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Radiopharmacokinetic and dosimetric parameters of ^{188}Re-lanreotide in athymic mice with induced human cancer tumors

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Abstract

Radiolabeled peptides, like the somatostatin analogs, have been used for peptide receptor-mediated radionuclide therapy (PRMRT) in metastatic neuroendocrine tumors.

The eight amino acid peptide 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threonin-amide,cyclic(2 → 7)-disulfide (9Cl) (lanreotide) was found to bind to the five somatostatin tumor receptors. Lanreotide has been labeled via the bifunctional chelating agent, DOTA, to ^{111}In, and ^{90}Y. A direct labeling method was used to label lanreotide with ^{188}Re. Athymic mice with implanted human cancer tumors (uterine-cervix, renal, and neuroblastoma) were injected with radiochemically pure ^{188}Re-lanreotide (1.11 MBq). The percent injected activity (%IA/g) from serial blood samples was the input data for the WinNonlin computer program to obtain radiopharmacokinetic parameters. The organs' percent injected activity per gram of tissue (%IA/g) was extrapolated to the weights of a 70 kg male model organs and the number of nuclear transitions (*N*) were the input for the OLINDA/EXM program to obtain dosimetry estimates. Induced uterine-cervix tumors (HeLa cells) show a mean 2.4 %IA/g uptake up to 24 h and the tumor/blood ratio was over 1.85 (1.5–24 h post-injection) confirming ^{188}Re-lanreotide remains bound to the tumor. The estimated tumor absorbed dose was 460 mGy/MBq. Human effective dose was 0.0182 mSv/MBq. Therefore, ^{188}Re-lanreotide is a good candidate for PRMRT and a clinical trial is being planned in order to acquire individual dosimetric data.

Keywords: ^{188}Re-lanreotide; Implanted tumors in athymic mice; Pharmacokinetics; Dosimetry; OLINDA code

1. Introduction

The selection of a labeled peptide with a radionuclide that maximizes the radiation dose in the tumor and minimizes the dose in the normal tissues constitutes an important radiopharmaceutical for targeted radiotherapy. Radiolabeled somatostatin analog peptides have been used for peptide receptor-mediated radionuclide therapy (PRMRT) in metastatic neuroendocrine tumors. The vast majority of human tumors seem to over-express one or the other of five known distinct hSSSTR subtype somatostatin receptors and ^{111}In-DTPA-D-Phe^{1}-octreotide, which binds to hSSTR2 and 5 with high affinity, has been considered a valuable tool for the visualization of human endocrine tumors and their metastasis (Krenning et al., 1993; Reubi et al., 2000).

Recently, other somatostatin analogs have been synthesized for receptor-expression molecular imaging and therapy. The

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yttrium-90-labeled eight amino acid peptide 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide,cyclic(2 → 7)-disulfide (9Cl) (lanreotide), was found to bind to the five somatostatin tumor receptors: to hSSTR2, 3, 4 and 5 with high affinity and to hSSTR1 with lower affinity. It has been successfully used in clinical trials labeled with indium-111 for diagnosis (^{111}In-DOTA-lanreotide) and with the pure beta emitter yttrium-90 for therapy (^{90}Y-DOTA-lanreotide) via the bifunctional chelating agent DOTA (Virgolini et al., 2002).

A better radionuclide for lanreotide labeling would be the beta emitter ^{188}Re (β_{max}, 2.19 MeV) with a 17 h half life, obtained in a hospital radiopharmacy from a tungsten-rhenium generator (^{188}W–^{188}Re). Because of its energetic β-particles, and γ-photons (0.155 MeV) for molecular image acquisition, ^{188}Re has been successfully used to label inorganic complexes, monoclonal antibodies and somatostatin peptide-analogs (Knapp et al., 1997; Ferro-Flores and Hashimoto, 1997; Ferro-Flores et al., 1999, 2005; Meléndez et al., 1999; García-Salinas et al., 2001; Arteaga de Murphy et al., 2001).

In order to determine the biological behavior and to estimate the absorbed radiation dose of rhenium-188 labeled lanreotide in humans it is important to calculate radiopharmacokinetic and dosimetric data in an animal model (Konijnemberg et al., 2004).

Therefore, the purpose of this investigation was to implant in athymic mice, human cancerous cells from uterine-cervix, kidney, and neuroblastoma, to obtain radiopharmacokinetic and dosimetric parameters and estimate the absorbed radiation dose of ^{188}Re-lanreotide in humans.

