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Re-188-BMEDA-liposome 奈米標靶藥物第一期學術研究臨床試驗(2/2)

Exploratory Investigational New Drug (eIND) Study for Re-188-liposome Nanoparticle Human Clinical Trial

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目　錄

中文摘要

微脂質體作為化療藥物的輸送系統已被廣泛用於治療癌症。加上藥物的脂質體較易分布於具滲漏性的腫瘤相關血管，通過一個所謂"增強通透性和保留(Enhanced Permeation Retention, EPR)"的過程而達到脂質體藥物累積至腫瘤的優勢，如此可改善常規化療藥物的藥理學特性 。核研所發展之 脂質體包覆 銖-188藥物 (Re^{188}-liposome)已在皮下及肺部轉移之大腸癌 動物模型中顯 現療效 。根據這些令人振奮 的腫瘤與毒性測試實驗數據，我們將利用脂質體包覆 銖-188藥物進行 一個探索性新藥研究以評估其體內分佈、藥 物 動力學及安全性，受試病人 將為傳統 治療失敗之轉移性癌症患者 。

關鍵詞：銖-188 (Re^{188});脂質體(liposome); 新藥研究(investigational new drug); 藥 物 動力學 (pharmacokinetics)

Abstract

Liposomes coupled with therapeutics are more easily distributed into leaky tumor-associated blood vessels, through so-called "enhanced permeation retention" (EPR), leading to preferable accumulation of liposomal drugs within tumor microenvironment. ^{188}Re-liposome is a novel liposomal therapeutic coupling radioisotope, ^{188}Re, developed by Institute of Nuclear Energy Research (INER). In preclinical studies, it displayed therapeutic effect on subcutaneous tumor growth of murine CT26 and human LS174T colon cancers. The inhibitory effect was also shown in lung (and peritoneal) metastatic models of CT26. Given the encouraging results of preclinical efficacy and toxicity studies, an exploratory investigational new drug study for evaluation of distribution, pharmacokinetics and safety of ^{188}Re-liposome is proposed for treatment of metastatic cancer patients who failed or cannot tolerate standard chemotherapy.

Keywords: ^{188}Re; liposome; investigational new drug; pharmacokinetics

壹、計畫緣起與目的

Nanoscale liposomes as drug delivery systems containing chemotherapy drugs have been widely used for treatment of cancer[1,2]. Many of the pharmacological properties of conventional chemotherapy drugs can be improved using this drug delivery system, which composed primarily of lipids and/or polymers. These novel therapeutic complexes are designed to improve the pharmacokinetics (PK) and biodistribution (BD) of the coupled chemotherapy drugs. As compared with conventional chemotherapy, circulation of liposome coupled chemodrugs could be prolonged. Moreover, the liposome coupled drugs could be redirected to relatively leaky tumor-associated blood vessels, leading to superior accumulation in tumors via a process often referred to as the "enhanced permeability and retention" (EPR) effect[3,4]. The most notable examples are the pegylated liposomal doxorubicin, which is approved for cancer treatment with substantial decrease in toxicity as compared to doxorubicin free drug[5,6].

Although liposomal doxorubicin displayed superior localization of doxorubicin in relatively leaky tumor microenvironment, killing of tumor cells required release of this chemodrug and the coupling to its target, DNA. To take advantage of the EPR effect of liposomal drug and the cytotoxic effect of radiation even in the absence of internalization of liposome by cancer cells, we had developed a liposomal therapeutics, ^{188}Re-BMEDA-labelled pegylated liposome

(^{188}Re-liposome), and examined its biodistribution, pharmacokinetics and cytotoxic effects, compared with unencapsulated ^{188}Re-BMEDA control in a subcutaneous murine C26-colon tumor model[7]. MicroSPECT/CT images were evaluated to characterize the distribution and tumor targeting of ^{188}Re-liposome in mice. The highest uptake of liposome in tumors was 3.62% +/- 0.73% at 24 h after ^{188}Re-liposome administration, and the tumor to muscle ratio of RBLPL was 7.1-fold higher than that of ^{188}Re-BMEDA[7]. The results of the pharmacokinetics revealed that the area under the tissue concentration-time curve (AUC) of ^{188}Re-liposome was 4.7-fold higher than that of unencapsulated ^{188}Re-BMEDA. These results suggested the potential benefit and advantage of ^{188}Re-labeled nanoliposomes for imaging and treatment of malignant diseases[8].

