Preliminary Studies of ^{177}Lu -Diethylenetriamine Penta-Acetic Acid-Deoxyglucose in Hepatic Tumor-Bearing Mice

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Abstract

Objective: The purpose of this study was to explore the potential use of ^{177}Lu -diethylenetriamine penta-acetic acid-deoxyglucose (^{177}Lu -DTPA-DG) as a radiopharmaceutical for hepatic tumor treatment.

Methods: Lutetium-177 (^{177}Lu) was labeled with DTPA-DG by adding 2 mCi $^{177}\text{LuCl}_3$ to 0.05 mg DTPA-DG (pH 5–6) at room temperature for 1 h. The quality of the ^{177}Lu -DTPA-DG solutions was determined by thin-layer chromatography and high-performance liquid chromatography. Cellular uptake studies with ^{18}F -fluorodeoxyglucose (FDG), ^{177}Lu -DTPA-DG and ^{177}Lu -DTPA and a blocking study with 1.0 mg D-glucose were performed. Biodistribution, imaging, and radiotherapy studies of ^{177}Lu -DTPA-DG were performed with the SMMC-7721 model.

Results: ^{177}Lu -DTPA-DG had a high radiochemical purity (>97%). The cellular uptake of ^{177}Lu -DTPA-DG was much higher than that of the ^{177}Lu -DTPA. The biodistribution of ^{177}Lu -DTPA-DG demonstrated that the complex accumulated in the tumor with high tumor/blood and tumor/muscle ratios. The tumors in mice in the ^{177}Lu -DTPA-DG group clearly displayed the high uptake of ^{177}Lu -DTPA-DG. After radiotherapy with ^{177}Lu -DTPA-DG, tumor growth decreased, and the overall survival was longer than that in the $^{177}\text{LuCl}_3$ group ($268.58 \pm 17.96 \text{ mm}^3$ vs. $507.43 \pm 55.72 \text{ mm}^3$, $p=0.002$) and the normal saline group ($268.58 \pm 17.96 \text{ mm}^3$ vs. $483.68 \pm 27.51 \text{ mm}^3$, $p<0.05$).

Conclusions: This preliminary study suggests that ^{177}Lu -DTPA-DG has the potential to become a liver radiopharmaceutical agent and should be further investigated.

Keywords: ^{177}Lu , DTPA-DG, label, biodistribution, radionuclide imaging, radiotherapy, hepatic tumor

Introduction

Primary liver cancer includes hepatocellular carcinoma (HCC, accounting for 75%–85%), intrahepatic cholangiocarcinoma (accounting for 10%–15%) and other rare types.¹ Liver cancer is predicted to become the sixth most commonly diagnosed cancer in 2018.¹ China is a high-risk area for primary liver cancer, the main risk factors for HCC are chronic infection with hepatitis B virus (HBV) and aflatoxin exposure.¹ There are many treatments for liver cancer, including hepatectomy, liver transplantation, and local ablation therapy.² Surgical treatment is the most important method for

patients with HCC to achieve long-term survival. Transcatheter chemoembolization has been recognized as one of the most common nonsurgical treatments for liver cancer, but tumor recurrence, contraindications, and adverse reactions pose serious challenges.² In addition, more than 70% of patients diagnosed with HCC have disease that is not amenable to treatment with liver transplantation or locoregional therapy.¹ Therefore, exploring new and effective treatment methods has become an urgent task in current clinical research.

^{18}F -fluorodeoxyglucose (FDG), a glucose analog, enters cells through glucose transporters (GLUTs). FDG has been