2. Experimental

2.1. Preparation of ^{188}Re-lanreotide

Lanreotide (3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide,cyclic(2 → 7)-disulfide (9Cl)) (β-(2-(naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-amide[disulfide bridge:2–7]) (Sigma–Aldrich, Corp. St. Louis, MO, USA) was rhenium labeled by a modified direct method using HEDP as a weak competing ligand and $SnCl_2{\cdot}2H_2O$ to reduce both rhenium (to a reactive species) and the peptide's disulphide bridge for metal chelation (Meléndez et al., 1999). The vial with the final preparation contained 0.027 mg peptide in 0.1 mL of sterile apyrogenic water, 1.7 mg HEDP in 0.1 mL of the same water for injection and 0.21 mg of $SnCl_2{\cdot}2H_2O$ in 0.1 mL 12N HCl. The kit was labeled with approximately 225 MBq (0.8–1.0 mL) of $^{188}ReO_4^-$, recently eluted from a ^{188}W/^{188}Re generator (Oak Ridge Laboratories). The reaction was carried out at pH 2 with a 90 min incubation period in boiling water (92 °C). Before injection the pH was raised to pH 7.0 with a citrate buffer and the radioactivity assayed with a CAPINTEC CRC-15R dose calibrator (Arteaga de Murphy et al., 2001).

2.2. Radiochemical purity

The presence of radiochemical impurities in the radiopharmaceutical as determined by chromatography with ITLC-SG silica gel glass fiber (Gelman Sciences Ann Arbor, MI, USA) with three solvents: saline solution (0.9% NaCl), acetone and acid ethanol (10% 0.3 M HCl). The radiochemical stability was evaluated 24 h after preparation by the same ITLC-SG method. The radiochromatographic profile was determined by HPLC molecular exclusion ProteinPak column and by reverse phase with a C-18 μBondpak column as previously described (Arteaga de Murphy et al., 2001).

2.3. Animal model

Tumor uptake, biodistribution and radiopharmacokinetic studies in mice were carried out according to the rules and regulations of the Official Mexican Norm 062-ZOO-1999, Technical Specifications for the production, care and use of laboratory animals (Villanueva and Hernández, 2004).

Athymic female mice (25–30 g) were kept in sterile cages with sterile wood-shavings beds. Female normal BALB/c mice (20–25 g) were kept in plastic cages with wood-shavings beds. All the mice had constant temperature, humidity, noise and 12:12 light periods. Water and feed (standard PMI 5001 feed) were given ad libitum.

2.4. Cell lines

HeLa cells of epithelial origin were derived from an epidermoid carcinoma of a human uterine-cervix. These cells harbor transcriptionally active sequences from the human papilloma virus 18 (HPV18), including E6 and E7 oncogenes, which lead HeLa cells to progress uninterruptedly through the cell cycle (Schwarz et al., 1985). Renal cancer cells were originally derived from the SK29 human cell line and the brain cancer cells were of a human neuroblastoma. All cell lines were originally obtained from ATCC (Atlanta, GA, USA). The cells were routinely grown al 37 °C, with 5% CO_2 atmosphere and 100% humidity in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% newborn calf serum and antibiotics (100 units/mL penicillin and 100 μg/mL streptomycin).

2.5. Tumor induction in athymic mice

Uterine-cervix tumors were induced by a subcutaneous injection of HeLa cells (1×10^6) resuspended in 0.2 mL of phosphate-buffered saline, into the dorsal side of 30–40-days-old nude mice. Neuroblastoma tumors were induced with the same procedure. The renal tumor cells (1×10^6 cells) were injected intraperitoneally. The sites of injection were observed at regular intervals for the appearance of tumor formation and progression.

2.6. Pathology studies

Tumors taken from the mice were formalin-fixed and paraffin-embedded. In order to determine their microscopic

characteristics the tumor sections were eosin–hematoxylin stained and were observed under a light microscope (Zeiss).