Similar biodistribution and pharmacokinetics studies were also conducted in a C26 colon carcinoma ascites mouse model[9]. The biodistribution studies indicated that the radioactivity in ascites was 69.96±14.08 percentage injected dose per gram (% ID/g) at 1h to 5.99±1.97% ID/g at 48 h after ip administration of ^{188}Re-liposome. The levels of radioactivity in tumor were progressive accumulation to a maximum of 6.57±1.7% ID/g at 24 h. The radioactivity of ^{188}Re-BMEDA in ascites reached the maximum level of 54.89±5.91% ID/g at 1 h and declined rapidly with time. Pharmacokinetic studies revealed that the terminal half-life, total body clearance and area under the curve of ^{188}Re-liposome were 5.3-, 9.5- and 9.4-fold higher than that

of ^{188}Re-BMEDA in blood, respectively. These results suggested that the long circulation, bioavailability and localization of ^{188}Re-liposome in tumor and ascites sites, which also demonstrate that the ip administration of ^{188}Re-liposome is a potential multifunctional nanoradiotherapeutics and imaging agents on a C26 colon carcinoma ascites mouse model.

Most significantly, the therapeutic effects of ^{188}Re-liposome were explored on various tumor models, including subcutaneous inoculated murine CT26 and human LS-174T models as well as C26 colon carcinoma ascites mice model. ^{188}Re-liposome suppressed tumor growth and increased survival time of tumor-bearing mice[10,11]. While comparing 5-FU with ^{188}Re-liposome, both delivered at 80% of MTD, ^{188}Re-liposome demonstrated superior anticancer effect and prolonged survival time of either CT26- or LS-174T-bearing mice. Additionally, preclinical toxicity study performed by the research team at INER did not displayed discernible toxicity in both mice and rats. The dosimetry data of ^{188}Re-liposome regarding the distribution and absorbed radiation doses of tumor and normal tissues will be a great indicator for both potential therapeutic and side effects. The OLINDA/EXM program was adopted to calculate mean values of %IA/g for the organs in mice which were extrapolated to uptake in organs and tumor of various sizes of a 70 kg adult. The deduced absorption doses were about 20 mGy/MBq for 40-gram tumor and up to more than 100 mGy/MBq for small tumors (0.5 – 6 grams).

Whereas, the deduced absorption doses of normal organs were well below the upper limits.

Based on the encouraging preclinical efficacy and toxicity results as well as favorable dosimetry data, it will be worthwhile to explore the potential toxicity and benefit of 188Re-liposome in human clinical trial for treatment of detrimental diseases such as colonrectal cancer with multiple metastases.

貳、研究方法與過程

This is an open-label, single-arm, Phase 0 study, and will e conducted in single medical center: Taipei Veteran General Hospital (台北榮民總醫院). Following the guidance of exploratory IND study published by US Food and Drug Administration (FDA0, the study aims to investigate the safety of microdose ^{188}Re-liposome in patients with metastatic cancers and who are refractory to current standard/available therapies. A total of 18 eligible subjects with malignancies are projected to be enrolled. Subjects will be recruited one after another, i.e., no new subject will be recruited until the previous subject has completed the study.

The screening duration will be no more than 10 days. Each subject will be hospitalized prior to drug administration (e.g., day 0) and stay in the hospital for 3 days and 3nights (till Day 3 after completion of SPECT and related examination procedures). Subjects are allowed to stay in the hospital for up to 4 days and 4 nights for the last imaging time point, i.e., 72h. If subjects do not want to stay in the hospital for the last day, they will e asked to return to the clinic visit for radioactivity and SPECT scan.

At 0h, Day 1, each subject will receive a microdose of less than 3 mCi ^{188}Re-liposome (<3 mCi in 0.7 ml per injection) by intravenous drip at day 1 (0 h).The time with drug administration will be regarded as 0 h of the study. The SPECT scan, which provides information for biodistribution and dosimeter, will be

conducted one hour after drug administration, as well as at 4h, 8h, 24h, 48h and 72h post-injection. Similarly, blood sample will be taken at the mentioned time points (namely 1h, 4h, 8h, 24h, 48h and 72h) right before SPECT scan for blood and plasma radioactivity analysis. Urine sample will be collected on a 24-h basis for estimating the daily and cumulative urinary excretion of ^{188}Re-liposome.

For pharmacokinetics, blood samples with anticoagulants were collected at 1h, 4h, 8h, 24h, 48h and 72h. The concentrations of radioactivity in blood were expressed as percentage injected dose (%ID) per milliliter (%ID/ml).Pharmacokinetic parameters were determined using the WinNonlin software version 5.3 (Pharsight Corp., Mountain View, CA). Noncompartmental analysis was used with the log/linear trapezoidal rule. Parameters, including terminal half-life (T1/2λz), Tmax, Cmax, total body clearance (Cl) and area under the curve (AUC) were determined.

Vital signs, physical examination, laboratory tests (hematology, biochemistry and urinalysis) will be performed at the Screening Visit (≦ 10 days prior to Day 1) and the results will serve as baseline. Subsequent examinations for safety monitor will be conducted at Day 1 (right before and after drug administration), Day 2 (24h), Day 3 (48h), Day 4 (72h), 9 to 16 days and 28 to 30 days after ^{188}Re-liposome injection. Any adverse events (Graded by CTCAE v4.03) and concomitant medications/therapies will be recorded on the CRFs throughout the study.

