Re-186 and Sm-153 dosimetry based on scintigraphic imaging data in skeletal metastasis palliative treatment and Monte Carlo simulation

M Andreou, N Lagopati and M Lyra
Radiation Physics Unit, A’ Radiology Department, Kapodistrian University of Athens, 76 Vas. Sophias Ave, Athens, Greece
E-mail: mlyra@med.uoa.gr

Abstract. Optimum treatment planning of patients suffering from painful skeletal metastases requires accurate calculations concerning absorbed dose in metastatic lesions and critical organs, such as red marrow. Delivering high doses to tumor cells while limiting radiation dose to normal tissue, is the key for successful palliation treatment. The aim of this study is to compare the dosimetric calculations, obtained by Monte Carlo (MC) simulation and the MIRDOS model, in therapeutic schemes of skeleton metastatic lesions, with Rhenium-186 (Sn) -HEDP and Samarium-153 -EDTMP. A bolus injection of 1295 MBq (35mCi) Re-186–HEDP was infused in 11 patients with multiple skeletal metastases. The administered dose for the 8 patients who received Sm-153 was 1 mCi /kg. Planar scintigraphic images for the two groups of patients were obtained, 24 h, 48 h and 72 h post injection, by an Elscint Apex SPX gamma camera. The images were processed, utilizing ROI quantitative methods, to determine residence times and radionuclide uptakes. Dosimetric calculations were performed using the patient specific scintigraphic data by the MIRDOS3 code of MIRD. Also, MCNPX was employed, simulating the distribution of the radioisotope in the ROI and calculating the absorbed doses in the metastatic lesion, and in critical organs. Summarizing, there is a good agreement between the results, derived from the two pathways, the patient specific and the mathematical, with a deviation of less than 9% for planar scintigraphic data compared to MC, for both radiopharmaceuticals.

1. Introduction
Skeletal metastases, appears in the majority of patients with breast and prostate cancer and frequently in patients with lung, renal, thyroid cancer and multiple myeloma. Actually, two-thirds of patients with breast cancer develop metastatic bone disease. Delivering high doses to tumor cells while limiting radiation dose to normal tissue, is the key for successful palliation. Consequently, optimum treatment planning of patients suffering from painful skeletal metastases requires accurate calculations concerning absorbed dose in metastatic lesions and critical organs, such as red marrow.

The use of therapeutic radionuclides, which have the property of localizing in metastatic sites, has proved successful for alleviation of pain, especially for multiple sites for which the use of external beam irradiation is impractical. Systemic metabolic radiotherapy uses a variety of radionuclides conjugated to pyrophosphate analogues.
The aim of this study is to make a comparison between the dosimetric calculations, obtained by Monte Carlo (MC) simulation and the MIRDOSSE model, in therapeutic schemes with Rhenium-186 (Sn) - HEDP, 1,1 hydroxyethylidene diphosphonate, Re-186 – HEDP, and Samarium-153 -EDTMP (ethylenediamine tetramethylene phosphonate), Sm-153-EDTMP.

Samarium-153 - EDTMP is a 1:1 complex of the radioisotope Samarium-153 and a Tetraphosphonate (ethylenediamine-tetramethylene phosphonic acid). Samarium-153 - EDTMP concentrates in areas of high metabolic activity in skeletal tissue, where it is associated with the hydroxyapatite crystal [1]. It is injected into a vein and distributes throughout the body. It homes in on metastatic lesions. Once there, the radioisotope emits beta particles, which kill the nearby cancer cells. Pain begins to improve in the first week for most people and the effects can last several months [2]. Samarium-153 has a half life of 46.3 h, with maximum beta-particle energies of 810 keV (20%), 710 keV (49%), 640 keV (30%) and gamma photon emission of 103 keV (28%) which is suitable for imaging purposes during therapy. The short half-life of 46 h and its beta emissions allow the delivery of a high dose rate in regions of enhanced osteoblastic activity over a short period of time. This fact accounts for the reduced residual long-term activity in the bone marrow. Mean absorbed dose, a widely used parameter for prediction of the efficacy of a treatment can either overestimate or underestimate actual doses delivered in the organs/tissues of interest (TOIs), so it is far from being perfect.

186Re (Sn) – 1,1 hydroxyethylidene diphosphonate, 186Re – 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 [3]. 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 the areas of concentration.[4, 5]. 186Re is a mainly beta-emitting radionuclide with a physical half-life of 89.3 h (3.78 d). Its main beta-emissions have maximum energies of 1.077 MeV (71%) and 0.939 MeV (22%) respectively [6-9].

2. Methods and materials
A bolus injection of 1295 MBq (35 mCi) Re-186–HEDP was infused in 11 patients with multiple skeletal metastases. It is proved to be a highly justified and efficient dose. The administered dose for the 8 patients, who received Sm-153, was 1 mCi/kg.

Planar scintigraphic images (anterior and posterior) for the two groups of patients, (Re-186 and Sm-153 patients), were obtained 24 h, 48 h and 72 h post injection, by an Elscint Apex SPX gamma camera. The images were processed utilizing ROI (regions of interest) quantitative methods to determine residence times and radionuclide uptakes by TOIs and by specific skeletal sites. Dosimetric calculations were performed using MIRDOSSE3.

The analysis of these values lead 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. The bone ratios M/N and B/RM deduce the selective concentration of 186Re – HEDP in metastatic lesions and conserving normal bone tissue.