2.7. Biodistribution

Normal BALB/c mice and athymic mice with induced tumors were used for biodistribution and radiopharmacokinetic studies. ^{188}Re-lanreotide, 1.11 MBq (30 μCi) in 0.1 mL was injected in a tail vein. The mice ($n = 3$ per time point) were sacrificed 0.083, 0.25, 0.5, 1.5, 3, 4 and 24 h post-injection. Whole heart, spleen and kidneys and samples of lung, liver, blood, stomach, intestines, muscle and bone were saline rinsed, paper blotted and placed into pre-weighed plastic test tubes. The activity was determined in a well-type scintillation detector (*Canberra*) along with six 0.25 mL aliquots of the diluted standard representing 100% of the injected activity. The mean activity was used to obtain the percentage of injected activity per gram of tissue %IA/g.

2.8. Standardised tumor uptake value S_tUV

S_tUV was calculated as follows (Wahl, 1994):

$$S_tUV = \frac{\text{decay corrected activity in the tumor (MBq)/mass of tumor (g)}}{\text{total injected activity (MBq)/rat weight (g)}} \quad (1)$$

2.9. Radiopharmacokinetic parameters

To calculate pharmacokinetic parameters the activity of all the blood samples were the input data for the *WinNonlin* computer program. A non-compartmental model (NCA) with a single i.v. bolus dosing was chosen and the following parameters were obtained: apparent volume of distribution zeta V_z; apparent volume of distribution at stationary state V_{ss}; $T_{1/2}$ λ z; total clearance Cl; area under the curve AUC and mean residence time MRT.

2.10. Absorbed radiation dose calculations

The absorbed dose D or energy per unit mass deposited in a target organ from a source is calculated according to the OLINDA/EXM code as

$$D = N \times \mathrm{DF} \quad (2)$$

where N is the sum of all nuclear transitions that occur in source region (given by the biologically distributed beta emitter ^{188}Re-lanreotide in a time interval) (μCi-h or MBq-s) and DF is a dose factor which includes the sum of several time-independent factors:

$$\mathrm{DF} = \frac{k\sum_i n_i E_i \phi_i}{m} \quad (3)$$

n_i = number of radiations with energy E emitted per nuclear transition; E_i = energy per radiation (MeV); ϕ_i = fraction of radiation energy absorbed in the target; m = mass of target region (g or kg) and k = proportionality constant Gy-kg/MBq-s-MeV) (Stabin, 2003; Stabin et al., 2005).

The calculated %IA/g for the organs in mice were referred to the weight of the organs in a 70 kg male model (Stabin, 2003).

$$\left[\left(\frac{\%\mathrm{IA}}{g_{\mathrm{organ}}}\right)_{\mathrm{animal}} \times (\mathrm{kg}_{\mathrm{TB\ weight}})_{\mathrm{animal}}\right] \times \left(\frac{g_{\mathrm{organ}}}{\mathrm{kg}_{\mathrm{TB\ weight}}}\right)_{\mathrm{human}} = \left(\frac{\%}{\mathrm{organ}}\right)_{\mathrm{human}} \quad (4)$$

The extrapolated percents of injected activity in each source human organ at 0.083, 0.25, 0.5, 1.5, 3, 4 and 24 h, were fitted as exponential biokinetic models to calculate N values and input to the OLINDA/EXM computer program. Radiation doses for 23 organs and total body are given in Table 2. The code also displays the contributions of different source organs to a target organs' total dose. For the estimation of the tumor absorbed dose it was assumed that once the radiopharmaceutical is inside the tumor, there is no biological elimination.

2.11. Statistical strategy

Net cpm and g of tissue data obtained were used to calculate IA/g tissue for each organ and for each time interval from each mouse. The mean net cpm of the diluted standard representing 100% of the injected activity was used to calculate %IA/g tissue. Mean and standard deviation were calculated for each organ and for each time interval from mice. Ratios of the %IA/g found for tumor/blood were obtained ($n = 3$–4 mice).

3. Results

3.1. Preparation and radiochemical purity of ^{188}Re-lanreotide

The radiopharmaceutical was prepared with ≈176 MBq (4.76 mCi) of $^{188}ReO_4^-$. Its purity determined by ITLC-SG system was 96 ± 2%. The labeled peptide remained at the origin with saline (R_f, 0.0) and migrated with the front with both acetone and acid ethanol (0.7–1.0). Free perrhenate migrated with the front in the three solvents while ^{188}Re-HEDP traveled with the front with both saline and acid–ethanol (R_f, 1.0) and in acetone the R_f was 0.0. Reduced hydrolyzed rhenium had an R_f 0.0 with the three solvents. The stability was >95% up to 24 h. The radiochemical impurities were ^{188}Re–HEDP (2 ± 1%) ^{188}Re–O_2 < 1% and <2% $^{188}ReO_4^-$.

