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# A phase I clinical and pharmacokinetic study of paclitaxel liposome infused in non-small cell lung cancer patients with malignant pleural effusions

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ARTICLE INFO

*Article history:*
Received 16 August 2009
Received in revised form 16 November 2009
Accepted 5 February 2010
Available online 6 March 2010

*Keywords:*
Paclitaxel
Liposome
Non-small cell lung cancer
Malignant pleural effusions
Intrapleural injection
Treatment
Phase I
Clinical efficacy
Toxicity
Pharmacokinetics

ABSTRACT

*Purpose:* To investigate the feasibility, pharmacokinetics, efficacy and toxicity of intrapleural paclitaxel liposome injection in non-small cell lung cancer (NSCLC) patients with malignant pleural effusions.

*Patients and methods:* Twelve of 15 NSCLC patients with malignant pleural effusions were treated with paclitaxel liposome and three were treated with free paclitaxel. Adequate pleural fluid, blood and urine were collected for pharmacokinetic study. The clinical efficacy and toxicity were synthetically evaluated according to the correlative criteria.

*Results:* The overall toxicity of paclitaxel liposome was lower than that of free paclitaxel. In the patients treated with paclitaxel liposome, there were minimal local chest pain, anaphylaxis, anaemia, neutropaenia and hepatotoxicity. The complete response rates of pleural effusion at the first, second, third and sixth month were, respectively, 27.3%, 18.2%, 9.1% and 9.1%, and overall response rates were 90.9%, 72.7%, 63.6% and 54.5%, respectively. Pharmacokinetic study showed that mean $C_{max,IP}$, $T_{1/2}$ and $AUC_{0\rightarrow 96,IP}$ in pleural fluid were, respectively, about 2-fold, 2-fold and 2.5-fold than those of free paclitaxel, and $AUC_{0\rightarrow 96,Pla}$ in plasma was also much higher than that of free paclitaxel, however, excretory rate in 24 h from urine was lower than that of free paclitaxel.

*Conclusions:* This study demonstrated that paclitaxel liposome was a more useful agent than free paclitaxel for the treatment of malignant pleural effusions because of its relatively low toxicity and distinct pharmacokinetic characteristics. The phase II study of a large number of patients was recommended to confirm this finding.



## 1. Introduction

Malignant pleural effusions, which were often attended with symptoms of dyspnoea, cough and chest pain that could negatively affect the patients' quality of life, occured frequently in patients with advanced or disseminated cancer. Lung cancer was the major cause of malignant pleural effusion.[1–3] Malignant pleural effusions caused by small cell lung cancer were likely to respond to systemic chemotherapy,[4] but those caused by non-small cell lung cancer (NSCLC), accounting for 80–85% of cases of lung cancer, did not, and often required local treatment. Specifically local treatment was likely to be

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doi:10.1016/j.ejca.2010.02.002

more important for the advanced NSCLC patients, who did not bear surgery therapy.

The most widely used local therapy for malignant pleural effusions was tube drainage with intrapleural instillation of sclerosing agents to prevent fluid reaccumulation. Sclerosing agents principally consisted of bleomycin, doxycycline, tetracycline and talc.[5,6] In addition to sclerosing agents, local chemotherapy agents, including cisplatin and paclitaxel, had be used in intracavitary chemotherapy for malignant pleural effusions due to their double abilities to treat the underlying malignancy and provide local control of the effusion.[7,8] Results of phases I and II clinical trials of intrapleural-free paclitaxel in patients with malignant pleural effusions showed that effective intrapleural paclitaxel injection dose was 125 mg/m$^2$ and intrapleural paclitaxel chemotherapy was promising.[8,9] However, some side-effects, including anaphylaxis, chest pain and fever, which might be caused by Cremophor EL solvent, still brought sufferings to patients. To overcome the problem, liposome as a biodegradable, low toxical and solubilised delivery system had been widely accepted in clinical trial.

In this study, the aims were to investigate whether paclitaxel liposome could decrease the toxicity and increase the efficacy and improve pharmacokinetics parameters in comparison with free paclitaxel for the treatment of NSCLC patients with malignant pleural effusions. Its effective dose was selected as 125 mg/m$^2$, and this phase I feasibility, pharmacokinetics, efficacy and toxicity study of intrapleural paclitaxel liposome injection in NSCLC patients with malignant pleural effusions would be reported.

