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Research Article

Dosimetry and Therapeutic Ratios for Rhenium-186 HEDP

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Rhenium-186 (Re-186) is a β-emitting radionuclide. Emitted β-particles have ranges up to 4.5 mm in tissue, capable of delivering high doses to skeletal regions of high Re-186 concentrations while sparing adjacent radiosensitive regions and thus making the irradiation well tolerated for the patient. Along with the β-emissions, γ-rays are emitted having an adequate energy for imaging during therapy and biodistribution assessment for patient-specific dosimetry calculations. The relatively short physical half-life combined with the β-emissions allows the delivery of relatively high activity rate for a short period of time in areas of concentration. This study is a short review concerning the palliative treatment of skeletal metastases using ^{186}Re-HEDP. After presenting the dominant ways of ^{186}Re production, special emphasis is given to dosimetry issues while the effect of palliation therapy can be evaluated through the comparison of the absorbed dose in metastatic lesion relatively to the normal bone region. Accurate dose estimation is required taking into account the anatomic individual difference of each patient. For this purpose a patient specific dosimetric model considering metastatic lesions as spherical nodules is introduced. In order to quantify in a representative way the results of palliation treatment, the concept of therapeutic ratios is analyzed.

1. Production of Re-186

Re-186 can be produced either at a nuclear reactor or at a particle accelerator (cyclotron). The first method utilizes neutron capture of enriched Re-185 $^{185}\text{Re}(n,\gamma)\,^{186}\text{Re}$ [1, 2]. Although the thermal and epithermal cross-sections for neutron capture are high (106 and 1632 barns, resp.), the specific activity of Re-186 required for antibody labeling is hardly achieved using low neutron flux reactors. However, it is marginally sufficient for preparation of phosphonates for palliative treatment of bone pain from osseous metastases. Re-186 when produced at a nuclear reactor is in carrier-added form. To prepare the target material, rhenium metal is dissolved in either concentrated nitric acid or hydrogenperoxide and then it reacts with aluminum chloride to yield the aluminum perrhenate solution $[\text{Al}(\text{ReO}_4)_3]$. The solution is irradiated in neutron flux and dissolved in sterile water. The chemical recovery exceeds 90% in the chemical form of $^{186}\text{ReO}_4^-$.

Because very few of reactors with higher neutrons fluxes are operating in the world, methods of enhancing the specific activity of Re-186 by other means are desirable. In spite of the advantages of isotope production at reactors in terms of quantity and unit cost, cyclotrons remain the most appropriate sources for radionuclides production. Cyclotrons have the unique ability of producing radionuclides that decay by electron capture or positron emission, in non-carrier-added form. In this case, Re-186 is produced mainly via proton bombardment of natural tungsten W-186 as target, $^{186}\text{W}(p,n)\,^{186}\text{Re}$ or $^{186}\text{W}(d,2n)\,^{186}\text{Re}$ [3]. Because of the considerable discrepancies in the literature, the excitation function of the above reaction was remeasured [4–6]. In non-carrier-added form, Re-186 is separated radiochemically from enriched W-186 (96.9%) targets using high-purity methyl ethyl ketone (MEK) after irradiation of targets with protons. The ^{186}Re-MEK is then loaded onto a small alumina column to separate the resulting non-carrier added Re-186 from any remaining W-186 and its radionuclidic purity approximates 99,6%. Cross sections for the production of Re-186 from natural tungsten have been measured using the stacked foil technique for proton energies up to 17.6 MeV [3].

Table 1: Physical properties of rhenium-186.

Property	Re-186
Physical half-life	89.3 h
Daughter nuclei (branching ratios)	W-186 (7.5%) Os-186 (92.5%)
Mean beta energy	346,7 keV
Max. beta energy (abundance)	1077 keV (71%) 939 keV (22%)
Gamma energy (abundance)	137 keV (9%)
Max. penetration in tissue	4.5 mm (average 1.1 mm)

2. Radiopharmaceutical Form and Biokinetics

Re-186 physical properties are demonstrated in Table 1. The Re-186 HEDP (1-hydroxy-ethylidene-1,1 diphosphonic acid) complex, provided by Mallinckrodt Medical Inc. (St. Louis, MO), is widely used for palliative treatment of bone metastases originating from breast or prostate cancer. It is preferred with regard to toxicity, pharmacokinetics, and bone marrow dosimetry as well as the palliating effect on bone pain [8, 9]. Advances in imaging enable evaluation of the spatial distribution of radioactivity in tumors and normal organs over time [10]. HEDP is taken up as a bone mineral metabolite. In vivo, it is mainly concentrated on primary and metastatic bone lesions. Concerning the uptake and biokinetic properties, a sensitive method of bone uptake quantification is measurement of whole-body retention at 24 h 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 [4]. The bone uptake is measured by scintigraphic images taken in a sequence 24 h to 5 days after administration. The relatively short physical half-life combined with the beta emissions allows the delivery of relatively high dose rate within a short period of time in areas of concentration. Furthermore, problems of radioactive waste handling and storage are significantly reduced compared to long-living isotopes of iodine. The mean skeletal uptake was found to be about 55% of the injected dose.