With molecular size exclusion HPLC the radiochromatographic profile correlated with the UV chromatogram. Retention times for perrhenate were 8.5–10.0 and 18–19 min for the labeled lanreotide. Greater than ninety-five percent of the total radioactivity was bound to the peptide.

With the C-18 gradient column "cold" lanreotide and labeled lanreotide showed a retention time of 30–31 min and 3 min for ^{188}Re-HEDP. More than 98.5% of the radioactivity was recovered from the column. Stability was >95%, 24 h after radiolabeling as determined by paper and column chromatography,

3.2. Induced cancer tumors

Tumors induced with HeLa cancer cells were due to a carcinogenic process, as confirmed by the pathology study, and not only to a foreign body reaction. Tumors were approximately 0.8 cm diameter and 2.0 g after 39 days post-dorsal muscle inoculation. Microscopically the tumor rests on a fibrous stroma surrounded by abundant lymphocytic exudate. There are pavement cells with large vacuolated hyperchromatic nuclei and cells with chromatin aggregates. Many mitosis are seen and most of the cells present scarce pallid eosinophylic cytoplasm. The pathological diagnosis, based on these morphological characteristics, was that of a malignant, metastatic, implanted tumor of epidermoid human cervix cancer.

Neuroblastoma cells had a neoplastic appearance, as seen on the microscopic slides before injection, but they did not produce a carcinogenic process. Uptake of ^{188}Re-lanreotide was 0.02% 4 h post-injection and therefore somatostatin receptors were not detected. The pathology studies of the small tumors observed (0.1 g) show that the growth was due to a foreign-body reaction. The microscopic slides of the kidney cancer cell line show abundant nests of atypical epithelial neoplastic cells. The kidney cancer cells injected into the peritoneum produced ascitis after 45 days of inoculation. In one athymic mouse up to 2.7 mL were extracted. The microscopic slides of ascitis show abundant nests of atypical epithelial neoplastic cells with round pleomorphic, hyperchromatic nuclei and with variable amounts of cytoplasm. No mitosis, red blood cells nor bacteria are seen in the smears. The pathological findings confirm that the origin of the ascitis was not septic but it was cancerous. The cells in the peritoneum did not form tumors.

3.3. Biodistribution

Blood clearance in normal BALB/c mice and in athymic mice, with induced cervix cancer tumor, was rapid (Table 1). Uptake in the organs of athymic mice, in %IA/g is shown in Table 2. The tumor/blood concentration ratio was over 1.5 from 90 min to 24 h as shown in Fig. 1. There was renal and hepatobiliary elimination in both species.

3.4. Standardised tumor uptake value S_tUV

Three, 4 and 24 h post-^{188}Re-lanreotide injection S_tUV was 0.6, 0.65, 0.6, respectively confirming that the peptide remains bound to the receptors in the HeLa-induced tumor.

Table 1
Blood clearance of ^{188}Re-lanreotide-in mice

Time (h)	BALB/c (mean ± S.D.)	Athymic (mean ± S.D.)
0.083	3.54 ± 0.91	12.50 ± 1.20
0.25	1.87 ± 0.40	2.30 ± 0.28
0.5	1.03 ± 0.14	1.90 ± 0.14
1.5	0.68 ± 0.13	1.55 ± 0.07
3	0.52 ± 0.06	1.30 ± 0.49
4	0.27 ± 0.03	1.20 ± 0.49
24	0.11 ± 0.08	0.90 ± 0.21

$n = 3$ mice.

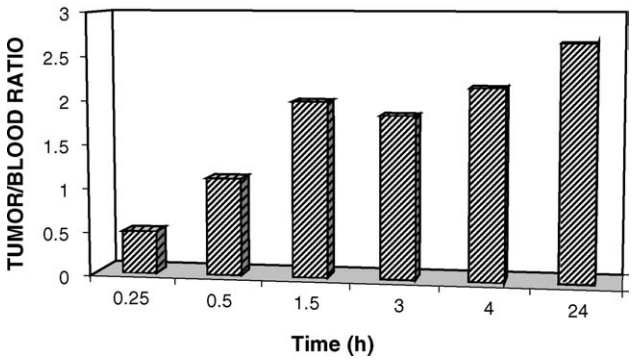

Fig. 1. Tumor/blood ratio concentration of ^{188}Re-lanreotide in athymic mice ($n = 3$).