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used for clinical positron emission tomography (PET) applications. Due to factors such as difficult access and high cost, the use of ^{18}F -FDG in clinical practice is still limited. Theoretically, D-glucosamine is a glucosyl ligand, and the derivatives of D-glucosamine are substrates for GLUTs and hexokinase. Several reports have been published on the application of various other nuclide-labeled glucose or deoxyglucose analogs in different types of tumor cells and animal models.^{3–7} Among these analogs, ethylenedicysteine-deoxyglucose (EC-DG) has been used in clinical research.⁴ There are at least two mechanisms for the cellular processes involving glucosamine: one is similar to the cellular mechanism involving glucose, and the other is that glucosamine enters cells and directly forms glucosamine-6-phosphate.⁷ Some studies have reported that DTPA-DG can easily enter tumor cells and could be advantageous for the diagnosis of cancer by magnetic resonance imaging.⁸ Chen et al. showed that $^{99\text{m}}\text{Tc}$ -DTPA-DG might be appropriate for detecting tumors⁶ and that ^{188}Re -DTPA-DG had apoptotic effect on carcinoma cells and has potential as a cancer radiopharmaceutical.⁵

Lutetium-177 (^{177}Lu) is an ideal medical radionuclide because it has a suitable half-life ($T_{1/2}=6.17\text{ d}$). ^{177}Lu emits β -particles with energies of 497 KeV (78.6%) and 176 KeV (12.2%), which are useful for therapy; and γ -photons with energies of 113 KeV (6.4%) and 208 KeV (11%), which are useful for imaging with a conventional γ camera equipped with a low-energy, high-resolution collimator.⁹ Recently, ^{177}Lu -PSMA and ^{177}Lu -DOTA-TATE have been used in prostate cancer and neuroendocrine tumors, respectively, and achieved satisfactory results.^{10–13}

DTPA can be easily and efficiently labeled with ^{177}Lu with high radiochemical purity and stability.¹⁴ Previous studies have shown that DTPA-DG may be used as a radiopharmaceutical agent for tumors. The aim of this study was to explore whether ^{177}Lu -diethylenetriamine penta-acetic acid-deoxyglucose (^{177}Lu -DTPA-DG) has potential as a radiopharmaceutical for hepatic tumor treatment.

Materials and Methods

Materials and reagents

^{177}Lu was produced by the Institute of Nuclear Physics and Chemistry, China Academy of Engineering Physics (CAEP, Mianyang, China). DTPA was purchased from Sigma-Aldrich (Shanghai, China), and DTPA-DG was synthesized based on the authors' previous research report.¹⁵ HCl was purchased from Chengdu Jinshan Chemical Reagent Co., Ltd. Sodium hydroxide (NaOH), ammonium acetate, methanol, and potassium dihydrogen phosphate (KH_2PO_4) were purchased from the Chengdu Kelong Chemical Reagent Factory.

A calibrator (CRC-15R; Capintec, Inc., Florham Park, NJ) and a γ -counter (SN-695B; Hesuo Rihuan Photoelectric Instrument, Co., Shanghai, China) were used to measure the radioactivity of the samples. The radiochemical yield was documented by paper chromatography using Xinhua No. 1 chromatography paper (Hangzhou Xinhua Paper Company, Hangzhou, China) and a thin-layer chromatography (TLC) scanner (Mini-Scan; Bioscan, Inc., Washington, DC). Images were recorded by a pinhole collimator single-photon emission computed tomography (SPECT; GE Infinia Hawkeye 4; GE Medical Systems, Milwaukee, WI) scanner and a micro-PET/

CT (computed tomography) scanner (SIEMENS InveonTM, Munich, Germany). SMMC-7721 tumor cells are a hepatic cell cancer cell line. Nude mice were purchased from Chongqing Tengxin Biotechnology Co., Ltd. The mice were kept under specific pathogen-free conditions and were handled and maintained according to the Institutional Animal Care and Use Committee guidelines. All studies were approved by the Ethics Committee of Southwest Medical University.

Radiosynthesis of ^{177}Lu -DTPA-DG

$^{177}\text{LuCl}_3$ solution (2 mCi) was added to a tube containing 0.05 mg DTPA-DG (10 mg/mL). The pH was adjusted to 5–6 using 0.1 N HCl and 0.1 N NaOH. After the addition of all reagents, the resulting solution was incubated for 1 h at room temperature.