Detailed timing for performing assessments and procedures could refer to Table 1, which show the study flow chart.

Table 1. The Flow Chart lists all of the assessments and indicates with an “X” the visits when they are performed.

EVENT	Screen	188Re Adim.	Follow-up					
Day	≦10 days	Day1	Day 1	Day 2	Day 3	Day 4	Day 9~16[2]	Day 28~30[2]
Hour		0h[1]	1h, 4h and 8h	24h	48h	72h		
Informed consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographic Data & Medical History	X							
Serum or Urine Pregnancy Test	X							
Karnofsky Performance Scale/ECOG	X	X		X	X	X		

SPECT for biodistribution and dosimetry			X	X	X	X		
Radioactivity of blood, plasma and urine[3]			X	X	X	X		
Vital Sign	X	X[4]	X	X	X	X	X	X
Physical Examination	X	X[4]	X	X	X	X	X	X
Hematology Test	X	X[5]		X	X	X	X	X
Biochemistry Test	X	X[5]		X	X	X	X	X
Urinalysis	X				X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Drug Administration		X						
Concomitant Medications	X	X		X	X	X	X	X

[1] KPS or ECOG will be evaluated before drug injection. Additionally, each subject will be hospitalized prior to drug administration (e.g., day 0) and stay in the hospital for 3 days and 3 nights (till Day 3 after completion of SPECT and related examination procedures). Subjects are allowed to stay in the hospital for up to 4 days and 4 nights for the last imaging time point, i.e., 72h. If subjects do not want

to stay in the hospital for the last day, they will be asked to return to the clinic visit for radioactivity and SPECT scan.

[2] There will be two visits scheduled for safety monitor. The first visit within 9 to 16 days after drug administration and another visit within 28-30 days after drug administration will be scheduled for safety monitor. Laboratory tests, such as hematology, biochemistry and urinalysis, will be conducted. Any AEs occur throughout the study will be graded by CTCAE v4.03 and shall be recorded on the CRFs.

[3] Urine will be collected in a 24-h basis except for Day 4. Thus, daily and cumulative urinary excretion of ^{188}Re-liposome can be determined.

[4] The vital sign and physical examination will be performed twice before and right after drug administration.

[5] Samples will be taken before drug administration and the result will serve as baseline. If the visit window between Screening Visit and Day 1 is less than 7 days, blood/urine sample will not be taken and the lab test results at screening will serve as baseline instead.

The SPECT imaging will be performed using low-energy, high-resolution collimators at 1 h right after drug injection, as well a at 4 h, 8 h, 24 h, 48 h and 72 h after intravenous injection of less than 3 mCi (in 0.7 ml) of ^{188}Re-liposome.The energy window will be set as 155 KeV.

The SPECT images will be acquired using the scanner ECAM+ (Siemens). The source and detector are mounted on a circular gantry, allowing it to rotate 360° around a subject positioned on a stationary bed. The SPECT images will be reconstructed and analyzed using filter-back projection methods. The standard uptake value (SUV) will be employed to calculate the ratio of tissue/organ radioactivity concentration. The SUV will be determined from the radioactivities in the region of interest (ROI) on the tumor or organs (e.g., brain, skin, bone, spleen, kidney, heart, liver, lung, intestine (large/small), bladder, muscle, stomach, testes (male only), ovaries (female only), tumor, pancreas, etc). The SUV will be calculated according to the following formula:

$$\text{SUV(tumor or organs)} = \frac{\text{Mean ROI activity (mCi/kg) (at various time points)}}{\text{[total injected dose (mCi)/subject body weight (kg)]}}$$

$$\text{\%ID/kg(tumor or organs)} = \frac{\text{Mean ROI activity (mCi/kg) (at various time points)}}{\text{[total injected dose (mCi)]}}$$

To determine the blood clearance profile for ^{188}Re-liposome, the blood samples will be collected approximately 1 h after drug administration, as well as at 4h, 8h, 24h, 48h and 72 h post-injection. The weight of each blood sample will be determined by counting the volume of the blood sample.

Blood sample will be taken into tube containing anticoagulant (lithium heparin).

Whole blood radioactivity will be measured by continuing triplicate 1-mL specimens of whole blood and standard dilutions (10^{-1} to 10^{-4}) of the injected liposome by the dose-calibrator. The remainder of the blood sample will be then centrifuged to separate the cellular components from the plasma fraction. The radioactivity of the triplicate samples of plasma will be measured separately.

The activity level immediately after injection will be calculated assuming that initially, 100% of the activity is in the blood and that the total blood weight represented 7% of the body weight. The results will be expressed as the percentage of injected dose per gram of blood/plasma (%ID/mL).

Serial 24h urine collection will be performed on a 24h basis for estimating the total amount of radioactivity excretion/day in the urine in that day except for day 4 (72h) since subjects may not stay in the hospital. The activity level immediately after injection will be regarded as 100% of the activity in the urine.

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