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Preparation and primary biological evaluation of novel nitrido-^{188}Re complexes/lipiodol

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Abstract Two new nitrido-^{188}Re complexes were prepared by a modified method in high yield. These complexes were stable *in vitro*. The biodistribution in normal mice showed that these nitrido-^{188}Re complexes could accumulate in liver and dissipate quickly from almost all organs. TAE was performed with the use of lipiodol solutions of two complexes to rabbit VX2 liver tumor models. SPECT images showed that the two lipiodol solutions could remain in tumor for about 9 h (^{188}ReN-NEPTDD/lipiodol) and 12 h (^{188}ReN-NEMMPTDD/lipiodol), respectively.

Key words Nitrido, TDD derivatives, Lipiodol, Liver cancer

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1 Introduction

Liver cancer, in particular, hepatocellular carcinoma (HCC), is a common malignant tumors[1]. Hepatectomy and liver transplantation are the main curative treatment. However, most patients are not eligible for surgery because of their liver dysfunction or considerable tumor size. For such situation, transcatheter arterial embolization (TAE) is a good alternative for HCC treatment[2].

Blood supply of liver cancer cells is mainly obtained from the hepatic artery, while that of normal hepatic cells is mainly obtained from the portal vein. Consequently, embolic agents could accumulate in liver cancer cells by embolization through the hepatic artery. Lipiodol is just an excellent embolic agent. In recent years, many attempts have been made to label lipiodol with therapeutic radioisotopes, including ^{131}I[3,4], ^{90}Y[5,6], and ^{188}Re[7-9] to develop promising TAE agent. Among the radioisotopes, ^{188}Re is an excellent candidate for radionuclide therapy. It possesses suitable nuclear characteristics ($E_{\beta max}$=2.1 MeV, 71%, $t_{1/2}$=16.9 h) and its preparation is easy. $^{188}ReO_4^-$ could be obtained from ^{188}W/^{188}Re generator like the ^{99}Mo/^{99m}Tc generator currently in use and its γ-rays can be used to monitor biodistribution and calculate the dose.

Researchers have made great efforts to develop new labeled compounds of ^{188}Re, such as ^{188}Re-TDD, ^{188}Re-HDD, ^{188}Re-SSS, etc. Their lipiodol solutions could remain in liver tumor for hours, but the labeling yields and stability of ^{188}Re-L were not satisfying. The research presented herein was inspired by recent researches on ^{99m}Tc≡N core complexes for their better stability than ^{99m}Tc=O core complexes[10-12]. Rhenium (Re) and technetium (Tc) belong to the same group in the periodic table, hence similar chemical behavior of the two elements. Therefore, the method for preparing ^{99m}Tc labeling compounds from $^{99m}TcO_4^-$ could be modified for preparing ^{188}Re labeling compounds from $^{188}ReO_4^-$. The difficulty of reduction and the instability of reduced ^{188}Re compounds are however the main challenge[13]. The modification used in this research was based on an improved two-step method used to prepare ^{99m}Tc≡N core compound[14]. $[^{188}ReN]_{int}^{2+}$ and

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^{188}ReN-L were obtained in the presence of oxalate and acetic hydrazide (AH) in high yield. The stability of ^{188}ReN-L *in vitro* and the biodistribution in normal mice were then studied. Furthermore, rabbit VX2 liver tumor models were established and TAE was performed to evaluate primary biological characters of ^{188}ReN-L/lipiodol solutions.

2 Materials and methods

2.1 Materials

Acetic hydrazide (AH), succinic dihydrazide (SDH), oxalic dihydrazide (ODH) and stannous chloride dihydrate were purchased from Aldrich Chemical Co., USA. Polyamide strip was from Sijia Biochemistry Plastic Factory, China. ^{188}W/^{188}Re generator was from Shanghai Institute of Applied Physics, Chinese Academy of Sciences. All other chemicals were of reagent grade and were used without further purification.

2.2 Analysis methods

Radiochemical purity (RCP) was measured by thin layer chromatography (TLC) and HPLC. TLC was performed on polyamide strip and was eluted with saline and acetonitrile (CH_3CN). R_f values for some selected moieties are shown in Table 1.

Table 1 R_f value for some selected moieties

Samples	$^{188}ReO_4^-$	$^{188}ReO_2{\cdot}nH_2O$	$[^{188}ReN]_{int}^{2+}$	^{188}ReN-complexes
Saline	0.1	0.1	0.8~1.0	0.1~0.2
CH_3CN	0.3~0.4	0.1	0.1	0.7~0.8

HPLC was carried out on a System Gold instrument equipped with a solvent Module 110B, and a radioisotope detector Module 170 (Beckman Instruments). HPLC solvents consisted of solvent A, trifluoroacetic acid (TFA) (0.1% v/v in water), and solvent B, CH_3CN. TLC analyses were carried out using a C-18 reversed-phase column (250×4.6 mm, Diamonsil™) at a flow rate of 1 mL·min^{-1} with a gradient elution: 0~7 min, 100% B; 7~18 min, 20% A and 80% B; 18~20 min, 100% A; 20~25 min, 100% B.

2.3 Preparation of ^{188}ReN-NEPTDD and ^{188}ReN-NEMMPTDD/lipiodol

NEPTDD(2,2,9,9-tetramethyl-4,7-diaza-4-ethyl-piperidinyl-1,10-decanedithiol) and NEMMPTDD(2,2,9,9-tetramethyl-4,7-diaza-4-ethyl-(3,5-dimethyl)-piperidinyl-1,10-decanedithiol), the two TDD derivatives, were synthesized by six steps according to procedures in Refs.[7,15-17] and were stored as hydrochloride salts.

The nitrido-^{188}Re complex was prepared by an improved two-step synthesis:

(1) $^{188}ReO_4^- + AH + SnCl_2{\cdot}2H_2O + (HOOC)_2 \rightarrow [^{188}ReN]_{int}^{2+}$

(2) $[^{188}ReN]_{int}^{2+}$ + NEPTDD/NEMMPTDD → ^{188}ReN-NEPTDD/NEMMPTDD

Generator-eluted [$^{188}ReO_4^-$] solution (approximately 74 MBq) were added to the mixture of AH, oxalate and $SnCl_2{\cdot}2H_2O$ in a test tube. The mixture was adjusted to pH 2.0 before a 30-min reaction at room temperature to obtain $[^{188}ReN]_{int}^{2+}$. NEPTDD or NEMMPTDD was then added to intermediate system and increased the pH value to 7.0. It was subsequently heated at 70℃ for 30 min to prepare ^{188}ReN-L. The yields were measured by TLC. All the mixtures were also measured by HPLC.

Stability of the nitrido-^{188}Re complexes was studied by measuring the RCP using TLC at different time intervals after preparation.

Lipiodol was added to the prepared system of ^{188}ReN-L and the mixture was shaken properly to extract the nitrido-^{188}Re complexes into lipiodol. The mixture was centrifuged for 10 min in a centrifuge tube to layer the water and the lipiodol phase. The lipiodol phase containing ^{188}ReN-L was washed by normal saline and collected by a syringe with a long needle.