Biological assessment and human absorbed dose estimation of [^{111}In]In-DTPA-antiMUC1 as a radioimmunoconjugate for breast cancer imaging

Original Article

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ABSTRACT

Introduction: The aim of this study was to evaluate the human organ absorbed dose of [^{111}In]In-DTPA-antiMUC1, as a newly developed radioimmunoconjugate.

Methods: [^{111}In]In-DTPA-antiMUC1 was prepared at optimized conditions while the radiochemical purity of the tracer was investigated using ITLC method. Biodistribution of the radiolabeled complex was assessed in tumor bearing BALB/c mice and the human absorbed dose of the radiotracer was estimated based on the gathered data in animals according to the standard methods.

Results: The highest absorbed dose is observed in the spleen and the liver with 0.112 and 0.087 mGy/MBq, respectively. In addition, the estimated human equivalent and effective absorbed dose were 0.008 mGy/MBq and 0.041 mSv/MBq, respectively.

Conclusion: [^{111}In]In-DTPA-antiMUC1 radioimmunoconjugate can be considered as an effective and safe radiolabeled compound for MUC1 positive breast cancer SPECT imaging.

Key words: Indium-111; AntiMUC1; Breast cancer; Absorbed dose; RADAR

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INTRODUCTION

High incidence of breast cancer with increased mortality and morbidity [1] along with invasive nature of this malignancy with early distant metastasis especially to the bone [2] has been a challenge for early diagnosis and treatment. Among imaging modalities, nuclear medicine techniques has shown great promise in the recent years for diagnosis and overall management of these patients [3].

While different radiopharmaceuticals have been prepared and suggested for breast cancer imaging [3-6], 16α-[^{18}F]-fluoro-17β-estradiol (FES) for PET imaging of the ER expression and the radiolabeled mAb trastuzumab both for SPECT and PET imaging of the human epidermal growth factor receptor 2 (HER2) are known as the most attractive radiopharmaceuticals [3]. Nonetheless, attempts are ongoing to produce better candidates for breast imaging.

With the introduction of antiMUC1 monoclonal antibody (mAb), PR81 [7], different research groups have expressed interest on PR81 as an intact or fragmental antiMUC1 mAb tracers to use as imaging and therapeutic anti-breast tumors in combination with ^{99m}Tc [8,9], ^{131}I [10], ^{177}Lu [11], ^{64}Cu [12] and ^{111}In [13]. The overall results indicate that these radiotracers could be contemplated as appropriate agents in oncology.

MUC1, a highly glycosylated transmembrane protein which is overexpressed (at least tenfold) in 80% of breast cancers and represents a useful target for radio-immunoscintigraphy. Among the cyclotron-produced radionuclides [14, 15], ^{111}In with excellent physical characteristics [$t_{1/2}$=2.8 days, Eγ=171.28 keV (90%), 245. 395 keV (94%)] can be considered as a good candidate for SPECT imaging [16]. Recent research results showed the localization of the [^{111}In]In-DOTA-PR81 definitely in the site of tumor at 24 h post injection of the complex, which indicated the ability of the new complex for specific binding in the breast cancer cell.

The human radiation absorbed dose based on the animals' biodistribution is considered the first step in evaluating the risks associated with the administration of radiolabeled compounds and is essential in developing of new radiopharmaceuticals [17]. This study was performed to estimate the human organ absorbed dose after injection of [^{111}In]In-DTPA-PR81 (a newly developed RIS tracer), applying the RADAR method (as the most commonly resource for calculation of the absorbed dose) as previously reported [18-20].

In the current study, [^{111}In]In-DTPA-PR81 was prepared in optimal condition and its radiochemical purity and in vitro and in vivo stabilities were studied. The final radiolabeled compound was injected to normal rats and tumor bearing mice, and the biodistribution of the radioimmunoconjugate was assessed in different intervals up to 96 h post injection. Finally, the human absorbed dose of the radiotracer was estimated based on the gathered data in animals according to the standard methods.

