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Original Article

^{177}Lu-EDTMP radiation absorbed dose evaluation in man based on biodistribution data in Wistar rats

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ABSTRACT

Skeletal metastases are common in patients suffering from various primary cancers. Radiopharmaceuticals are an effective option for bone pain palliation. In this work, the radiation absorbed dose of ^{177}Lu-EDTMP radiopharmaceutical was estimated for adult man based on biodistribution data in Wistar rats. The MIRD dose calculation method and the Sparks and Aydogan methodology were applied. The results shows that about 46% of injected activity is cumulated on the surface of the trabecular and cortical bones. Radiation absorbed doses of red bone marrow and osteogenic cells were estimated to about 1.1 and 6.2 mGy/MBq, respectively. The maximum administrated activity was obtained 27 MBq/kg of body weight with an effective dose of 0.23 mSv/MBq. The results were compared with other available data from literature. This study indicated that ^{177}Lu-EDTMP provides therapeutic efficacy for achieving bone pain palliation with low undesired dose to other normal organs.

1. Introduction

Bone metastases occur in many patients with solid malignant tumors and nearly half of them experience bone pain [1,2]. Currently, bone-avid beta emitting radiopharmaceuticals are used for the selective delivery of radiation absorbed dose to tumor cells and bone marrow for bone pain palliation and bone marrow ablation [3,4].

Lutetium-177 with appropriate half-life of 6.73 day, three medium energy beta particles (498.30 keV [78.6%], 385.35 keV [9.1%] and 176.98 keV [12.2%]) and gamma rays for imaging studies (208.37 keV [11%] and 112.95 keV [6.4%]) is an excellent radionuclide for delivering of interested dose for bone metastases [5]. The comparatively longer half-life of lutetium-177, provides an outstanding advantage in delivering the radiopharmaceutical to locations far away from the reactors. In addition, lutetium-177 has high thermal neutron capture cross section of about 2100 b through ^{176}Lu(n,γ)^{177}Lu interaction [5,6]. This radionuclide's medium energy beta particles ensures minimum bone marrow suppression. Previously sodium orthophosphate (^{32}P) and $^{89}SrCl_2$ radiopharmaceuticals have been used for treatment of multiple osseous metastases and for bone pain palliation, but their high energy beta particles and half-lives in addition to their pure beta-decay modalities without emission of any low energy gamma rays (in order to follow up radiopharmaceutical in body) led to the development of other suitable bone surface and volume-seeking beta and alpha emitter radiopharmaceuticals such as ^{153}Sm-EDTMP, ^{177}Lu-EDTMP, ^{166}Ho-DOTMP, $^{186/188}$Re-HEDP, ^{90}Y-EDTMP and $^{223}RaCl_2$ [7–11].

Recently, alpha emitter radionuclides are shown to exhibit acceptable results for treatment of bone metastases. Radium-223 dichloride is one of bone volume-seeking alpha emitters that emits high energy alpha particles. Radium-223 dichloride radiopharmaceutical with trade name of “Xofigo” has successfully passed through phase III clinical trial in treatment of bone metastases [10,11]. However high price and difficult accessibility of radiuom-226 radioisotope and the high cost of each injection dose of Xofigo radiopharmaceutical, justifies the production and application of radiolabeled phosphonates such as ^{177}Lu-EDTMP.

Various aminophosphonic acid conjugates of lutetium-177 radionuclide have been used in human and normal animal studies for bone pain palliation including: ^{177}Lu-CTMP [12], ^{177}Lu-TTHMP [13], ^{177}Lu-PYP [14], ^{177}Lu-MDP [15], ^{177}Lu-DOTA-ZOL [16], ^{177}Lu-DOTMP [17–19], ^{177}Lu-EDTMP [6,13,17,20–27], ^{177}Lu-DOTA-TATE [26,28], ^{177}Lu-HEDP [29] and ^{177}Lu-DPD [29], which among them ^{177}Lu-EDTMP is the only radiopharmaceutical of lutetium-177 radionuclide which has been clinically used as pone pain palliative agent.

Although, the radiation absorbed dose of ^{177}Lu-EDTMP

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radiopharmaceutical for human has been reported in some articles [25,27,30], but they contain some defects and imperfections. Only a few specific tissues were considered as source organs and less time points were chosen for comparatively long life-time radionuclide of lutetium-177.

The aim of this study is to estimate the radiation absorbed dose of ^{177}Lu-EDTMP radiopharmaceutical for organs of an adult man based on biodistribution data in Wistar type rats [17,31]. Although the extrapolation between nonhuman primates (such as beagle, baboon, mice and rat) and human data may lead to overestimation or underestimation of absorbed dose, previously published numerous studies in literature have justified the usefulness of these models for initial absorbed dose evaluations [32,33]. Much more time points (0.5, 3, 24, 48 and 168 h) and more tissues (about 12 tissues) were considered as the source organs. Wherever possible, the result will be compared with other published data from literature.