Quality control of ^{177}Lu -DTPA-DG

The quality of the ^{177}Lu -DTPA-DG solutions was determined with TLC and high-performance liquid chromatography (HPLC), as follows. By TLC, the starting point was labeled by a pencil ($\sim 2\text{ cm}$ from one end of a Xinhua No. 1 paper), and 3–5 μL of each final solution ($n=3$) was applied at the origin of paper chromatography strips ($\sim 3\text{ mm}$ in diameter). The developing agent was an ammonium acetate (10%): methanol solution (1:1 v/v). ^{177}Lu -DTPA-DG was obtained by reaction of ^{177}Lu and DTPA-DG (1:1 mol/mol). HPLC was performed using a C18 column (5 μm , $250\times 4.6\text{ mm}$, ZORBAX Bonus-RP; Agilent, Inc.) and isocratic elution with 5 mM KH_2PO_4 and methanol (90:10 v/v) as the mobile phase with a flow rate of 1 mL/min. The injection volume of the radiochemical solution was 20 μL .

In vitro stability

For determination of the stability of this complex, the aliquots ($n=3$) from three vials containing the ^{177}Lu -DTPA-DG complex were spotted on paper strips at different time intervals (0.5, 1, 2, 5, 10, 24 h). The change in stability of ^{177}Lu -DTPA-DG was analyzed at each time interval by TLC, as described in Quality Control of ^{177}Lu -DTPA-DG section.

Cellular uptake rates of radiotracers

SMMC-7721 cells were grown at 37°C in RPMI-1640 containing 10% fetal bovine serum in a humidified atmosphere with 5% CO_2 . SMMC-7721 cells (4.0×10^5 cells/well) were seeded into six-well plates and were randomly divided into groups A, B, and C ($n=3/\text{group}$). Approximately 5 μCi ^{18}F -FDG, ^{177}Lu -DTPA-DG, and ^{177}Lu -DTPA were added to groups A, B, and C, respectively. After the cells were incubated for 1–24 h, a digestive enzyme was used to terminate the cell culture. A blocking study was performed with 1.0 mg D-glucose, 5 μCi ^{18}F -FDG and 5 μCi ^{177}Lu -DTPA-DG ($n=3/\text{group}$). After the cells were incubated for 1 h, a digestive enzyme was used to terminate the cell culture. Cells and supernatants were collected in test tubes. The cellular uptake experiments were repeated three times. A γ -counter was used to measure the radioactivity counts. The formula used to calculate the radioactive drug cellular uptake rate = radioactivity of cells/total radioactivity $\times 100\%$.

FIG. 1. The reaction scheme of ¹⁷⁷Lu-DTPA-DG. ¹⁷⁷Lu-DTPA-DG, ¹⁷⁷Lu-diethylenetriamine penta-acetic acid-deoxyglucose.

Biodistribution

Tumor cells were subcutaneously injected into the left forelimb of each nude mouse. Biodistribution and imaging studies were conducted when the tumor volume reached at least $10 \times 10 \times 10 \text{ mm}^3$. A 0.1 mL (0.1 mCi) solution of ¹⁷⁷Lu-DTPA-DG was injected into the tail vein of nude mice bearing SMMC-7721 tumors. The mice were sacrificed at 1, 4, and 24 h (four mice at each time point) after injection. Blood samples and relevant organs were collected and weighed, and a γ -counter was used to measure the radioactivity counts of the organs. The results are expressed as the percentage uptake of the injected dose per gram (%ID/g).

Imaging

For imaging, 0.1 mL (0.3 mCi) ¹⁷⁷Lu-DTPA-DG was injected into the tail vein of 3 mice bearing SMMC-7721 tumors. As a control, 0.1 mL (0.3 mCi) ¹⁷⁷Lu-DTPA was injected into the tail vein of another 3 nude mice with tumors. Serial images (10 min, 128×128 matrix) were recorded by SPECT at 30, 60, 90, 120, 180, 210, and 240 min after injection. Then, 0.1 mCi ¹⁸F-FDG in ~ 0.1 mL was injected through the tail vein. Serial images were recorded by micro-PET at different times, as described above. Before the acquisition of images, the animals were maintained without food or water for more than 6 h.