METHODS

^{111}In was produced in Radiation Application Research School, Karaj, Iran, by ^{112}Cd(p,2n)^{111}In reaction. p-SCN-Bn-DTPA was purchased from Macrocyclics (NJ, USA). Fetal Bovin Albumin (FBS), RPMI-1640 medium and L-Glutamine were bought from Gibco Co. (Dublin, Ireland). PD10 De-salting column was inquired from Amersham Pharmacia Biotech; other chemicals were bought from Sigma Chemical Co. (MO, USA). Sprague-Dawely rats were obtained from Pasteur Institute (Tehran, Iran). A Bioscan AR-2000 radio TLC scanner instrument (Bioscan, Paris, France) was used for Radio-chromatography purposes. A p-type coaxial high-purity germanium (HPGe) detector (model: EGPC 80-200R) coupled with a multichannel analyzer card system and a dose calibrator ISOMED 1010 (Dresden, Germany) were utilized for the measurement of the activity. Calculations were carried out based on the 245 keV peak for ^{111}In. The United Kingdom Biological Council's Guidelines on the Use of the Living Animals in Scientific Investigations, 2nd edition was used to determine the framework of animal experiments. The results are displayed as mean ± standard deviation (Mean ± SD) and Student's T-test was used to compare the data based on statistical significance defined as $P < 0.05$.

Preparation and quality control of [^{111}In]In-DTPA-PR81

Indium-111 was produced according to the previously reported procedure [21]. Briefly, cadmium was electroplated on a copper surface in compliance with other publications [22] and irradiated by 22 MeV proton at a 30 MeV cyclotron for 100 μAh to produce ^{111}In which was eluted with 1 N HCl (25 ml) as $^{111}InCl_3$ for labeling use. Then, p-SCN-Bn-DTPA-PR81 conjugate was added to 74 MBq of $^{111}InCl_3$. The mixture was incubated at 37°C for 1 hour. The radiochemical purity of the complex was investigated by ITLC using Whatman No. 2 and 1 mM DTPA as the stationary and mobile phase, respectively. The mixture was finally passed through a disposable PD10 desalting column to remove the low molecular weight impurities and increase the radiochemical purity. The final solution was then filtered in order to achieve higher radioactive concentration.

Stability tests

About 18.5 MBq of the final radioimmunoconjugate was added to the PBS buffer and freshly prepared

human serum while keeping at 4°C and 37 °C, respectively. Samples were taken from the complex up to 96 h after preparation and the stability of the final complex in PBS buffer and human serum was assessed by measuring radiochemical purity.

Mouse model with breast tumor

The tumor was established by subcutaneous implantation of spontaneous breast tumor fragments (2–3 mm^3) in the right side of the abdominal region (Flank) of inbred female BALB/c mice (16–25 g, 6–8 weeks old). The bio-distribution and imaging studies were performed when the tumor volume reached 70–80 mm^3. All the animal experiments were approved by the Animal Care Committee of Tarbiat Modares University, Tehran, Iran.

Biodistribution of radiolabeled complex in normal rats and tumor bearing mice

5.5 MBq of [^{111}In]In-DTPA-PR81 was injected intravenously into tumor bearing BALB/c mice. The mice were sacrificed at 3, 24, 48, 72 and 96 h post injection (n=5). Their organs including blood, liver, spleen, kidneys, stomach, small and large intestine, heart, lung, muscle, skin, bone and tumor were taken, rinsed with normal saline, weighted and their activity was measured by a p-type coaxial HPGe detector using the standard method presented by IAEA [23].

Estimation of accumulated activity for human organs

The non-decay corrected percentage of the injected activity versus time for different animal organs were plotted while a linear approximation was used between each two consecutive time point. The curves were extrapolated to infinity by fitting the tail of each curve to a monoexponential curve with the exponential coefficient equal to the physical decay constant of ^{111}In. The cumulated activity in the organs was calculated according to Equation 1:

$$\tilde{A} = \int_{t_1}^{\infty} A(t)\, dt \qquad (1)$$

Then, Sparks et al. method was used to extrapolate the cumulated activity for animal organs to the cumulated activity for human organs (Equation 2) [24]. The standard mean weights for each human organ were utilized for the extrapolation [25].