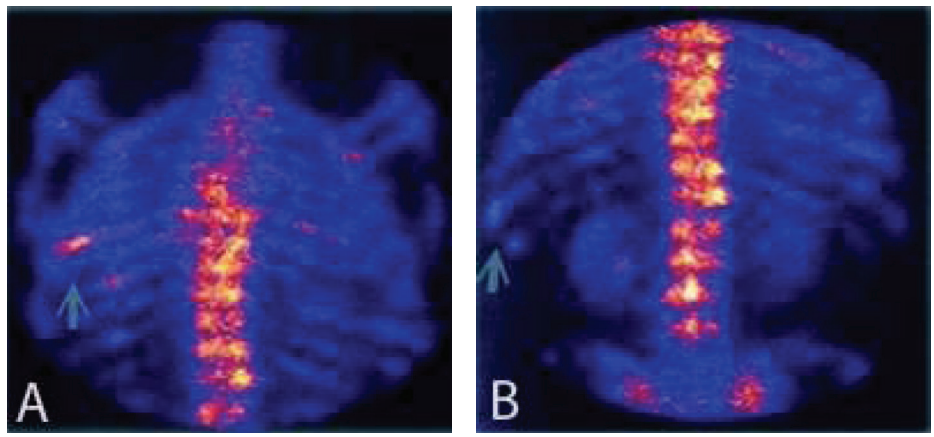
3. Clinical Applications

Skeletal metastases are the most common 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. Bone pain, hypocalcaemia, loss of function following pathological fractures, and neurological symptoms from nerve compression are some of the effects of these malignancies. Re-186 palliative treatment is recommended to patients with persisting bone pains after chemotherapy or external beam therapy and having life expectancy at least 6 months (corresponding to Karnofsky index over 30%). Pregnants, patients under 18 years old, subjected to chemotherapy or having renal failures should be excluded. Treatment is usually performed in accordance with the detailed guidelines of the European Association of Nuclear Medicine regarding radionuclide administration for palliative purposes [11]. Studies of bone metastases from breast and prostate cancer showed palliation of bone pain in more than 90% of patients treated with ^{186}Re-HEDP whereas the maximum tolerated dose of HEDP appears to be 65 mCi (2.405 GBq) [12–14]. A randomized controlled trial of ^{186}Re-HEDP versus placebo administration showed a significantly higher rate of pain responders (65% versus 36%, resp.) [15]. Moreover, the number of patients in this study requesting palliative external beam radiotherapy was higher in the placebo group than in the treatment group (67% versus 44%). Recent investigations also showed that a scheme of repeated administration of ^{186}Re-HEDP [16, 17] appears to be both safe and more effective in select patients. The results of palliation treatment with Re-186 HEDP are demonstrated in bone scintigraphies of a patient in Figure 1. The improvement of a metastatic lesion (marked by the arrow) in the rib (Figure 1(a)), after two administrations of Re-186 HEDP, is apparent (Figure 1(b)). The emitted particles following Re-186 decay enable not only the delivery of dose required for metastases therapy (β-particles) but also the imaging of radiopharmaceutical biodistribution (γ radiation). In other studies the pain response and hematologic toxicity between single and multiple therapies with ^{186}Re-HEDP under zoledronic acid in patients suffering from painful osseous metastases from prostate or breast cancer were investigated, whereas the predictive value of various bone formation and resorption markers in patients with bone metastases from prostate cancer after palliative treatment with ^{186}Re-HEDP was also evaluated [18–20]. The delivery of a substantial dose to bone marrow may result in marrow toxicity side effects, for example, thrombocytopenia or most rarely leucopenia. The baseline white blood cells and platelets counts are 4×10^9/L and 100×10^9/L. Patients with counts below the baseline values and with serum creatinine above 0.15 mmol/L indicating a severe renal failure, should be excluded. Platelets and white blood cells counts decrease during therapy; however, according to Sciuto et al. a restoration to normal levels is achieved within 8 weeks after administration [21].