Radiotherapy

Seven days before the start of radiotherapy, 0.1×10^7 tumor cells (SMMC-7721) were subcutaneously injected into

the shoulder region of nude mice. Mice bearing subcutaneous SMMC-7721 tumors were used to study radiotherapy ($n=5/\text{group}$). Each group was administered ¹⁷⁷Lu-DTPA-DG (0.1 mL, 0.3 mCi), ¹⁷⁷LuCl₃ (0.1 mL, 0.3 mCi), and 0.9% sodium chloride (0.1 mL) once every 3 d, with four total doses. Animals were kept alive for tumor growth and survival monitoring for 30 d. Tumor volumes were calculated by the following formula: $V = 1/2 L \times W^2$ (where L = long axis and W = short axis). The authors also evaluated the biodistribution after 12 d of ¹⁷⁷Lu-DTPA-DG treatment.

Statistical analysis

SPSS 21.0 software was used for analysis. The results are shown as the mean $\pm$ standard deviation. Differences between two groups were determined by a Student's *t* test. A probability value of $p < 0.05$ was considered significant. The radiochemical labeling data were analyzed by using Origin Pro8 software. Survival analysis was performed by the Kaplan-Meier method and long-rank tests (GraphPad Prism 5.0 software; GraphPad Software, Inc.).

Results

Radiochemistry and characteristics of the labeled compounds

The following experimental conditions were used for ¹⁷⁷Lu-DTPA-DG: 2 mCi (50 μL) ¹⁷⁷LuCl₃ solution (40 mCi/mL) was added to a tube containing 0.05 mg (5 μL) DTPA-DG (10 mg/mL), pH 5–6, and incubated at room temperature for 1 h. The final mixture had a specific activity of 40 mCi/mg.

FIG. 2. HPLC analysis of ¹⁷⁷Lu-DTPA-DG (A) and ¹⁷⁶Lu-DTPA-DG (B). HPLC, high-performance liquid chromatography.

FIG. 3. TLC patterns of $^{177}\text{LuCl}_3$ (A) and the $^{177}\text{Lu-DTPA-DG}$ complex (B); this experiment was repeated three times. TLC, thin-layer chromatography.

The reaction scheme of $^{177}\text{Lu-DTPA-DG}$ is shown in Figure 1. As shown in Figure 2, the radiochemical purity of the $^{177}\text{Lu-DTPA-DG}$ complex was $>97\%$. The radiochemical yield of $^{177}\text{Lu-DTPA-DG}$ was also confirmed as $>97\%$, and $^{177}\text{LuCl}_3$ ($R_f=0-0.1$) remained at the point of origin, whereas $^{177}\text{Lu-DTPA-DG}$ ($R_f=0.9-1.0$) moved to the solvent front under the same conditions (Fig. 3). With regard to the *in vitro* stability, the radiochemical yield of $^{177}\text{Lu-DTPA-DG}$ was still $>95\%$ ($n=3$) after 24 h at room temperature ($25^\circ\text{C} \pm 2^\circ\text{C}$), as shown in Figure 4. Hence, the compound was stable.

Cellular uptake rates of radiotracers

Figure 5 shows the results of the analysis of the cellular uptake of radiotracers. The uptake rate of $^{177}\text{Lu-DTPA-DG}$ was slightly lower than that of $^{18}\text{F-FDG}$ but was obviously higher than that of $^{177}\text{Lu-DTPA}$. The cellular uptake rates of $^{177}\text{Lu-DTPA-DG}$ were higher than those of $^{177}\text{Lu-DTPA}$ ($3.66\% \pm 0.45\%$ vs. $0.10\% \pm 0.01\%$, $t=15.879$, $p=0.001$) at 1 h. As shown in Figure 6, the addition of 1.0 mg D-glucose

per well reduced the uptake of $^{18}\text{F-FDG}$ ($p<0.005$) but had no effect on the $^{177}\text{Lu-DTPA-DG}$ uptake.