## 2. Patients and methods

### 2.1. *Patient selection*

Fifteen NSCLC patients with a cytologically or histologically confirmed diagnosis of malignant pleural effusion were eligible for this study. Eight were men and seven were women, who had not undergone previous intrapleural therapy, radiotherapy, systemic chemotherapy or endocrine therapy for at least 4 weeks, and all of them had adenocarcinoma. Median patient age was 53 years (range, 37–76 years). All patients met the following criteria: age $\geqslant$ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant$ 2; estimated life expectancy $\geqslant$ 8 weeks; white blood cell (WBC) count $\geqslant 3.0\times10^9$/l; absolute neutrophil count $\geqslant 1.5\times10^9$/l; platelet count $\geqslant 100\times10^9$/l; serum creatinine $\leqslant 1.5\times10^{-2}$ g/l and total bilirubin $\leqslant 1.5\times10^{-2}$ g/l. Those patients who had a small amount of pleural effusion and hepatic renal insufficiency and had any contraindications to instruction of paclitaxel liposome were excluded from this study. This trial was approved by the Hospital Medical Ethics Committees and all patients gave written informed consent before study entry.

### 2.2. *Plan and evaluation of treatment, and response criteria*

Paclitaxel liposome, which was approved by State Food and Drug Administration of China (No. H20030357), was purchased from Nanjing Si Ke Pharmaceutical Co., Ltd. (Nanjing, China) as freeze-dried powder for injection in glass vials containing 30 mg of active drug. Before treatment, the patients were required to have a complete medical history and physical examination including height, weight, performance status and history of therapy, as well as white blood cell count, serum biochemistry, chest radiograph, B-type ultrasonic inspection and computed tomography (CT). To evaluate the amount of pleural effusion and clinical efficacy, B-type ultrasonic inspection and CT scan were performed at 1, 2, 3 and 6 months after therapy unless treatment failure or death.

All patients were admitted to the hospital. A pig-tail catheter was inserted into the pleural cavity under sonographic guiding. Following suction drainage, B-type ultrasonic inspection to confirm lung re-expansion and serve as the baseline for follow-up evaluation of recurrence of effusion was needed. A drainage rate of less than 100 ml/24 h or sonographic evidence of minimal residual effusion was required before intrapleural administration of the drug. For the safe administration of the drug, premedication with corticosteroids was required for all patients, including dexamethasone 20 mg and ranitidine 150 mg intravenously 30 min prior to treatment,[10] and diphenhydramine 20 mg intramuscularly. Then paclitaxel liposome was dissolved in 250 ml of 5% glucose and was instilled into the pleural cavity through the catheter in 30 min as an effective dose (equal to free paclitaxel dose of 125 mg/m$^2$). The dose of free paclitaxel was also set for 125 mg/m$^2$ and it was administered following the same method. After instillation, the patients were asked to change positions at 15 min intervals for 2 h to ensure good dispersion of the drug throughout the pleural space. B-type ultrasonic inspection and CT scan were performed weekly in a month to observe the change of pleural effusion after treatment. If there was a moderate to large amount of effusion remaining, pig-tail catheter drainage was performed and drainage was continued until daily drainage was under 100 ml. The pig-tail catheter was retained in the pleural cavity for a maximum of 4 days when tolerated. Then, the catheter was removed. Only a single instillation of intrapleural paclitaxel liposome or free paclitaxel therapy was carried out for all patients. During hospitalisation, the patients were evaluated for toxicity weekly for 4 weeks after treatment containing anaphylactic reaction, digestive reaction, cardiovascular toxicity, neurotoxicity,

**Table 1 – Chest pain score.**

| Grade | Performance |
|---|---|
| 0 | No pain |
| 1 | Mild pain<br>Narcotic analgesia not required<br>Minimal interference with daily activities<br>Lasts for less than 72 h |
| 2 | Moderate pain<br>Narcotic analgesia required<br>Moderate interference with daily activities<br>Lasts for more than 72 h |
| 3 | Severe pain<br>Narcotic analgesia required<br>Confines patient to bed<br>Severe interference with daily activities |

**Table 2 – Validation parameters of the UPLC method of paclitaxel in plasma, pleural fluid and urine.**

| Validation parameter | Plasma | Pleural fluid | Urine |
|---|---|---|---|
| Analytical wavelength | 227 nm | 227 nm | 227 nm |
| Linearity (μg/ml) | 0.5–20 | 0.5–20 | 0.025–1 |
| *n* | 5 | 5 | 5 |
| Slope (mean ± SD) | 9172 ± 96 | 6822 ± 44.38 | 685,600 ± 24,744 |
| Intercept (mean ± SD) | 805 ± 72 | 1400 ± 275.95 | 3106 ± 279 |
| Correlation coefficient (*R*) | 0.9991 | 0.9996 | 0.9999 |
| LOD (μg/ml) | 0.075 | 0.059 | 0.0091 |

anaemia, hepatotoxicity and chest pain. Then, B-type ultrasonic inspection and CT scan were performed at the second month, the third month and the sixth month to assess the reaccumulation of pleural effusion and therapeutic effect. Toxicity was evaluated and graded according to the Eastern Cooperative Oncology Group (ECOG) Toxicity Criteria[11] and chest pain score was used as given in Table 1, which was modified from abdominal pain scoring of the phase I trial of intraperitoneal paclitaxel.[12] The treatment response of malignant effusion was evaluated according to the criteria as those of Perng and colleagues.[8]