Table 3
Radiopharmacokinetic parameters of ^{188}Re-lanreotide in mice

Parameters	BALB/c	Athymic
V_d z (mL)	76.59 ± 10.37	72.65 ± 3.54
V_{ss} (mL)	68.41 ± 19.89	69.62 ± 10.19
$T_{1/2}$ λ z (h)	5.6 ± 2.49	43.05 ± 6.84
Cl (mL/min)	9.48 ± 3.61	1.17 ± 0.37
AUC ($0 \rightarrow \infty$) (mL/min)/h	10.55 ± 3.62	85.50 ± 13.23
MRT (h)	7.22 ± 4.08	59.49 ± 13.66

Calculated with WinNonlin pro program for a non-compartmental model (mean $n = 3$).

3.5. Radiopharmacokinetics

The radiopharmacokinetic data for ^{188}Re-lanreotide in BALB/c and athymic mice calculated with the WinNonlin program using a non-compartmental model is given in Table 3. The apparent distribution volumes are quite similar in both species. In athymic mice the clearance is slower and the elimination half life and residence time are prolonged in comparison with the values for BALB/c mice. Consequently the AUC is 85.5 in the athymic and 10.55 in the BALB/c mice. The differences in the other parameters might be due to ^{188}Re-lanreotide uptake in the implanted tumor in the athymic mice.

3.6. Radiation dose calculations

The value of N (MBq-s) for spleen, kidneys, cortical and trabecular bone, liver, small intestine and stomach were the input for the OLINDA/EXM program. The data for other target organs are shown in Table 4. The effective dose is 0.0182 mSv/MBq. For the 2 g tumor a spherical model was used (OLINDA/EXM program) and the absorbed dose was 460 mGy/MBq.

4. Discussion

The direct labeling method, without a bifunctional chelating agent, is an easy, fast and efficient method for rhenium peptide labeling. The stable radiopharmaceutical ^{188}Re-lanreotide is of high specific activity (8×10^3 MBq/mg peptide), radiochemical purity (>95% up to 24 h) and shows favorable biodistribution and specific binding to uterine-cervix tumors up to 24 h.

Table 2
Biodistribution of ^{188}Re-lanreotide in athymic mice with induced cervix cancer tumor[a]

Time (h)	0.083	0.25	0.5	1.5	3	4	24
Blood	12.5 ± 1.2	2.3 ± 0.28	1.9 ± 0.14	1.55 ± 0.07	1.3 ± 0.48	1.2 ± 0.21	0.9 ± 0.21
Heart	–	0.8 ± 0.06	1.0 ± 0.14	0.85 ± 0.07	0.5 ± 0.07	–	0.6 ± 0.10
Lung	–	–	1.4 ± 0.57	1.2 ± 0.07	0.9 ± 0.07	1.1 ± 0.07	1.2 ± 0.1
Liver	1.5 ± 0.28	–	2.7 ± 0.28	2.1 ± 1	1.3 ± 0.1	1.6 ± 0.35	1.1 ± 0.23
Spleen	1.6 ± 0.57	0.3 ± 0	0.5 ± 0	0.3 ± 0.07	0.5 ± 0.35	0.5 ± 0.57	0.4 ± 0.14
Kidney	–	2.9 ± 0.35	2.9 ± 0.14	1.6 ± 0.78	2.9 ± 0.99	4.6 ± 1.2	3.8 ± 0.21
Stomach	3.5 ± 0.35	1.6 ± 0.21	1.9 ± 0.07	2.3 ± 0.14	–	2.2 ± 0.21	1.2 ± 0
Small intestine	4.5 ± 0.35	1.6 ± 0.21	0.8 ± 0.14	2.3 ± 0.07	0.4 ± 0.14	–	1.6 ± 0.07
Large intestine	3.7 ± 0.35	1.6 ± 0.57	1.3 ± 0.14	1.2 ± 0.07	0.6 ± 0.21	–	–
Muscle	1.50.± 49	0.9 ± 0	0.7 ± 0.21	1.3 ± 0.49	1.5 ± 0.21	1.4 ± 0.21	0.7 ± 0.07
Bone	1.3 ± 0.14	2.9 ± 0.35	1.0 ± 0.07	2.2 ± 0.07	1.5 ± 0.07	0.9 ± 0.14	1.6 ± 0.07
Tumor	–	1.10 ± 0.57	2.1 ± 0.07	3.1 ± 0.57	2.4 ± 0.07	2.6 ± 0.28	2.4 ± 0.14

[a] %IA/g ± S.D.