$$\tilde{A}_{\text{Human organ}} = \tilde{A}_{\text{Animal organ}} \times \frac{\text{Organ mass}_{\text{human}}/\text{Body mass}_{\text{human}}}{\text{Organ mass}_{\text{animal}}/\text{Body mass}_{\text{animal}}} \qquad (2)$$

Equivalent absorbed dose and effective absorbed dose calculation

The absorbed dose in human organs was calculated utilizing RADAR formalism using Equation (3):

$$D = \tilde{A} \times DF \qquad (3)$$

where, $\tilde{A}$ is the accumulated activity for each human organ, and DF is defined as Equation (4)

$$DF = \frac{k \sum_i n_i E_i \phi_i}{m} \qquad (4)$$

Where, n_i is the number of radiations with energy E emitted per nuclear transition, E_i is the energy per radiation (MeV), ϕ_i is the fraction of energy emitted that is absorbed in the target, m is the mass of the target region (kg) and k is some proportionality constant ($\frac{\text{mGy.kg}}{\text{MBq.s.MeV}}$). In this research, DFs presented in OLINDA/EXM software was employed [26].

The effective absorbed dose was calculated by multiplying the equivalent absorbed organ dose and W_T is the tissue-weighting factor obtained from the reported value in ICRP 103 [27].

RESULTS

Preparation and quality control of [^{111}In]In-DTPA-PR81

[^{111}In]In-DTPA-PR81 was prepared at optimized conditions. Radiochemical purity of the radiolabeled complex was assessed by ITLC method using DTPA, as the mobile phase. While the free cation migrates to higher R_f (0.8), the radiolabeled compound remains at the origin (Figure 1). The radiochemical purity of the complex was measured to be greater than 99 %.

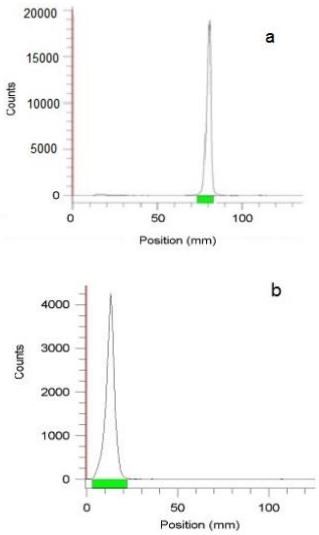

Fig 1. Radiochromatogram of free $^{111}In^{3+}$ (a) and [^{111}In]In-DTPA-PR81 (b) using Whatman No. 2 in 1 mM DTPA, pH 5.0 (n=3).