### 2.3. *Sample collection, drug analysis and statistical analysis*

For pharmacokinetic analysis, adequate blood and pleural fluid samples were collected into tubes containing EDTA at designated time points of 0, 2, 4, 6, 8, 12, 24, 48, 72 and 96 h, respectively, and urine was also obtained from patients at the time of 24 h after the end of infusion. All samples were centrifuged immediately at 3000 rpm for 10 min at 4 °C and the supernatants were stored at –20 °C until analysis.

The concentrations of paclitaxel in plasma, pleural fluid and urine samples were determined according to the respective validated methods (Table 2). Plasma and pleural fluid were pretreated using acetonitrile for protein precipitation and urine was extracted by methyl tertiary butyl ether. The resulting 10 μl solution was injected into the ultra-performance liquid chromatography (UPLC) system for analysis. The UPLC was performed on a Waters Acquity UPLC system (Waters Corp., Milford, MA, USA) equipped with a binary solvent delivery system and an autosampler. The chromatographic separation was carried out on a Waters Acquity UPLC™ BEH $C_{18}$ column (50 × 2.1 mm, 1.7 μm) and the detection was carried out at 227 nm. Elution was performed with acetonitrile (solvent *A*) and water (solvent *B*) at a flow rate of 0.25 ml/min with a following gradient programme: 0–1 min, *A*% = 45–53 (v/v); 1–3.5 min, *A*% = 53–60 (v/v); 3.5–4 min, *A*% = 60–95 (v/v); and 4–5.5 min, *A*% = 95–45 (v/v). Paclitaxel concentrations in samples were extrapolated from standard curves. The concentration ranges of standard curves were 0.5–20 μg/ml in plasma, 0.5–20 μg/ml in pleural fluid and 0.025–1 μg/ml in urine, respectively.

All pharmacokinetic parameters were calculated with the Drug and Statistics (DAS) software, version 2.1.1, edited and published by the Mathematical Pharmacology Professional Committee of China.

### 2.4. *Pharmacokinetic analysis*

Estimates of pharmacokinetic parameters for paclitaxel were derived from individual concentration–time data sets by one-compartment model analysis. The values of the maximum concentration ($C_{max}$) and the time to maximum concentration ($T_{max}$) were recorded directly from the measured values. Then the values of the terminal disposition half-life ($T_{1/2}$), the area under the concentration–time curve ($AUC_{0\rightarrow T}$), the total body clearance (CL) and the volume of distribution ($V_d$) were calculated using a one-compartmental analysis approach with the DAS software.

## 3. Results

Between October 2006 and March 2008, 15 NSCLC patients with malignant pleural effusions, whose main characteristics are listed in Table 3, were enrolled onto this phase I clinical study. Twelve were treated with paclitaxel liposome and three were treated with free paclitaxel. All patients were assessable

**Table 3 – Patient characteristics.**

| Characteristic | Number of patients | Percentage (%) |
|---|---|---|
| *Sex* | | |
| Male | 8 | 53.3 |
| Female | 7 | 46.7 |
| Median age (range) | 53 (37–76) | |
| *Performance status* | | |
| 1 | 7 | 46.7 |
| 2 | 8 | 53.3 |
| *Primary site* | | |
| Left lung | 7 | 46.7 |
| Right lung | 8 | 53.3 |
| *Histology* | | |
| Adenocarcinoma | 15 | 100 |
| *Stage* | | |
| IIIB | 6 | 40 |
| IV | 9 | 60 |
| *Prior therapy* | | |
| No | 8 | 53.3 |
| Chemotherapy | 2 | 13.3 |
| Chemotherapy and surgery | 2 | 13.3 |
| Chemotherapy and radiation | 2 | 13.3 |
| Biotherapy | 1 | 6.67 |