Biodistribution

Table 1 shows the results of the biodistribution studies. The blood and organs were harvested at different time points, and the radioactivity was measured. The mean percentage uptakes of the injected dose per gram of tumors at 1, 4, and 24 h after injection were $3.96 \pm 0.49\% \text{ID/g}$, $1.80 \pm 0.74\% \text{ID/g}$, and $0.77 \pm 0.11\% \text{ID/g}$, respectively. The activity of $^{177}\text{Lu-DTPA-DG}$ decreased with time in all the organs tested. At 24 h postinjection, the radioactivity that accumulated in the blood and organs was $<0.85\% \text{ID/g}$. The primary route of clearance was renal. The uptake ratio of the tumor/muscle, tumor/liver, and tumor/blood was 5.07, 3.22, and 3.12, respectively, at 1 h. After 12 d of $^{177}\text{Lu-DTPA-DG}$ treatment, the tumor/blood uptake ratio was 3.09.

FIG. 4. TLC patterns of the stability of $^{177}\text{Lu-DTPA-DG}$ after 24 h ($n=3$).

FIG. 5. The cellular uptake of $^{18}\text{F-FDG}$, $^{177}\text{Lu-DTPA-DG}$, and $^{177}\text{Lu-DTPA}$ in SMMC-7721 cells at different times ($n=3$). FDG, fluorodeoxyglucose.

FIG. 6. The cellular uptake of ¹⁸F-FDG and ¹⁷⁷Lu-DTPA-DG when 1.0 mg D-glucose was administered ($n=3$). $*p<0.005$.

Imaging

Micro-PET images of nude mice after ¹⁸F-FDG injection and whole-body scintigraphic images after ¹⁷⁷Lu-DTPA-DG injection are shown in Figure 7. Both ¹⁸F-FDG and ¹⁷⁷Lu-DTPA-DG uptake in tumors in mice could be observed in 4 h. Furthermore, the ¹⁷⁷Lu-DTPA-DG was evident in the tumors in mice (Fig. 8B, arrow), but the ¹⁷⁷Lu-DTPA uptake at the same location (Fig. 8A) was unremarkable at 90 min after injection.

Radiotherapy

The therapeutic effect of ¹⁷⁷Lu-DTPA-DG on tumor-bearing mice was compared with that of ¹⁷⁷LuCl₃ and normal saline. Kaplan–Meier curves (Fig. 9) demonstrated that mice that received ¹⁷⁷Lu-DTPA-DG survived longer than animals that received ¹⁷⁷LuCl₃ (25.5 d vs. 14.5 d, $p=0.0007$, log-rank test) and normal saline (25.5 d vs. 14 d, $p=0.0001$, log-rank test). ¹⁷⁷Lu-DTPA-DG induced the

most efficient tumor growth inhibition. The ¹⁷⁷Lu-DTPA-DG group exhibited significantly lower tumor volumes on day 12 than the ¹⁷⁷LuCl₃ group ($268.58 \pm 17.96 \text{ mm}^3$ vs. $507.43 \pm 55.72 \text{ mm}^3$, $p=0.002$) and the normal saline group ($268.58 \pm 17.96 \text{ mm}^3$ vs. $483.68 \pm 27.51 \text{ mm}^3$, $p<0.05$), as shown in Figure 10.

Discussion

In their study, DTPA-DG could be labeled with ¹⁷⁷Lu with high efficiency and stability at room temperature. Compared with the ¹⁷⁷Lu-DTPA group, the ¹⁷⁷Lu-DTPA-DG group showed higher cellular uptake of the radiotracer. In the biodistribution study, the authors also found that the distribution of ¹⁷⁷Lu-DTPA-DG in the tumor was higher than that in other organs. The tumor/muscle, tumor/liver, and tumor/blood ratios were high after treatment with ¹⁷⁷Lu-DTPA-DG for 12 d. In addition, imaging studies revealed that ¹⁷⁷Lu-DTPA-DG injections could clearly identify tumors. These findings suggest that ¹⁷⁷Lu-DTPA-DG can enter tumor cells and shows a good Target/Non-Target ratio.