2. Materials and methods

2.1. Biodistribution studies of ^{177}Lu-EDTMP in wistar rats

Production and quality control of ^{177}Lu-EDTMP radiopharmaceutical have been fully-described by Chakraborty et al. [17,31]. Biodistribution of ^{177}Lu-EDTMP was studied in normal Wistar rats injected with 0.1 mL (3–4 MBq of ^{177}Lu) of radioactive solution through their tail vein. The animals were sacrificed by cardiac puncture post-anesthesia at selected times after injection (30 min, 3 h, 1 d, 2 d and 7 d). Five rats were killed in each time interval. After drawing blood from the aorta, organs were weighed and counted in a flat-type NaI(Tl) scintillation counter. The tissues' radioactivities were stated as percentage of injected activity per organ (%IA/organ).

2.2. ^{177}Lu-EDTMP's biodistribution in humans

The following methods are used to adapt biodistribution pattern of ^{177}Lu-EDTMP radiopharmaceutical between rats and humans; the Medical Internal Radiation Dosimetry (MIRD) dose calculation method [34] and the methodology for extrapolation of the percent of injected activity (%IA) in human organ from the percent of injected activity (%IA) in animal organ.

Several investigations have previously published to extrapolate biokinetic and biodistribution data from animals to humans in cases where there is no human data or is insufficient [35,36]. Regarding the considerable difficulties to extrapolate biokinetic data from animals to human, the methodology outlined by Sparks and Aydogan is applied in this study in order to have a rough approximation of radiation absorbed dose in man from ^{177}Lu-EDTMP [36]. Based on this method, in relative organ mass scaling, the percent of injected activity (%IA) in human organ is assumed to be equal to the ratio of the fraction of the total body mass of the organ in human to the fraction of the total body mass of the organ in animal multiplied by the percent of injected activity (%IA) in animal organ:

$$\%IA\ Human\ organ\ =\ \%IA\ Animal\ organ\ \times \frac{\frac{Organ\ mass_{human}}{Body\ mass_{human}}}{\frac{Organ\ mass_{animal}}{Body\ mass_{animal}}} \quad (1)$$

The weight of selected organs of the adult man and normal Wistar rats are given in Table 1 according to ICRP report [37] for humans and Peters and Boyd [38] and Miller et al. [39] articles for Wistar rats.

The activity of organs in any time interval after injection of A_0 Bq of ^{177}Lu-EDTMP is calculated from the following equation and the time-activity curves are produced for each source organs according to this equation:

$$A(t)\ = \frac{\%IA(t)}{100} \times\ A_0 e^{-\lambda t} \quad (2)$$

2.3. Dosimetric calculations

The radiation absorbed dose of interested target organs was estimated using methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [34]. The calculations are based on the methodology described below:

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) S(r_T \leftarrow r_S) \quad (3)$$

where, $D(r_T)$ stated in (mGy) is the radiation absorbed dose to a target organ, r_T, from a source organs, r_S. $\tilde{A}(r_S)$ is the cumulated activity in the source organ, r_S, which is calculated by the following equation:

$$\tilde{A}(r_S) = \int_0^\infty A(r_S,\ t)\ dt \quad (4)$$

and, the $S(r_T \leftarrow r_S)$ expressed in [mGy/(MBq s^{-1})], is the specific absorbed fraction of energy for the target organ, r_T, per unit cumulated activity in source organ, r_S. In this study the S-values of adult man for lutetium-177 radionuclide are taken from the OLINDA/EXM software [40].

Table 1
Weight of selected organs of the adult man and Wistar rat.

Organ	Human (g)	Organ	Rat (g)
Total body	70000	Total body	190
Heart, without blood in chambers	330	Heart	0.7
Kidneys (both)	310	Kidneys (both)	1.5
Stomach	150 Wall; 250 contents	Stomach	1.0 wall
Small intestine	640 Wall; 400 contents	Small bowel	1.9 wall
Muscle, skeletal	28000	Muscle	73.7
Lungs, including blood	1000	Lungs	1.2
Liver	1800	Liver	8.1
Upper large intestine (ULI)	210 Wall; 220 contents	Cecum	0.6 wall
Lower large intestine (LLI)	160 Wall; 135 contents	Colon	1.0 wall
Spleen	180	Spleen	0.7
Cortical (compact) bone	4000	Bone	17.3
Trabecular (cancellous) bone	1000	Brain	1.8

The cumulated activity of each source organ was calculated as the integral of the time-activity curves up to 168 h (7 days) using the trapezoidal method, plus the integral of the rest of the curve to infinity using fit to exponential functions with effective half-life constants of organs. The time-activity curves after 168 h were assumed with a rational assumption that, organs' activities decrease with an effective half-life of that organ (radioactive decay and biological elimination of the radionuclide). The last three time points (1, 2 and 3 days) on the activity-time curves of organs were used for extraction of effective half-lives of those organs through fitting monoexponential equation on curves.

Finally, the effective dose was calculated according to the latest recommendations of the International Commission on Radiological Protection (ICRP) publication 103 [41], and was calculated from the following equation for both male and female, and then averaged:

$$E = \sum_T w_T \left[\frac{H(r_T)^{Male} + H(r_T)^{Female}}{2} \right] \quad (5)$$

where w_T is the weighting factor for tissue or organ T and H_T, is the equivalent dose in tissue T, given in Sv. Since the gamma rays and beta particles are involved in this research, the equivalent dose of tissues are directly calculated from the radiation absorbed dose of tissues (the radiation weighting factor of gamma and beta radiations is equal to 1).