4. Dosimetry Calculations

A successful palliative treatment requires a high dose to tumor but a minimal dose to normal tissues. ^{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.

The MIRD schema is widely accepted for absorbed dose calculations in the scale of human organs. Summing up the contribution of each source region to the target and the contribution of the target region itself gives the target absorbed dose [22]. The mean absorbed dose can be roughly estimated by the use of standard biokinetic models, that deviate considerably from the proper one for each patient's size and physiology.



(a) (b)

Figure 1: Posterior views of first and second Re-186 HEDP administrations in time interval of 6 months (courtesy of our department).

For systematic radiotherapy patient-specific dose calculation is essential. Internal dosimetry based on 3D images involves the use of patients own anatomy and spatial distribution of radioactivity over time to obtain an absorbed dose calculation that provides as output the spatial distribution of absorbed dose. The results of such a patient-specific 3D imaging-based calculation can be represented as a 3D parametric image of absorbed dose, as dose-volume histograms over user-defined regions of interest, or as the mean (or range) of absorbed doses over such regions. A number of groups have pursued and contributed to 3D imaging-based patient-specific dosimetry [23, 24]. The standard phantom geometry was modified to include on-line Monte Carlo calculation and therefore the ability to adjust tumours and organ masses and shapes.

For internal dosimetry of photons and electrons, the parameters influencing the organ doses are mainly the relative position of source and target organs (for photon organ cross-fire) and organ mass (for organ self-absorption). As a consequence of these findings, the ICRP decided to use voxel phantoms for the update of organ dose conversion coefficients. Voxel models, introduced during the last two decades, are derived mostly from (whole-body) medical image data of real persons instead of the older mathematical "MIRD-type" body models and are currently the state of the art for the update of dosimetry calculations encompassing organ topology masses and dimensions of the male and female reference adults [25–28]. The skeleton is considered as a complex structure of the body, composed of cortical bone, trabecular bone, red bone marrow and yellow bone marrow, cartilage, and endosteum ("bone surfaces").

However, the dimensions of the trabecular, the cavities containing bone marrow, and the endosteum layer lining these cavities are clearly smaller than the resolution of a normal CT scan and, thus, these volumes could not be segmented in the voxel models. Therefore, the skeletal dosimetry has to be based on the use of fluence-to-dose response functions that are multiplied with the particle fluence inside specific bone regions to give the dose quantities of interest to the target tissues [29, 30].

MIRDOSE 3.1 software calculates absorbed dose per cumulative activity (S values) using anthropomorphic phantoms [31]. The calculation is fast, and dose estimation is accurate and patient-specific, as residence times are calculated separately for each patient from his own planar images. Analogous techniques are currently implemented in the RADAR (http://www.doseinfo-radar.com/) and OLINDA/EXM software using the stylized phantom series of the Oak Ridge National Laboratory (ORNL) [32, 33].

The target tissue that are needed in the skeleton for dose calculations are the endosteum and the red bone marrow. For radionuclides that are accumulated in the skeleton, cortical and trabecular bone as well as yellow bone marrow are also sources that should be taken into account [34]. In last decade studies gamma-camera images (whole-body scintigrams and SPECT) of radiopharmaceutical distribution, in patients injected with ^{186}Re-HEDP, were analyzed to measure activity in specifically selected normal and metastatic regions of interest [7, 8, 35]. According to the study [7], dosimetric calculations have been performed in 11 patients after receiving a bolus injection of 35 mCi (1.295 GBq). Spot volume for each lesion was determined after reconstruction of tomographic slices, by adding the number of voxels of each slice. Volume estimation was evaluated using phantoms of known volume with ^{99m}Tc inside as a tracer. Total volume accuracy was found to be 4.8%. Gamma camera was calibrated in order to convert the count rate that was measured from planar images to activity according to the function

$$A = \frac{R_{\text{ant}} R_{\text{post}}}{T} \frac{1}{2} \frac{f}{E}, \tag{1}$$

where R_{ant}, R_{post} are the measured count rates from anterior and posterior images. Count rate is corrected with the transmission factor $T = e^{-\mu L}$, where L is the patient's body parameter and μ is the linear absorption coefficient for water. The gamma-camera sensitivity, due to collimator and dead time, is represented by E. Factor f was required to take into

account the radiation self-absorption by the source [36]. It is calculated from the function