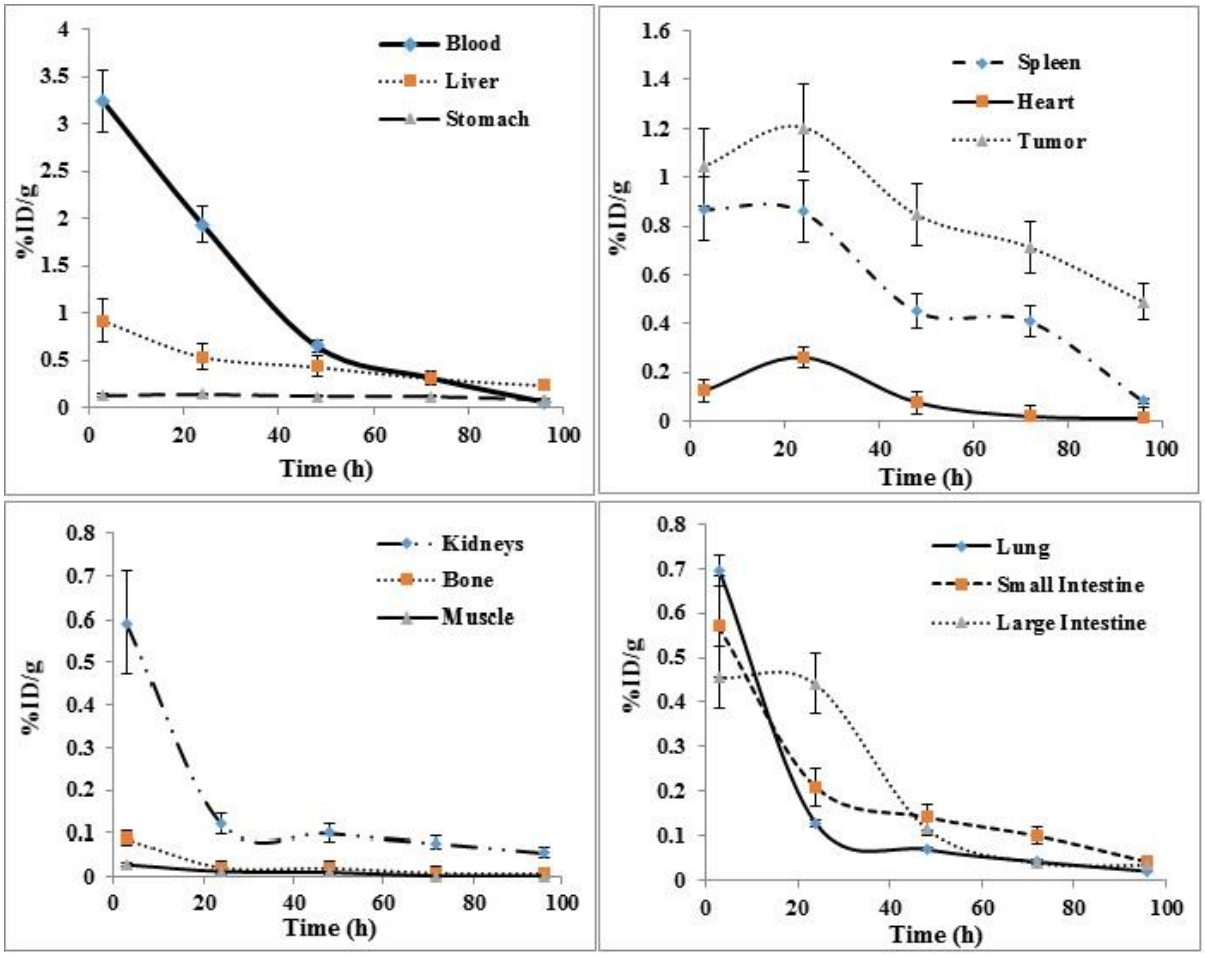

Fig 2. Non-decay corrected clearance curves of the animals' organs after injection of [111In]In-DTPA-PR81.

Stability test

Instant thin-layer chromatography indicated the radiochemical purity of higher than 90% in PBS buffer at 96 h next preparation. However, the stability of the complex in human serum was reduced and the radiochemical purity was 81% after 96 hrs.

Biodistribution of [111In]In-DTPA-PR81 in normal and tumor bearing animals

The percentage of the injected dose per gram in animal organs was calculated up to 96 hrs after injection of [111In]In-DTPA-PR81. The non-decay corrected clearance curves from the main organ sources of the animals for the radiolabeled compound are shown in Figure 2.

Equivalent absorbed dose calculation

Human absorbed dose of [111In]In-DTPA-PR81 was estimated using RADAR formalism based on biodistribution data in the Sprague-Dawely rats (Table 1). As seen, the highest amounts of the absorbed dose following injection of the radiolabeled compound was observed in the spleen (0.112 mGy/MBq) and liver (0.087 mGy/MBq).

DISCUSSION

[111In]In-DTPA-PR81 is a newly developed radioimmunoconjugate for SPECT imaging of MUC1 positive breast cancer. Non-decay corrected clearance curves of the animal organs after injection of [111In]In-DTPA-PR81 (Figure 2) indicated high uptake of the tumor compared to the other non-target organs and an increment of the accumulation in tumor site at 24 h post injection. Whereas, the clearance of antibodies is mainly by the reticuloendothelial system, further accumulation was observed in the liver and the spleen.

In this research, the absorbed dose of different human organs was estimated after [111In]In-DTPA-PR81 injection. Human organ absorbed dose estimation based on the animals' data is a prerequisite for the clinically application of a new radiopharmaceutical [28].

Table 1: Equivalent and effective absorbed dose delivered into human organs after injection of [^{111}In]In-DTPA-PR81.