3. Results and discussion

3.1. ^{177}Lu-EDTMP's biodistribution in normal wistar rats and humans

The biodistribution of ^{177}Lu-EDTMP in different organs of Wistar rats up to 7d (168 h) after injection is given in Fig. 1.

As shown in Fig. 1, the major portion of injected activity is washed out from the blood circulation after 3 h and is rapidly taken up in bones after administration and is retained almost constant up to 7 d.

The percentage of injected activities per organs of human (%IA/organ) extrapolated from Wistar rats' biodistribution data, are given in Fig. 2. As seen in Fig. 2, most of the activity is cumulated in bone tissue. Radiolabeled phosphonates such as ^{177}Lu-EDTMP, primarily tend to be localized uniformly on bone surfaces [42,43]. In accordance with the recommendations of the ICRP, human bone surface uptake was considered as the trabecular (cancellous) and the cortical (compact) bones' surface proportion at a ratio of 62%–38% of the total skeletal surface [44].

Totally, more than 46% of injected activity is cumulated on the surface of the trabecular and cortical bones. Because of the larger surface area of trabecular bone against cortical one (10.5 m^2 vs. 6.5 m^2), contribution of the trabecular bone from activity distribution on bone is more than the cortical one [44]. In addition, about 1.5% of injected activity will be deposited in muscle organ in the first time intervals post-injection due to the large weight fraction of muscle in human body (about 40% of total body weight). The percent of injected activity in the remaining source organs is less than 0.5%.

The time-activity curves for source organs of human are given in Fig. 3 a and b per injection of 1MBq of ^{177}Lu-EDTMP. Fig. 3 shows that most of the activity is rapidly taken up in cortical (~0.18 MBq) and trabecular (~0.28 MBq) bone surfaces. Approximately after 1 half-life of ^{177}Lu radionuclide (about 162 h), there are insignificant activities in source organs except for bone tissues.

As shown in Fig. 3, more than half of the injected activity would be excreted via the urinary tract, therefore absorbed dose of urinary bladder wall and its content's delivered dose to other organs should not be neglected. Unfortunately, chakraborty et al. [17,31] did not directly measured the time-activity curve of urinary bladder tissue. Instead, they calculated the excretion percent of injected radiopharmaceutical by subtracting the activity accounted in all the organs/tissues from the total activity injected to the rats. In order to make an approximate estimation for radiation absorbed dose of urinary bladder wall, cumulative urinary excretion data of Bal et al. work was employed [25]. Fractionated urine samples were collected over the first 48 h post-injection of radiopharmaceutical for human.

Since the frequency of urination and the activity of each urination should be known for the precise absorbed dose estimation of urinary bladder wall, conservatively the 4, 8, 24 and 48 h time points were considered as the number of bladder evacuations. It is clear that the bladder activity will be considered zero after any evacuation. The time-activity curve for urinary bladder content per injection of 1 MBq of ^{177}Lu-EDTMP is given in Fig. 3b.

3.2. Radiation absorbed dose calculations

The cumulated activities (from injection time to infinity) in the source organs of the adult man per injection of 1 MBq of the ^{177}Lu-EDTMP radiopharmaceutical are given in Table 2. Extracted

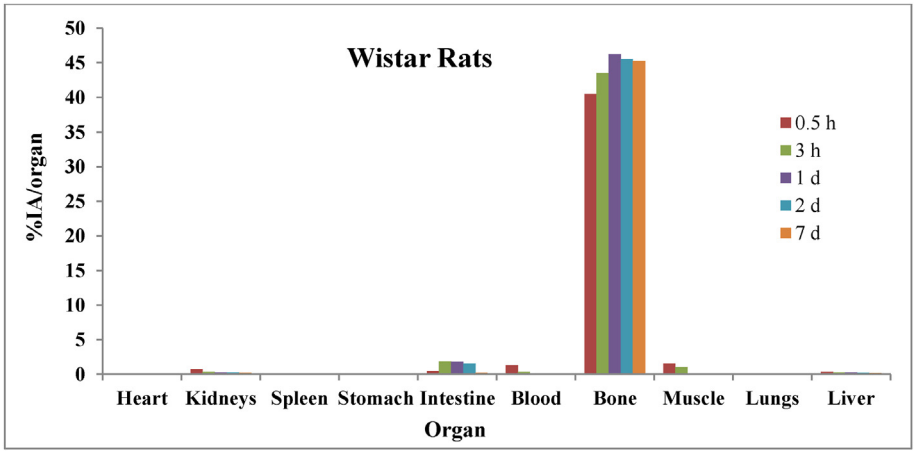

Fig. 1. Percentage of the injected activity per organ (%IA/organ) of ^{177}Lu-EDTMP in normal Wistar rats [17,31].