^{188}Re has excellent radionuclidic and chemical characteristics and ^{188}Re-lanreotide was studied for therapeutic application and not compared with lanreotide labeled with other radionuclides. Forrer et al. (2004) reported that for the somatostatin analog uptake depends on the radionuclide used and that octreotide (DOTA-TOC) labeled with ^{67}Ga/^{68}Ga instead of ^{111}In show differences in pharmacological parameters and metastatic neuroendocrine tumor uptake.

^{188}Re-lanreotide has affinity for lung carcinoma and also for cervical cancer of the epidermoid poorly differentiated variety. The ^{188}Re-lanreotide tumor activity ranged from 2.1 ± 0.07 to 2.4 ± 0.14%IA/g of tumor tissue from 0.5 to 24 h after injection showing in vivo stability. This fact would be very useful for therapeutic purposes. It is important to mention that the somatostatin analog uptake also depends on the number of somatostatin receptors of the tumor producing cells which could be different in type or completely lacking as in the neuroblastoma cells studied.

For biodistribution and radiopharmacokinetics a set of three or more mice are used for each time point and biological differences among the mice in the groups are quite large. Special emphasis was placed on the uptake and mean absorbed doses for tumor, kidney and bone (bone marrow) which are the dose-limiting organs. High inter-mice tumor-absorbed dose variability was found which is not unexpected as receptor densities vary markedly among subjects and tumors (Forrer et al., 2004).

For dosimetric calculations the OLINDA/MXM code is designed for specific human models of men, women and children of different weights. Entering extrapolated data from mice gives acceptable data for humans. The estimated absorbed dose for a 2 g tumor was 0.46 Gy/MBq with a 1.11 MBq dose injected in the mice and the mean calculated effective dose for the male model was 0.018 mSv/MBQ. The effective dose from a single diagnostic nuclear medicine procedure is typically 1–10 mSv while environmental radiation amounts to around 2–3 mSv/year (Cormack et al., 1994).

Considering the ^{188}Re-lanreotide tumor uptake and that the efficacy of radiation on a metastatic tumor depends on the patient's absorbed dose it is necessary to calculate individual dosimetry to determine the therapeutic dose without damaging non-target organs. A clinical trial is being planned in order to acquire individual dosimetric data.

Until then, we have to accept that the advantage of an animal model is that tissue radiation toxicity from radiopharmaceuticals is compared on a dose level (in Gy) instead of injected activities (in MBq) and the uncertainty in up-scaling from injected activities in rats to the equivalent in humans is avoided (Konijnemberg et al., 2004). And also, that extrapolation of animal biokinetic data to humans "... is far from certain, but these preliminary data provide a basis for going forward with clinical trials if the results are generally favorable ..." (Stabin, 2003).

Table 4
^{188}Re-lanreotide

Organ	Estimated *N* value MBq-s	Radiation dose *D* (mSv/MBq)
Spleen	0.0054	6.64E−05
Kidneys	0.0643	4.80E−04
Bone, cortical	0.9400	7.49E−03
Bone, trabecular	0.5260	1.84E−03
Liver	0.1650	1.98E−03
Small intestine	0.1230	1.42E−05
Stomach	0.0411	4.54E−03
Red marrow		7.49E−03
Osteogenic cells		1.84E−03
Urinary bladder wall		1.37E−04
Adrenals		1.54E−05
Brain		1.44E−05
Gall bladder wall		0.0
Lli wall		3.39E−04
Uli wall		1.42E−05
Lungs		3.41E−04
Thyroid		1.40E−0.4
Muscle		1.41E−05
Pancreas		1.50E−05
Skin		2.73E−05
Testes		0.0
Thymus		1.38E−05
Effective dose		1.82E−02

Extrapolated radiation dose for a 70 kg male model.

5. Conclusions

The athymic mice (with induced malignant tumors) model for estimating radiopharmacokinetic and dosimetric parameters of ^{188}Re-lanreotide gives an approximation to the real human values. In spite of its shortcomings it is the best model at hand and should be used for preclinical trials of peptide receptor-mediated radionuclide therapy in malignant tumors.

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