Because tumor cells do not rely on mitochondrial oxidation for energy, most of their energy is generated through glycolysis.¹⁶ Thus, cancer cells show high rates of glucose uptake and glycolysis. To meet the high energy needs of a malignant tumor, GLUTs are highly expressed on tumor cell membranes. There are more than 10 known GLUT subtypes. DTPA-DG is formed by the conjugation of D-glucosamine molecules to DTPA. Generally, GLUT-1 and GLUT-3 can transport glucosamine in addition to glucose and are over-expressed in different cancer cells. GLUT-2 has an ~20-fold higher affinity for glucosamine than for glucose.¹⁷ ¹⁸F-FDG is transported into cells by GLUTs, especially GLUT-1, and is subsequently phosphorylated by hexokinase. FDG uptake in HCC is related to the degree of tumor differentiation. Well-differentiated HCC has a lower level of GLUT-1 expression and higher expression of glucose-6-phosphatase.^{18,19} than poorly differentiated HCC, which contributes to the low accumulation of FDG uptake in well-differentiated HCC. However, some studies have shown the high uptake of FDG

TABLE 1. ¹⁷⁷Lu-DTPA-DG BIODISTRIBUTION (%ID/g) IN SMMC-7721 TUMOR-BEARING NUDE MICE AT 1, 4, AND 24 H AFTER INJECTION ($N=4$)

Organ/tissue	%ID/g			
	1 h	4 h	24 h	12 d ^a
Kidney	2.28 ± 0.03	1.33 ± 0.30	0.85 ± 0.35	0.81 ± 0.20
Liver	1.23 ± 0.32	0.88 ± 0.28	0.34 ± 0.19	0.62 ± 0.30
Spleen	1.09 ± 0.39	0.66 ± 0.20	0.35 ± 0.01	0.31 ± 0.20
Stomach	0.39 ± 0.09	0.34 ± 0.16	0.10 ± 0.17	0.27 ± 0.12
Colon	0.58 ± 0.22	0.18 ± 0.09	0.12 ± 0.04	0.07 ± 0.03
Heart	0.37 ± 0.02	0.19 ± 0.01	0.14 ± 0.01	0.22 ± 0.09
Lung	0.72 ± 0.02	0.61 ± 0.26	0.08 ± 0.08	0.25 ± 0.12
Bone	0.96 ± 0.32	0.67 ± 0.15	0.65 ± 0.12	0.79 ± 0.17
Muscle	0.78 ± 0.30	0.43 ± 0.16	0.06 ± 0.04	0.09 ± 0.05
Blood	1.27 ± 0.34	1.06 ± 0.24	0.31 ± 0.14	0.46 ± 0.35
Tumor	3.96 ± 0.49	1.80 ± 0.74	0.77 ± 0.11	1.42 ± 0.56
Tumor/muscle	5.07	4.19	12.8	15.8
Tumor/liver	3.22	2.04	2.26	2.29
Tumor/blood	3.12	1.70	2.48	3.09

^aIndicates the biodistribution after 12 d of ¹⁷⁷Lu-DTPA-DG treatment.

¹⁷⁷Lu-DTPA-DG, ¹⁷⁷Lu-diethylenetriamine penta-acetic acid-deoxyglucose; %ID/g, percentage uptake of the injected dose per gram.

FIG. 7. Scintigraphic images were acquired after the injection of ^{18}F -FDG (0.1 mCi) and ^{177}Lu -DTPA-DG (0.3 mCi) at different times (a, A, 30 min; b, B, 60 min; c, C, 90 min; d, D, 120 min; e, E, 150 min; f, F, 180 min; g, G, 210 min; h, H, 240 min) in a mouse bearing a hepatic tumor (three mice per group). Arrows indicate the position of the tumors.

in poorly differentiated HCC and cholangiocarcinoma.^{18,20} Theoretically, DTPA-DG is similar to FDG, and ^{177}Lu -DTPA-DG uptake in HCC might also be affected by the degree of differentiation. In their study, the cellular uptake of ^{177}Lu -DTPA-DG was not blocked by high levels of D-glucose, indicating that the mechanism of the cellular uptake of ^{177}Lu -DTPA-DG may be independent of GLUTs or may involve other related mechanisms that are different from the mechanisms of D-glucose. Based on the available data, they are unable to determine whether the tumor uptake of ^{177}Lu -DTPA-DG is specific or nonspecific. The mechanisms of glucose hypermetabolism in tumors are complex, and the

detailed mechanism of the cellular uptake of ^{177}Lu -DTPA-DG needs to be further studied.