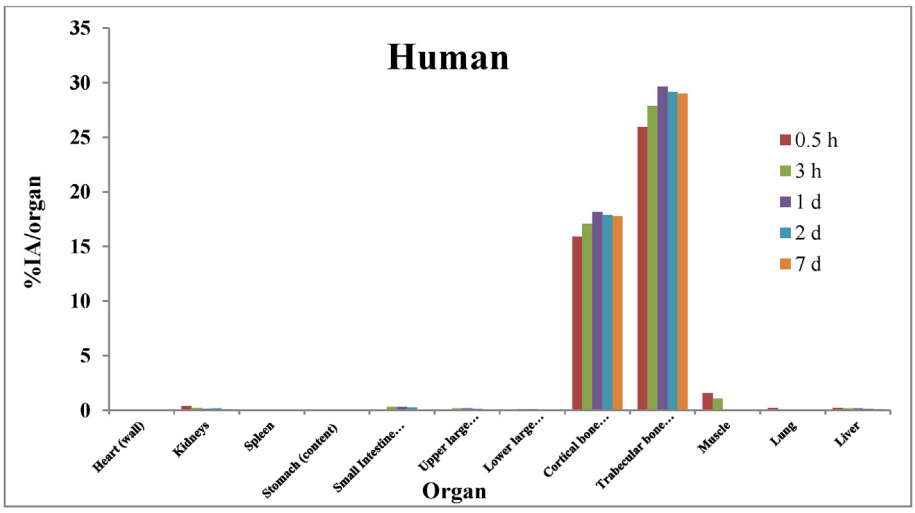

Fig. 2. Percentage of injected activity per organ (%IA/organ) of ^{177}Lu-EDTMP in the adult man organs.

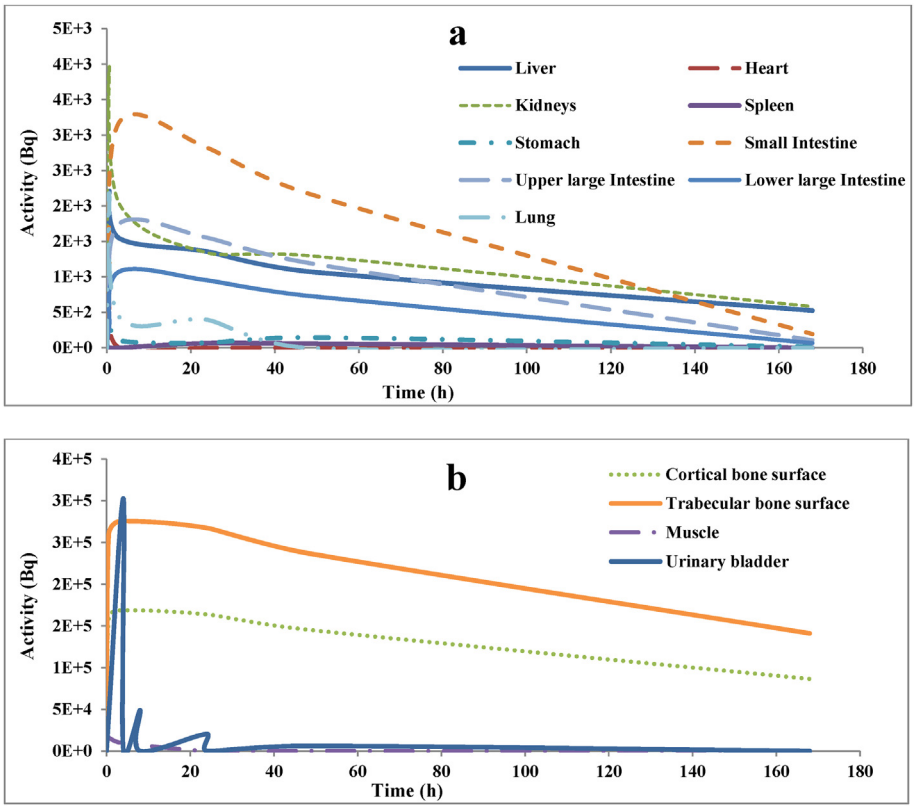

Fig. 3. Time-activity curves of ^{177}Lu-EDTMP for source organs of the adult man.

effective half-lives of organs through fitting monoexponential equation on the activity-time curves are given in this table as well. R-squared values were more than 95% during the fitting process.

As expected, the highest cumulated activity of ^{177}Lu-EDTMP radiopharmaceutical is observed in trabecular and cortical bones surfaces. ^{177}Lu-EDTMP radiopharmaceutical is settled in bone tissue and is approximately removed from this tissue with radiological half-life ($T_R = 161.5$ h). In other word, biological elimination of this radiopharmaceutical from bone tissue can be ignored due to the strong adhesive property of phosphonate agent (EDTMP) at bone tissue. Due to fast renal excretion of ^{177}Lu-EDTMP, the urinary bladder cumulated activity is the largest after the bone tissue.

Estimated radiation absorbed dose of the selected target organs of the adult man along with the effective dose of ^{177}Lu-EDTMP radiopharmaceutical are presented in Table 3 per injection of 1 MBq activity. The effective dose can be considered as a rough estimate of the comparable whole body irradiation. Sharma et al. [27] and Bal et al. [25] results are given in Table 3 for comparison as the only available radiation absorbed dose estimation of ^{177}Lu-EDTMP radiopharmaceutical in man.

Table 2
The cumulated activities (MBq s) in the source organs of the adult man per injection of 1 MBq of ^{177}Lu-EDTMP.