2.1. Monte Carlo simulation
To prepare the input file for the MCNPX code (Monte Carlo N - Particle Extended Code), it is obligatory to define the geometry of the theoretical experiment. The metastatic lesion was considered to be a sphere of 1.5 cm radius, inside a cylindrical form simulating the bone. The spherical cells inside and outside the tumour, were defined from 0 up to 1 cm every 0.2 cm, from 1 up to 3 cm every 1 cm and from 3 up to 10 cm every 4 cm.
The radioactive source was considered as a point source, with the appropriate energy definition, according to the simulated radiopharmaceutical. It is identified with the center of the tumour. One million events were counted for both cases.

Thus, MCNPX (Monte Carlo N - Particle Code) code was employed, simulating the distribution of the radioisotope in the ROI and calculating the absorbed doses in metastatic lesion in critical organs.

3. Results
Gamma camera images of radionuclide distribution (whole-body scintigrams & SPECT) of patients, who were administered Re186 - HEDP and Sm153- EDTMP, were analyzed to measure activity in specifically selected normal and metastatic regions of interest [10]. Calculations based on the MIRD schema, gave values of absorbed dose per unit volume (voxel) for metastatic and normal bone tissue for the two studied radiopharmaceuticals.

The calculated values are presented in table 1. The absorbed dose of metastatic lesion over normal bone tissue per volume ratio, M/B ratio, represents the absorbed dose to a target volume compared with normal bone tissue and provides valuable information in assessing tumor control probability and normal tissue toxicity as well as the radiopharmaceutical's qualification and superiority. Bone tissue mean absorbed dose per red marrow absorbed dose ratio, B/RM ratio, is also presented in table 1 to display the radiopharmaceutical’s toxicity on this critical organ during metastatic bone lesion therapy.

Table 1. Bone seeking radiopharmaceuticals' absorbed dose ratios: Metastatic/Normal bone tissue (M/B), Bone tissue/Red Marrow (B/RM).

| Radiopharmaceutical | Absorbed Dose (mGy/MBq per volume unit) |
|----------------------|----------------------------------------|
|                      | Normal Bone | Metastatic lesion | M/B ratio | B/RM ratio |
| Re-186-HEDP         | 3.12        | 16.2              | 5.2       | 3.4        |
| Sm-153-EDTMP        | 3.80        | 22.8              | 6.0       | 5.5        |

Table 1 compares the M/B and B/RM ratios for the 2 most commonly used radiopharmaceuticals in metastatic bone therapy. Sm-153-EDTMP provides an optimum combination of high M/B ratio (high therapeutic efficacy) as well as high B/RM ratio (low toxicity).

A deviation of about 7% between the results, obtained by the MIRDOS and Monte Carlo results was found, in both cases (Rhenium and Samarium). Furthermore absorption linearity of radiation was observed, with a maximum distribution of the dose at the center of the tumour and gradual decrease towards the periphery. This proves that Sm-153-EDTMP is the radionuclide of choice.

4. Discussion
A method of estimating the optimum dosage of the administrated radiopharmaceutical in order to avoid myelotoxicity is the acquisition and quantification of whole body scintigraphic images using a smaller quantity of the radionuclide. By administering 740 MBq of $^{153}$Sm-EDTMP anterior and posterior scintigraphic whole body images were obtained at 10 min and 5 h post-administration. Bone and bone marrow activity were calculated using the MIRD schema. The total activity delivering a limiting dose of 2 Gy at the bone marrow was determined. The total activity predicted was between 35% and 63% of the standard recommended value of 37 MBq/kg, which if administered, would have delivered bone marrow doses of 3.27-5.9 Gy resulting in myelotoxicity [11]

Toxicity side effects are also dose related. Dose distribution in individual bone marrow cavities, irradiated by a Sm-153 source and uniformly distributed on the bone surface, is different in reality from the uniform dose distribution, which is usually assumed. This difference affects the corresponding haematopoietic stem cell survival. In a study where Monte Carlo simulations were used to generate dose-volume histograms for a geometrical model of trabecular bone [12], the estimated cell survival for Sm-153 was markedly higher compared to a homogeneous dose distribution.
Therefore, the more realistic dose distribution models for individual bone marrow cavities can result in more accurate estimations of bone marrow toxicity.

However, with $^{186}$Re-HEDP for palliative bone metastases therapy, significant pain relief (at 75% of patients) was observed. The results appear shortly after the 1st administration (1st week) and could last up to the 16th week. Multiple administrations are possible with minimum toxicity effects [3, 13-14].

Because $^{186}$Re-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 myelo-suppression confined mainly to thrombocytopenia while leucopenia plays only a minor role. In a previously published study of 60 patients with painful bone metastases from different tumor types, who were treated with 1406 MBq of $^{186}$Re-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, respectively. In all patients, platelet and white blood cell counts returned to baseline levels within 8 weeks after administration of $^{186}$Re-HEDP [15].

5. Conclusion
Summarizing, the mean absorbed dose, usually results in overestimations and underestimations of actual doses in TOIs. Dose distribution and time dose rate curves in TOIs are crucial parameters for the assessment of the relative biological effectiveness of either an ongoing treatment or of a treatment that is about to start. There is a good agreement between the results, derived from the two pathways, the real and the theoretical, with a deviation less than 9% for planar data comparing to MC, for both radiopharmaceuticals.

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