$$f = \frac{y}{\sinh y}, \quad y \equiv \frac{\mu d}{2}, \tag{2}$$

where d is the anterior-posterior size of the source target. The count rates were measured with manually drawn regions of interest for liver, spleen, kidneys, and tumour. Background count rate was measured close to regions of interest and a simple background subtraction method was performed. Cumulative activity in *MBq hr* was measured from the area between activity curve for each source organ and time axis. Consequently, residence times τ are given by $\tau = \widetilde{A}/A_0$ (A_0 is the total injected activity) for each source organ. The renal excretion of ^{186}Re-HEDP is determined by collecting urine at intervals of 3–12 h over a time period of 72 h after the infusion of the isotope. In this study cumulated activities were calculated from measurements of activity excreted in the urine and the applications of 2 different methods, the noninvasive and the pharmacokinetic methods. According to the noninvasive method total body cumulated activity ($\widetilde{A}_{\mathrm{TB}}$) is the difference between injected activity and excreted activity, while trabecular ($\widetilde{A}_{\mathrm{TrB}}$) and cortical bone ($\widetilde{A}_{\mathrm{CrB}}$) cumulated activities are equal to each other and

$$\widetilde{A}_{\mathrm{TrB}} = \widetilde{A}_{\mathrm{CrB}} = 0.5\widetilde{A}_{\mathrm{TB}}. \tag{3}$$

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

$$\widetilde{A}_{\mathrm{TrB}} = 0.5\left(\widetilde{A}_{\mathrm{TB}} - \widetilde{A}_{\mathrm{Bl}} - \widetilde{A}_{\mathrm{RM}}\right), \qquad \widetilde{A}_{\mathrm{RM}} = 0.075\widetilde{A}_{\mathrm{Bl}}. \tag{4}$$

Calculations based on the use of MIRDOSE 3.1 software, considering metastatic regions as spheres (nodule module), gave values of absorbed dose per unit volume (voxel) for metastatic and normal bone tissue.

The next step after dosimetric calculation is to reveal the significant correlation between bone uptake rate and therapeutic effect. An index of the normal bone absorbed dose per activity (mGy/MBq) per volume unit (N/V) and the same of metastatic lesions (M/V) were determined. Further analysis of these values leads to calculations of two important parameters: metastatic/normal bone absorbed dose ratio (M/N ratio) and bone/red marrow mean absorbed dose ratio (B/RM ratio). M/N 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. Calculated mean ratios are presented in Table 2 [7]. The selective concentration of ^{186}Re-HEDP in metastatic lesions conserving the normal bone issue is apparent from mean values of metastatic/normal bone absorbed dose ratio (M/N) and bone/red marrow absorbed dose ratio (B/RM). For each lesion volume, accurate

Table 2: Re-186 HEDP therapeutic ratios.

Re-186 HEDP ratios	N/V	M/V	M/N	B/RM
Mean value	3.12	16.2	5.2	3.4

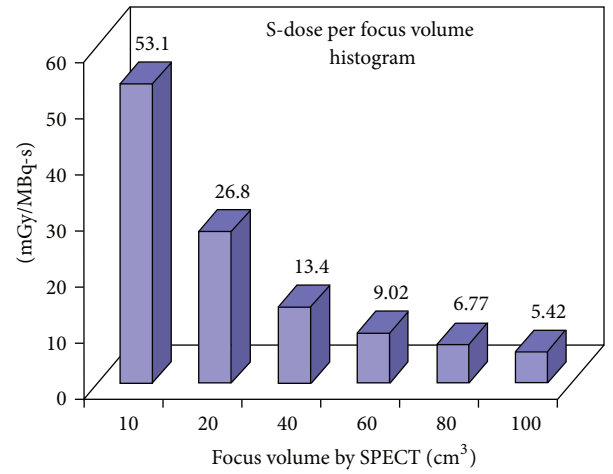


Figure 2: Dose Rate per Focus Volume (*S*-dose) from image processing data. The absorbed dose per activity is higher in small volumes [7].

foci volume and the dose rate are calculated using SPECT radionuclide distribution in defined ROIs. The results are presented in Figure 2 [7]. The smaller the lesion volume the higher the dose per activity is absorbed. Absorbed dose distribution, along with time-dose rate curves, was derived for both metastatic lesions and normal bone regions. In Figure 3 the estimated result of palliation therapy is shown. The absorbed dose per activity was estimated to be 5.8 times greater to metastatic lesions than to normal bone tissue (see also [37]). This is exactly the aim of a successful treatment and is clearly demonstrated by defining therapeutic ratios.