Source organ	Cumulated activity	Effective half-life (h)	Source organ	Cumulated activity	Effective half-life (h)
Heart	4	0.5	Lower large intestine (LLI) contents	341	38.5
Kidneys	977	99.0	Cortical bone surface	150154	161.5
Spleen	21	28.8	Trabecular bone surface	244988	161.5
Stomach contents	56	53.3	Muscle	525	4.7
Small intestine contents	1012	38.5	Lungs	62	9.5
Upper large intestine (ULI) contents	556	38.5	Liver	894	115.5
Urinary bladder content	3379	—			

Table 3
The radiation absorbed dose (mGy/MBq) of the adult man target organs per injection of 1 MBq of ^{177}Lu-EDTMP radiopharmaceutical.

Target organs	This work	Ref. [27].	Ref. [25].	Target organs	This work	Ref. [27].	Ref. [25].
Adrenal	0.012	0.058	0.05	Ovaries	0.008	0.057	0.05
Brain	0.013	0.058	0.05	Pancreas	0.007	0.054	0.04
Breasts	0.004	0.064	0.04	Red marrow	1.067	0.833	0.80
Gallbladder wall	0.005	0.052	0.04	Osteogenic cells	6.162	5.255	5.41
Lower large intestine (LLI) wall	0.037	0.096	0.05	Skin	0.005	0.058	0.04
Small intestine	0.035	0.060	0.04	Spleen	0.008	0.062	0.04
Stomach wall	0.007	0.050	0.04	Testes	0.005	0.052	0.04
Upper large intestine (ULI) wall	0.035	0.053	0.04	Thymus	0.005	0.050	0.04
Heart wall	0.007	0.054	0.04	Thyroid	0.008	0.053	0.04
Kidneys	0.085	0.060	0.04	Urinary bladder wall	0.198	1.356	1.53
Liver	0.017	0.072	0.04	Uterus	0.007	0.059	0.05
Lungs	0.009	0.054	0.04	Total body	0.139	0.194	0.16
Muscle	0.009	0.066	0.04	Effective dose (mSv/MBq)	0.23	0.264	0.38

Although the extrapolation between nonhuman primates and human data may lead to overestimation or underestimation of absorbed dose, but as shown in Table 3, the calculated radiation absorbed dose of tissues based on this method (especially for target organs such as osteogenic cells and red marrow) are close to the measured values through the imaging studies as a base for the absorbed dose assessments in nuclear medicine.

The highest radiation absorbed dose of ^{177}Lu-EDTMP radiopharmaceutical was delivered to skeletal tissue (Osteogenic cells and red bone marrow). Red bone marrow and osteogenic cells radiation absorbed doses were estimated about 1.1 and 6.2 mGy/MBq, respectively.

Bone and red bone marrow tissues receive radiation absorbed doses of more than 100 times the doses delivered to the most of the non-target organs. The urinary system is the next organ with the highest radiation absorbed dose (about 0.20 mGy/MBq and 0.08 mGy/MBq for urinary bladder wall and kidneys, respectively), demonstrating rapid clearance of radiopharmaceutical from the blood circulation. Calculated radiation absorbed dose of urinary bladder wall in our study is less than Sharma et al. [27] and Bal et al. [25] results. They assumed the cumulative urinary excretion as a urinary bladder content without considering the regular bladder evacuations and directly inserted anterior and posterior whole body images (including urinary bladder content) into the OLINDA software. We conservatively supposed that the bladder is evacuated at least two times in the first 8 h post-injection of radiopharmaceutical.

Also, the results show that because of the medium energy beta particles of lutetium-177 relative to high energy beta particles of holmium-166 and low energy beta particles of samarium-153, the effective dose of ^{177}Lu-EDTMP radiopharmaceutical (0.23 mSv/MBq) is lower than ^{166}Ho-EDTMP (0.29 mSv/MBq) and higher than ^{153}Sm-EDTMP (0.21 mSv/MBq) [33].

The maximum tolerated doses (MTD) of bone and bone marrow are about 50–70 and 1–2 Gy, respectively [43]. Radiation absorbed dose of 25 Gy to the red bone marrow can be considered as the ablative therapeutic dose [45,46]. The minimum therapeutic activity required to deliver a 25 Gy dose to the red bone marrow, along with the activity corresponding to the maximum tolerated dose (MTD) by bone and bone marrow tissues were given in Table 4 for various bone-avid radiopharmaceuticals. Assuming 2 Gy as the maximum tolerated dose to the red bone marrow, maximum activity to be administered to patients (in versus of MBq/kg of body weight) is given in this table as well.

As seen in Table 4, generally EDTMP ligand conjugate demands less activities than DOTMP and HEDP ligands to deliver required dose for bone marrow ablation for a given radionuclide. This is due to the relatively high bone uptake property of EDTMP ligand (up to

Table 4
The minimum activity of aminophosphonic acid radiopharmaceuticals required to deliver a therapeutic dose of 25 Gy to the red marrow.