**Table 4 – Toxicity in patients with non-small cell lung cancer with malignant pleural effusion after paclitaxel liposome intrapleural therapy.**

| Type of toxicity | No. of evaluable patients | Grade 0 (%) | Grade 1 (%) | Grade 2 (%) | Grade 3–4 (%) |
|---|---|---|---|---|---|
| Anaphylaxis | 12 | 100 | 0 | 0 | 0 |
| *Digestive reaction* | | | | | |
| Nausea | 12 | 100 | 0 | 0 | 0 |
| Vomiting | 12 | 100 | 0 | 0 | 0 |
| Diarrhoea | 12 | 91.7 | 8.3 | 0 | 0 |
| *Cardiovascular toxicity* | | | | | |
| Heart rate abnormal | 12 | 100 | 0 | 0 | 0 |
| Hypotension | 12 | 100 | 0 | 0 | 0 |
| Neurotoxicity | 12 | 100 | 0 | 0 | 0 |
| *Myelosuppression* | | | | | |
| Anaemia | 11 | 72.7 | 27.3 | 0 | 0 |
| Neutropaenia | 11 | 90.9 | 9.1 | 0 | 0 |
| Thrombocytopaenia | 11 | 90.9 | 9.1 | 0 | 0 |
| *Hepatotoxicity* | | | | | |
| AST | 11 | 100 | 0 | 0 | 0 |
| ALT | 11 | 90.9 | 0 | 9.1 | 0 |
| *Chest pain* | 12 | 66.7 | 0 | 33.3 | 0 |

for toxicity, only 14 patients (11 were treated with paclitaxel liposome and three were treated with free paclitaxel) were assessable for response and only 11 patients (nine were treated with paclitaxel liposome and two were treated with free paclitaxel) were assessable for pharmacokinetics.

### 3.1. *Toxicity*

Table 4 listed the toxicity observed at the 125 mg/m$^2$ effective dose level of paclitaxel liposome. Anaphylaxis, cardiovascular toxicity and neurotoxicity were all never observed in patients treated with paclitaxel liposome, however, anaphylaxis was one of the major side-effects on patients treated with free paclitaxel. There were no patients who had nausea and vomiting toxicity after intrapleural paclitaxel liposome, however, nausea and vomiting usually occurred 2 days later after intrapleural-free paclitaxel. Grade 1 diarrhoea occurred in only one (8.3%) patient at 24 h after intrapleural paclitaxel liposome and was easily controlled by loperamide treatment. Three patients had grade 1 anaemia and no patient suffered from grades 2–4 anaemia, one patient had grade 1 neutropaenia and no patient suffered from grades 2–4 neutropaenia, one patient had grade 1 thrombocytopaenia and no patient suffered from grades 2–4 thrombocytopaenia after intrapleural paclitaxel liposome, however, the majority of patients treated with free paclitaxel had grades 2–4 anaemia, neutropaenia and thrombocytopaenia. The evaluation of hepatotoxicity was performed by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. One patient had grade 2 abnormal ALT level and no patient suffered from grades 2–4 abnormal ALT level, and all patients had a normal AST level after intrapleural paclitaxel liposome. Four patients had grade 2 chest pain and no patients suffered from grades 1 and 3–4 chest pain after intrapleural paclitaxel liposome, however, all patients suffered from different extent chest pain after intrapleural-free paclitaxel.

### 3.2. *Efficacy*

After treated with paclitaxel liposome, 11 of the 12 patients were assessable for response of effusion control at the end of the first, second, third and sixth month and the result is listed in Table 5. One patient died from severe infection in the early study and did not seem to be related to the intrapleural paclitaxel liposome. Three patients had a complete response (CR) and seven patients had a partial response (PR) at 1 month for an overall initial objective response rate of 83.3% of effusion control and among the 11 patients assessable at 1 month, this overall response rate was 90.9% of effusion control. Two patients had a CR and six patients had a PR at 2 months for an overall response rate of 72.7% of effusion control in 11 assessable patients. The overall response rate

**Table 5 – Response of malignant pleural effusion control after paclitaxel liposome intrapleural therapy.**

| Months | No. of evaluable patients | Overall | | | |
|---|---|---|---|---|---|
| | | CR (%) | PR (%) | Response (%) | Failure (%) |
| 1 | 11 | 3 (27.3) | 7 (63.6) | 10 (90.9) | 1 (9.1) |
| 2 | 11 | 2 (18.2) | 6 (54.5) | 8 (72.7) | 3 (27.3) |
| 3 | 11 | 1 (9.1) | 6 (54.5) | 7 (63.6) | 4 (36.4) |
| 6 | 11 | 1 (9.1) | 5 (45.5) | 6 (54.5) | 5 (45.5) |

of effusion control in 11 patients at 3 and 6 months were, respectively, 63.6% and 54.5%. One of the two CR patients had a PS 1 and the another had a PS 2 at 2 months, and they were both females.