Target organs	Equivalent absorbed dose in humans (mGy/MBq)	Tissue weighting factors[a]	Effective absorbed dose in humans (mSv/MBq)
Adrenals	0.019	0.12	0.002
Brain	0.001	0.01	0
LLI Wall	0.011	0.12	0.001
Small Intestine	0.006	0.12	0.001
Stomach Wall	0.014	0.12	0.002
ULI Wall	0.007	0.12	0.001
Heart Wall	0.018	0.12	0.002
Kidneys	0.032	0.12	0.004
Liver	0.087	0.04	0.003
Lungs	0.020	0.12	0.002
Muscle	0.006	0.12	0.001
Pancreas	0.020	0.12	0.002
Red Marrow	0.007	0.12	0.001
Bone Surf	0.007	0.01	0.001
Spleen	0.112	0.12	0.013
Thymus	0.005	0.12	0.001
Thyroid	0.002	0.04	0
Total Body	0.008	-	0.041

LLI: lower large intestine; Int: Intestine; ULI: upper large intestine.

[a] Tissue weighting factors according to international commission on radiological protection, ICRP 103 (2007).

Albeit, this estimation may cause some underestimation or overestimation, but it is a common first step, compatible with the ICRP 62 recommendations [29].

So far, various radiolabeled compounds of ^{111}In (such as [^{111}In]In-pentetreotide and [^{111}In]In-trastuzumab) and ^{18}F (including [^{18}F]F-FES and [^{18}F]F-FDHT) have been utilized for breast cancer imaging [30-33]. While these compounds were used in the clinical studies, the human absorbed organ dose was determined using PET and SPECT images. In this study, the absorbed human organ dose was estimated based on the rat's data, which is different from method employed in the clinical studies. Nonetheless, comparison of the absorbed dose values of this new compound with the other clinically used complexes can be useful in evaluating its safety from the perspective of radiation protection.

Geykema et al. studied the human organs absorbed dose after [^{111}In]In-trastuzumab injection in patients with HER2-positive metastatic breast cancer. They observed the highest amounts of the absorbed dose in the liver and the spleen with 0.60 and 0.36 mGy/MBq, respectively [30]. Bombardieri et al. also reported the spleen, kidneys and liver as the organs with the highest absorbed dose (0.57, 0.41 and 0.1 mGy/MBq, respectively), in [^{111}In]In-pentetreotide scintigraphy [31].

[^{18}F]F-FES radiation dosimetry in 49 patients showed the liver, gallbladder and urinary bladder as the organs receiving the highest absorbed dose (0.13, 0.10 and 0.05 mSv/MBq, respectively), while, the effective absorbed dose was determined as 0.022 mSv/MBq. The radiation dosimetry of [^{18}F]F-FDHT in women with metastatic breast cancer indicated an effective absorbed dose of 0.020 mSv/MBq and the urinary bladder with 0.061 mSv/MBq absorbed dose was recognized as the critical organ [33].

The results of this study demonstrated the effective absorbed dose of 0.044 mSv/MBq. The highest amounts of the absorbed dose were observed in the spleen (0.112 mGy/MBq) and liver (0.087 mGy/MBq), in accordance with both previous studies [30, 31]. These values are higher in comparison to the ^{18}F-labeled radiopharmaceuticals for breast cancer. Although, further investigations are needed, this new agent might lead to the lesser human organ absorbed dose as compared to the known ^{111}In agents and could be a potential advantage.

CONCLUSION

In this study, [^{111}In]In-DTPA-antiMUC1 radioimmunoconjugate was prepared with radiochemical purity of >99% as a suitable agent for SPECT imaging of MUC1 positive breast cancer. Human organs absorbed dose of the complex was estimated based on animals' data according to the RADAR and Spark et al. methods. Spleen and liver receive the highest absorbed dose equal to 0.112 and 0.087 mGy/MBq, respectively. In addition, the estimated human equivalent and effective absorbed dose were 0.008 mGy/MBq and 0.041 mSv/MBq, respectively. In summary, [^{111}In]In-DTPA-antiMUC1 can be considered as a safe radiolabeled compound for MUC1 positive breast cancer SPECT imaging.

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