Tissue	^{90}Y-EDTMP	^{153}Sm-EDTMP	^{166}Ho-DOTMP	^{166}Ho-EDTMP	^{186}Re-HEDP	^{188}Re-HEDP	^{177}Lu -EDTMP
Activity (GBq) corresponding to MTD of bone (70 Gy)	3.9	16.2	77.8	22.7	22.4	18.4	11.3
Activity (GBq) corresponding to MTD of bone marrow (2 Gy)	1.1	2.9	3.9	1.4	2.2	3.3	1.9
Min. activity (GBq) required for bone marrow ablation (25 Gy)	13.9	35.7	48.4	17.4	27.2	41.0	22.7
Max. administered activity (MBq/kg)	15.7	41.4	55.7	20.1	31.4	47.1	27.1
Bone surface absorbed dose (mGy/MBq)	18	4.3	0.9	3.1	3.1	3.8	6.2
Red marrow absorbed dose (mGy/MBq)	1.8	0.7	0.5	1.4	0.9	0.6	1.1
Reference	[47].	[48].	[46].	[43].	[49].	[50].	This work

70%) relative to DOTMP and HEDP (up to 40%) ligands [42]. Only the ^{166}Ho compounds (^{166}Ho-EDTMP and ^{166}Ho-DOTMP) could result in complete extirpation of bone marrow, while bone tissue dose would not exceed the MTD limit. Other radiophosphonates' required activities in order to complete red marrow ablation would exceed the MTD limit of bone tissue. The results show that the injected activity of ^{177}Lu-EDTMP radiopharmaceutical should not exceed by 27 MBq/kg (0.73 mCi/kg) of body weight. This administrated activity will result in 11.7 Gy bone surface absorbed dose for a 70 kg adult man (inverses of 1.9 GBq injected activity). In addition, the results indicate that ^{177}Lu-EDTMP delivers more radiation absorbed dose to bone surface compared with other studied radiopharmaceuticals except for ^{90}Y-EDTMP.