Radionuclide therapy has become increasingly important for the treatment of malignant tumors. Many new radiotherapy agents for the targeted radiotherapy of tumors have been investigated, including ^{131}I ,²¹ ^{223}Ra ,²² and ^{188}Re .⁵ Internal radiotherapy is a viable method for the treatment of unresectable HCC. The main radiopharmaceuticals used for intra-arterial radionuclide therapy are ^{90}Y -labeled resin and glass microspheres. Two types of ^{90}Y -labeled resin or glass microspheres have been approved by the Food and Drug Administration.²³ Despite some studies showing that this

FIG. 8. Scintigraphic images were acquired 90 min after the injection of 0.3 mCi ^{177}Lu -DTPA (A, control group) and ^{177}Lu -DTPA-DG (B) in xenograft-bearing nude mice ($n=3$). The black arrow indicates the position of the tumors.

FIG. 9. Comparison of the Kaplan-Meier survival curve of the three groups of tumor-bearing mice after treatment (five mice per group).

FIG. 10. Comparison of the tumor volume within 12 d of treatment in the three groups (five mice per group).

treatment is useful for liver cancer, it may not be appropriate for some patients, such as patients with poor liver reserve function or extrahepatic metastatic disease.²⁴ Determining the quality and quantity required for ⁹⁰Y is complicated,²⁵ and the high cost and limited supply limit its clinical use. ⁹⁰Y emits pure β^- -particles with a half-life of 64.1 h. Since ⁹⁰Y lacks γ -emission, it is not easy to obtain any information about the positioning and biological distribution of ⁹⁰Y microspheres in patients by imaging after the administration of a therapeutic dose. ¹⁷⁷Lu has some physical characteristics that make it a promising radioisotope for radioimmunotherapy. One of the advantages of ¹⁷⁷Lu is that it can be inexpensively produced on a large scale.⁹ In their study, mice that received ¹⁷⁷Lu-DTPA-DG survived longer and had slower tumor growth than mice in the other groups. These results regarding the therapeutic response suggest that ¹⁷⁷Lu-DTPA-DG may be an efficient radiotherapeutic agent.

A previous study showed that ¹⁸⁸Re-DTPA-DG had an apoptotic effect on carcinoma cells.²⁶ Both ¹⁸⁸Re and ¹⁷⁷Lu can emit γ photons for imaging and β^- -particles for therapy, but the characteristics of these radionuclides are different. ¹⁸⁸Re is obtained from a ¹⁸⁸W/¹⁸⁸Re generator in clinical settings and has a half-life of 0.7083 d, with a complicated decay mechanism.²⁷ ¹⁸⁸Re can emit β^- -particles with maximum and mean energies of 2.12 and 0.76 MeV, respectively,²⁷ and the mean penetration distance in tissue is 3.8 mm. Compared with ¹⁸⁸Re, the ¹⁷⁷Lu decay mechanism is simple, with a half-life of 6.646 d, and the average soft tissue penetration distance is 2 mm, which is more suitable for small tumor radionuclide therapy. A large amount of ¹⁷⁷Lu can be obtained at one time through neutron irradiation energy in a nuclear reactor. The suitable half-life not only ensures the time required for radiolabeling and quality control but also provides a strong logistical advantage for site transportation away from radioisotope production sites or radioactive centers.

Conclusions

In their study, DTPA-DG could be labeled with ¹⁷⁷Lu with a high radiochemical purity. The *in vitro* stability of the complex was found to be adequate. The results of cellular uptake, biodistribution, imaging, and radiotherapeutic studies indicate that ¹⁷⁷Lu-DTPA-DG could become a liver

radiopharmaceutical agent, and this promising result deserves further study.

Disclosure Statement

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