5. Discussion and Conclusions

Apart from ^{186}Re, there are other radionuclides suitable for therapeutic purposes, having appropriate decay characteristics and biochemical reactivity. Strontium-89 is the most commonly used radionuclide in the treatment of metastatic bone cancer. It is a β-emitter, having a physical half-life of 50.5 days and maximum β particle energy of 1.46 MeV. The maximum and the average range in soft tissue are approximately 6.7 mm and 2.4 mm, respectively. It is typically used as chloride salt $^{89}SrCl_2$. According to a study performed on 10 patients after administration of 2.22 MBq/kg (60 μCi/kg) $^{89}SrCl_2$, the absorbed dose was found to range from 6 to 61 cGy/MBq with a mean value of 23 cGy/MBq. Ratios of tumor to bone marrow dose of around 10 : 1 for two of the patients were reported [38, 39].

Samarium-153 has a physical half-life of 46.27 h; β-emission energy at 0.64, 0.71, and 0.81 MeV; and γ-emission at 0.103 MeV. Sm153-EDTMP is a complex widely used as a palliative treatment for painful skeletal metastases. Skeletal

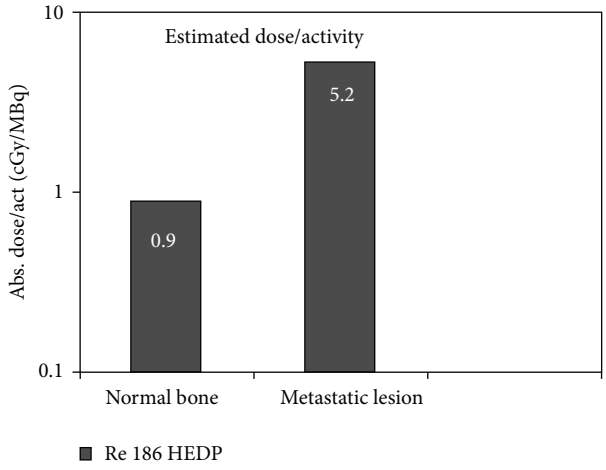


Figure 3: Normal bone and metastatic lesions dose estimated per activity [7].

metastasis lesion doses were ranging from 23 to 34 mGy/MBq for a standard administered activity of 37 MBq/kg (1 mCi/kg), while marrow doses ranged from 1.2 to 2.0 mGy/MBq and urinary bladder doses range from 0.36 to 1.30 mGy/MBq according to [40]. These values have been calculated by MIRDOSE 3.1, using MIRD schema for an individualized dosimetry. Nonskeletal sites were found to receive negligible doses.

Radionuclides that emit alpha particle, are of increasing interest. Unlike beta-emitting radiopharmaceuticals, alpha-pharmaceuticals deliver an intense and highly localized radiation dose (with a range of 2 to 10 cell diameters) to bone surfaces. Radium-223 is a first-in-class, highly targeted, alpha-pharmaceutical under clinical development to improve survival in patients with bone metastases. Alpharadin, radium-223 chloride (^{223}RaCl) in solution, is classified as an alpha-pharmaceutical and has a half-life of 11.4 days [41]. The localized action of Alpharadin alpha emission (with a short path length of 40–100 μm in tissue) helps to preserve the surrounding healthy bone tissue and bone marrow and limits distribution of the agent to soft tissue, thus also minimizing the risk of systemic side effects.

In this study dosimetry issues concerning the use of ^{186}Re-HEDP in bone pain palliation from multiple metastases are discussed. Departing from the standard methodology of MIRD based on fixed geometry phantoms of MIRD, patient-specific dosimetry can give accurate results of absorbed dose in metastatic lesions and healthy tissues. Gamma camera quantification and extraction of crucial metastasis indices can give all the data required to determine the optimum activity dosage for each patient, enhancing the therapeutic efficacy while minimizing toxicity side effects. Quantitative scintigraphic images analysis provides more realistic absorbed dose estimates for each individual. The dose rate-volume histogram of a target and relative indices provide information in assessing tumor control probability. Applying this method in the case of bone pain palliation with ^{186}Re-HEDP, therapeutic ratios of dose absorbed from metastatic lesions and normal bone were defined. These ratios are a useful tool for a physician, for the palliative therapy of bone metastases in order to achieve high doses to tumor cells while the radiation dose to normal tissue remains at acceptable levels, thus preserving the limits imposed by bone marrow toxicity. Patient-specific dosimetry calculations and the use of therapeutic ratios could be expanded for the evaluation of radionuclide therapy, to other cases.

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