4. Conclusion

Theoretical radiation absorbed dose, effective dose and effective half-lives of tissues for ^{177}Lu-EDTMP radiopharmaceutical was estimated in adult man based on biodistribution data in Wistar rats. The results indicate that the osteogenic cells will receive about 6 times more radiation dose than red bone marrow per unit of injected activity. The radiation absorbed dose of ^{177}Lu-EDTMP radiopharmaceutical for urinary bladder wall, red bone marrow and osteogenic cells were estimated about 0.2, 1.1 and 6.2 mGy/MBq, respectively. The present study indicates that ^{177}Lu-EDTMP provides therapeutic efficacy for achieving bone pain palliation with low undesired dose to other normal organs, but more clinical trials needs to be established in a large number of cancer patients prospectively.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A. Bahrami-Samani, R. Bagheri, A.R. Jalilian, S. Shirvani-Arani, M. Ghannadi-Maragheh, M. Shamsaee, Production, quality control and pharmacokinetic studies of ^{166}Ho-EDTMP for therapeutic applications, Sci. Pharm. 78 (2010) 423–433.
[2] S. Dalvand, M. Sadeghi, Bone marrow dosimetry for ^{141}Ce-EDTMP as a potential bone pain palliation complex: a Monte Carlo study, Appl. Radiat. Isot. 182 (2022), 110113.
[3] Z. Bayat, E. Saeedzadeh, N. Vahidfar, M. Sadeghi, et al., Preparation and validation of [67Ga]Ga-phytate kit and Monte Carlo dosimetry: an effort toward developing an impressive lymphoscintigraphy tracer, J. Radioanal. Nucl. Chem. 331 (2022) 691–700.
[4] R. Bagheri, A.R. Jalilian, A. Bahrami-Samani, M. Mazidi, M. Ghannadi-Maragheh, Production of Holmium-166 DOTMP: a promising agent for bone marrow ablation in hematologic malignancies, Iran J. Nucl. Med. 19 (2011) 12–20.
[5] S.A. Sahafi-Pour, S.P. Shirmardi, E. Saeedzadeh, S. Baradaran, M. Sadeghi, Internal dosimetry studies of ^{177}Lu-BBN-GABA-DOTA, as a cancer therapy agent, in human tissues based on animal data, Appl. Radiat. Isot. 186 (2022), 110273.
[6] F. Johari Daha, M. Shafiei, Sh. Sheibani, et al., Production of ^{177}Lu and formulation of Ethylene diamine tetramethylene phosphonate (EDTMP) kits as a bone-seeking radiopharmaceutical, Iran, J. Radiat. Res. 7 (2010) 229–234.
[7] M. Tomblyn, The role of bone-seeking radionuclides in the palliative treatment of patients with painful osteoblastic skeletal metastases, Cancer Control. 19 (2012) 137–144.
[8] S.P. Shirmardi, E. Saniei, T. Das, M. Noorvand, et al., Internal dosimetry studies of ^{170}Tm-EDTMP complex, as a bone pain palliation agent, in human tissues based on animal data, Appl. Radiat. Isot. 166 (2020), 109396.
[9] IAEA, Therapeutic Applications of Radiopharmaceuticals, IAEA, Vienna, 2001. TECDOC-1228.
[10] R. Bagheri, H. Afarideh, M. Ghannadi-Maragheh, A. Bahrami-Samani, S.P. Shirmardi, Dosimetric study of radium-223 chloride and ^{153}Sm-EDTMP for treatment of bone metastases using MCNPX code and available experimental data, J. Radioanal. Nucl. Chem. 303 (2015) 1991–1998.
[11] S. Nilsson, R.H. Larsen, S.D. Fossa, et al., First clinical experience with a-emitting radium-223 in the treatment of skeletal metastases, Clin. Cancer Res. 11 (2005) 4451–4459.
[12] T. Das, S. Chakraborty, P.R. Unni, S. Banerjee, G. Samuel, H.D. Sarma, M. Venkatesh, M.R.A. Pillai, 177Lu-labeled cyclic polyaminophosphonates as potential agents for bone pain palliation, Appl. Radiat. Isot. 57 (2002) 177–184.
[13] S. Chakraborty, T. Das, P.R. Unni, H.D. Sarma, G. Samuel, S. Banerjee, M. Venkatesh, N. Ramamoorthy, M.R.A. Pillai, 177Lu labelled polyaminophosphonates as potential agents for bone pain palliation, Nucl. Med. Commun. 23 (2002) 67–74.
[14] I.A. Abbasi, Preliminary studies on ^{177}Lu-labeled sodium pyrophosphate (^{177}Lu-PYP) as a potential bone-seeking radiopharmaceutical for bone pain palliation, Nucl. Med. Biol. 39 (2012) 763–769.
[15] I.A. Abbasi, Studies on ^{177}Lu-labeled methylene diphosphonate as potential bone-seeking radiopharmaceutical for bone pain palliation, Nucl. Med. Biol. 38 (2011) 417–425.
[16] M.P. Yadav, S. Ballal, M. Meckel, F. Roesch, C. Bal, [^{177}Lu]Lu-DOTA-ZOL bone pain palliation in patients with skeletal metastases from various cancers: efficacy and safety results, EJNMMI Res. 10 (2020) 1–13.
[17] S. Chakraborty, T. Das, H.D. Sarma, M. Venkatesh, S. Banerjee, Comparative studies of ^{177}Lu–EDTMP and ^{177}Lu–DOTMP as potential agents for palliative radiotherapy of bone metastasis, Appl. Radiat. Isot. 66 (2008) 1196–1205.
[18] T. Das, S. Chakraborty, H.D. Sarma, S. Banerjee, ^{177}Lu-DOTMP: a viable agent for palliative radiotherapy of painful bone metastasis, Radiochim. Acta 96 (2008) 55–61.
[19] N. Bollampally, J. Shukla, B.R. Mittal, et al., Efficacy and safety of ^{177}Lu-DOTMP in palliative treatment of symptomatic skeletal metastases: a prospective study, Nucl. Med. Commun. 42 (2021) 964–971.
[20] A. Bahrami-Samani, A. Anvari, A.R. Jalilian, et al., Production, quality control and pharmacokinetic studies of ^{177}Lu-EDTMP for human bone pain palliation therapy trials, Iran, J. Pharm. Sci. 11 (2012) 137–144.
[21] J. Yuan, C. Liu, X. Liu, et al., Efficacy and safety of ^{177}Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer, Clin. Nucl. Med. 38 (2013) 88–92.
[22] A.S. Shinto, D. Shibu, K.K. Kamaleshwaran, et al., ^{177}Lu-EDTMP for treatment of bone pain in patients with disseminated skeletal metastases, J. Nucl. Med. Technol. 42 (2014) 55–61.
[23] M. Alavi, Sh. Omidvari, A. Mehdizadeh, A.R. Jalilian, A. Bahrami-Samani, Metastatic bone pain palliation using ^{177}Lu-Ethylenediaminetetramethylene phosphonic acid, World J. Nucl. Med. 14 (2015) 109–115.
[24] K.K. Agarwal, S. Singla, G. Arora, C. Bal, ^{177}Lu-EDTMP for palliation of pain from bone metastases in patients with prostate and breast cancer: a phase II study, Eur. J. Nucl. Med. Mol. Imaging 42 (2015) 79–88.
[25] C. Bal, G. Arora, P. Kumar, et al., Pharmacokinetic, dosimetry and toxicity study of ^{177}Lu-EDTMP in patients: phase 0/I study, Curr. Radiopharm. 9 (2016) 71–84.
[26] H. Balter, T. Victoria, T. Mariella, ^{177}Lu-labeled agents for neuroendocrine tumor therapy and bone pain palliation in Uruguay, Curr. Radiopharm. 9 (2016) 85–93.
[27] S. Sharma, B. Singh, A. Koul, B.R. Mittal, Comparative therapeutic efficacy of ^{153}Sm-EDTMP and ^{177}Lu-EDTMP for bone pain palliation in patients with skeletal metastases: patients' pain score analysis and personalized dosimetry, Front. Med. 4 (2017) 1–9.
[28] T. Das, S. Banerjee, Theranostic applications of lutetium-177 in radionuclide therapy, Curr. Radiopharm. 9 (2016) 94–101.
[29] M. Mirković, Z. Milanović, D. Stanković, et al., Investigation of ^{177}Lu-labeled HEDP, DPD, and IDP as potential bone pain palliation agents, J. Radiat. Res. Appl. Sci. 13 (2020) 27–36.
[30] J. Zaknun, C. Bal, P. Dupont, Pharmacokinetics and dosimetry of the bone-seeking agent 177Lu-EDTMP in patients with metastatic prostate cancer, J. Nucl. Med. 52 suppl1 (2011) 1748.
[31] S. Chakraborty, T. Das, Sh. Banerjee, et al., ^{177}Lu-EDTMP: a viable bone pain palliative in skeletal metastasis, Cancer Biother. Radiopharm. 23 (2008) 202–213.
[32] M.J. Bélanger, S.M. Krause, C. Ryan, S. Sanabria-Bohorquez, W. Li, T.G. Hamill, et al., Biodistribution and radiation dosimetry of ^{18}F-PEB in nonhuman primates, Nucl. Med. Commun. 29 (2008) 915–919.
[33] W.K.A. Louw, C. Domehl, A.J. van Rensburg, N. Hugo, A.S. Alberts, O.E. Forsyth, et al., Evaluation of samarium-153 and holmium-166-EDTMP in the normal baboon model, Nucl. Med. Biol. 23 (1996) 935–940.
[34] W.E. Bolch, K.F. Eckerman, G. Sgouros, S.R. Thomas, MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry—standardization of nomenclature, J. Nucl. Med. 50 (2009) 477–484.
[35] J.A. Siegel, Establishing a clinically meaningful predictive model of hematologic toxicity in nonmyeloablative targeted radiotherapy: practical aspects and limitations of red marrow dosimetry, Cancer Biother. Radiopharm. 20 (2005) 126–140.

