect on micrometastases and on disease progression [15].
Another study suggested the importance of a more complete pain component evaluation and used a multi – dimensional pain evaluation model to objectify the effects of escalating doses of Re–186 HEDP, reporting an overall response of 54% [16].

4.2 Side – effects from therapeutic use of Re -186 HEDP

Because Re–186 HEDP delivers a substantial dose to bone marrow, bone marrow toxicity will be the dosage limiting factor. In most cases marrow toxicity is limited to temporary

myelosuppression confined mainly to thrombocytopenia while leucopenia plays only a minor role.

In the previously mentioned study of 60 patients with painful bone metastases from different tumor types who were treated with 1406MBq Re – 186 HEDP, a WHO grade 1 – 2 hematologic toxicity was apparent with a decrease in the mean platelet (32%) and mean leukocyte (18%) counts at 3 and 4 weeks respetively. In all patients platelet and white blood cell counts returned to baseline levels within 8 weeks after administration of Re – 186 HEDP [6].

In another study mentioned also before, absorbed bone marrow doses were related to the percentage of decrease in peripheral platelet count at the lowest point as reference for toxicity [1]. This relationship was described using the pharmacodynamic sigmoid E_{max} model since it is the simplest model that adequately describes drug effect over the whole range of concentrations. According to this model and the noninvasive approach the percentage of decrease in peripheral platelet count (%DEC) is related to red marrow absorbed dose (D_{RM}) by the following formula:

$$\%DEC = \frac{100 \cdot D_{RM}^{1,29}}{D_{RM}^{1,29} + 2{,}09^{1,29}}$$

In this formula 2,09 represents the effective red marrow absorbed dose in Gy that will lead to 50% decrease in peripheral platelet count (ED_{RM50}). The formula has an r – value of 0,8 which improves slightly when bone marrow mass is adjusted for each individual patient using the lean body mass (r = 0,84) with a slight decrease in ED_{RM50} (1,95Gy).

In a group of 39 prostatic cancer patients with multiple painful bone metastases who were injected with activities ranging from 1104 to 3479MBq of Re–186 HEDP a study was performed to correlate percentage decrease in platelet count (%DEC) to administered activity normalized to standard body surface of 1,73m^2 (ADN) as well as to bone scan index (BSI) [2]. Bone scan index is an index of the extent of metastatic disease and was determined from a diagnostic whole – body scintigram with Tc – 99m HDP two weeks prior to therapy.

Regression analysis showed a functional relation (R = 0,78; p < 0,001) of %DEC with BSI and AND expressed by the following formula:

$$\%DEC = (0{,}018 \cdot ADN) + (0{,}714 \cdot BSI) - (0{,}008 \cdot BSI^2) + 2{,}994$$

This formula clearly demonstrates that BSI is an important parameter, since ADN alone does not adequately predict %DEC, but its influence on platelet decrease seems to diminish for BSI values >50. This can be explained by the fact that patients with extensive metastatic disease will develop an impaired bone marrow function, leading to the so – called marrow expansion in the midshaft of long bones.

Another important result from this study is that a maximum tolerable administered activity can be calculated for each individual patient by an appropriate modification of the previous formula. A maximum %DEC ($\%DEC_{max}$) for each patient can be introduced

by patient's baseline count (PBC) and a lowest acceptable platelet count (LAPC) set by the treating physician (e.g. $75*10^9$/liter) from the following equation:

$$\%DEC_{max} = (1 - \frac{LAPC}{PBC}) \cdot 100$$

Maximum tolerable administered activity (A_{max}) can then be calculated by the following formula:

$$A_{max}(MBq) = \frac{(BSA \cdot \%DEC_{max}) - (0{,}714 \cdot BSI) + (0{,}008 \cdot BSI^2) - 2{,}994}{0{,}018 \cdot 1{,}73}$$

BSA stands for patient's body surface area and is calculated by:

$$BSA(m^2) = 0{,}2025 \cdot BW^{0{,}425}(kg) \cdot H^{0{,}725}(m)$$

BW is the patient's body weight and H his/her height [17].
Platelet decrease after the second injection was 49% ± 19% compared to 41% ± 16% observed after the first treatment in these patients and although these values are not significantly different there seems to be tendency to for a slightly higher platelet decrease after repeated treatment. Therefore the formula can also be used for second treatments but with some reservation.
A common ground in most of the studies mentioned was the fact that patients who had received prior external radiotherapy to the skeleton did not show a more severe drop in platelet count compared to those who were not previously irradiated [1 – 3].

5. Conclusion

The use of Re–186 HEDP in bone pain palliation from multiple metastases has proved to highly justified and efficient, reaching response rates of up to 80% of the patients treated with it, lasting from 3 weeks to 12 months . In addition to pain relief, several other parameters such as tumor markers or new sites of metastases, stressed out further the therapeutic effects of Re–186 HEDP. These results along with Re–186 HEDP properties and the fact that the main side effect was a reversible thrombocytopenia appearing in the third or fourth week post – injection and lasting up to the 8th week, demonstrate that repeated treatments would be a common approach in the future.
Patient – specific dosimetry with gamma – camera quantification methods can give the necessary data to the treating physician in order to determine the optimum activity dosage for each patient, enhancing the therapeutic efficacy while minimizing toxicity side effects.

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