[36] R.B. Sparks, B. Aydogan, Comparison of the effectiveness of some common animal data scaling techniques in estimating human radiation dose, in: Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Oak Ridge Associated Universities, Oak Ridge, TN, 1996, pp. 705–716.
[37] ICRP, ICRP Publication 23, Report of the Task Group on Reference Man, Pergamon Press, New York, 1975.
[38] J.M. Peters, E.M. Boyd, Organ weights and water levels of the rat following reduced food intake, J. Nutr. 90 (1966) 354–360.
[39] G. Miller, J.A. Klumpp, D. Poudel, W. Weber, R.A. Guilmette, J. Swanson, Americium systemic biokinetic model for rats, Radiat. Res. 192 (2019) 75–91.
[40] M.G. Stabin, R.B. Sparks, E. Crowe, OLINDA/EXM: the Second-generation personal computer software for internal dose assessment in nuclear medicine, J. Nucl. Med. 46 (2005) 1023–1027.
[41] ICRP, ICRP Publication 103, the 2007 Recommendations of the International Commission on Radiological Protection, ume 37, Elsevier, 2007.
[42] R. Bagheri, H. Afarideh, M. Ghannadi-Maragheh, S.P. Shirmardi, A. Bahrami-Samani, Study of bone surface absorbed dose in treatment of bone metastases via selected radiopharmaceuticals: using MCNP4C code and available experimental data, Cancer Biother. Radiopharm. 30 (2015) 174–181.
[43] R. Bagheri, A. Bahrami-Samani, M. Ghannadi-Maragheh, Estimation of radiation absorbed dose in man from ^{166}Ho-EDTMP based on biodistribution data in Wistar rats, Radiat. Phys. Chem. 187 (2021) 1–6.
[44] ICRP, ICRP Publication 89, Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values, Pergamon Press, New York, 2002.
[45] M.L. Barlett, M. Webb, S. Durrant, A.J. Morton, R. Allison, D.J. Macfarlene, Dosimetry and toxicity of Quadramet for bone marrow ablation in multiple myeloma and other hematological malignancies, Eur. J. Nucl. Med. 29 (2002) 1470–1477.
[46] H.B. Breitz, R.E. Wendt III, M.S. Stabin, S. Shen, W.D. Erwin, J.G. Rajendran, et al., ^{166}Ho-DOTMP radiation-absorbed dose estimation for skeletal targeted radiotherapy, J. Nucl. Med. 47 (2006) 534–542.
[47] F. Rösch, H. Herzog, C. Plag, B. Neumaier, U. Braun, H.W. Müller-Gärtner, et al., Radiation doses of yttrium-90 citrate and yttrium-90 EDTMP as determined via analogous yttrium-86 complexes and positron emission tomography, Eur. J. Nucl. Med. 23 (1996) 958–966.
[48] L. Vigna, R. Matheoud, S. Ridone, D. Arginelli, P. Della Monica, M. Rudoni, et al., Characterization of the [153Sm]Sm-EDTMP pharmacokinetics and estimation of radiation absorbed dose on an individual basis, Phys. Med. 27 (2011) 144–152.
[49] M. Lyra, G. Papanikolos, P. Phinou, A.P. Frantzis, J. Jordanou, G.S. Limouris, Rhenium-186-HEDP dosimetry and multiple bone metastases palliation therapy effects, Radionuclide Ther. Oncol. Curr. Status Future Aspects 10 (2003) 51–60.
[50] K. Liepe, R. Hliscs, J. Kropp, R. Runge, F.F. Knapp Jr., W.G. Franke, et al., Dosimetry of ^{188}Re-Hydroxyethylidene diphosphonate in human prostate cancer skeletal metastases, J. Nucl. Med. 44 (2003) 953–960.