### 3.3. *Pharmacokinetics analysis*

Only 11 patients (nine were treated with paclitaxel liposome and two were treated with free paclitaxel) were evaluable for pharmacokinetics, and the other patients were eliminated from pharmacokinetics study due to the wanting blood, pleural fluid or urine samples. At designated time points, adequate blood and pleural fluid and urine (24 h after intrapleural administration) were collected from these patients and analysed by ultra-performance liquid chromatography (UPLC). Pharmacokinetic parameters for individual patient are listed in Table 6 and a representative intrapleural elimination curve is depicted in Fig. 1. The result showed as follows: (1) The mean $C_{max,IP}$, $T_{1/2}$ and $AUC_{0\rightarrow96,IP}$ in the pleural fluid after intrapleural administration of paclitaxel liposome were, respectively, over 2-fold (585 μg/ml/246 μg/ml), about 2-fold (76 h/39 h) and over 2.5-fold (17,831 μg h/ml/7091 μg h/ml) than those of free paclitaxel. (2) The mean $C_{max,Pla}$ and $AUC_{0\rightarrow96,Pla}$ in the plasma after intrapleural administration

**Table 6 – Pharmacokintic parameters of intrapleural administration of paclitaxel liposome and free paclitaxel.**

| Patient no. | Dose ($mg/m^2$) | Total dose (mg) | Pleural fluid | | | | | Plasma | | $AUC_{0\rightarrow96,IP}$/$AUC_{0\rightarrow96,Pla}$ | Urine $M_{24h}$/Mo |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $C_{max,IP}$ (μg/ml) | $T_{1/2}$ (h) | $AUC_{0\rightarrow96,IP}$ (μg h/ml) | CL (l/h $m^2$) | Vd ($l/m^2$) | $C_{max,Pla}$ (μg/ml) | $AUC_{0\rightarrow96,Pla}$ (μg h/ml) | | |
| 1 | 125 | 175 | 547 | 133 | 14,628 | 0.004 | 0.86 | 13.41 | 1096 | 13.35 | 0.16 |
| 2 | 125 | 210 | 868 | 171 | 16,650 | 0.003 | 0.82 | – | – | – | 0.08 |
| 3 | 125 | 180 | 591 | 31 | 33,629 | 0.003 | 0.15 | 17.47 | 1082 | 31.08 | 0.10 |
| 4 | 125 | 210 | 495 | 47 | 15,597 | 0.006 | 0.42 | 18.01 | 1002 | 15.57 | 0.24 |
| 5 | 125 | 180 | 608 | 38 | 14,091 | 0.008 | 0.42 | 18.41 | 382 | 36.89 | 0.40 |
| 6 | 125 | 180 | 493 | 91 | 17,230 | 0.001 | 0.60 | 9.05 | 687 | 25.08 | 0.25 |
| 7 | 125 | 180 | 705 | 76 | 12,239 | 0.006 | 0.66 | – | – | – | 0.20 |
| 8 | 125 | 240 | 443 | 52 | 21,332 | 0.005 | 0.35 | 0.96 | 417 | 51.16 | 0.20 |
| 9 | 125 | 180 | 513 | 46 | 15,082 | 0.007 | 0.45 | – | – | – | 0.17 |
| | Mean | | 585 | 76 | 17,831 | 0.005 | 0.53 | 12.89 | 778 | 28.86 | 0.20 |
| | SD | | 44 | 48 | 6439 | 0.002 | 0.23 | 6.86 | 328 | 14.13 | 0.09 |
| 10 | 125 | 180 | 282 | 64 | 10,382 | 0.008 | 0.75 | 27.68 | – | – | 0.12 |
| 11 | 125 | 210 | 210 | 14 | 3799 | 0.033 | 0.65 | 25.13 | – | – | 0.36 |
| | Mean | | 246 | 39 | 7091 | 0.021 | 0.70 | 26.41 | – | – | 0.24 |
| | SD | | 51 | 35 | 4655 | 0.018 | 0.07 | 1.80 | – | – | 0.17 |

*Abbreviations*: $C_{max,IP}$, the values of the maximum concentration in pleural fluid; $C_{max,Pla}$, the values of the maximum concentration in plasma; $AUC_{0\rightarrow96,IP}$, the area under the concentration–time curve in pleural fluid during 96 h; $AUC_{0\rightarrow96,Pla}$, the area under the concentration–time curve in plasma during 96 h; $M_{24h}$, excretory content in 24 h from urine; Mo, total dose; and –, no detection or calculation.

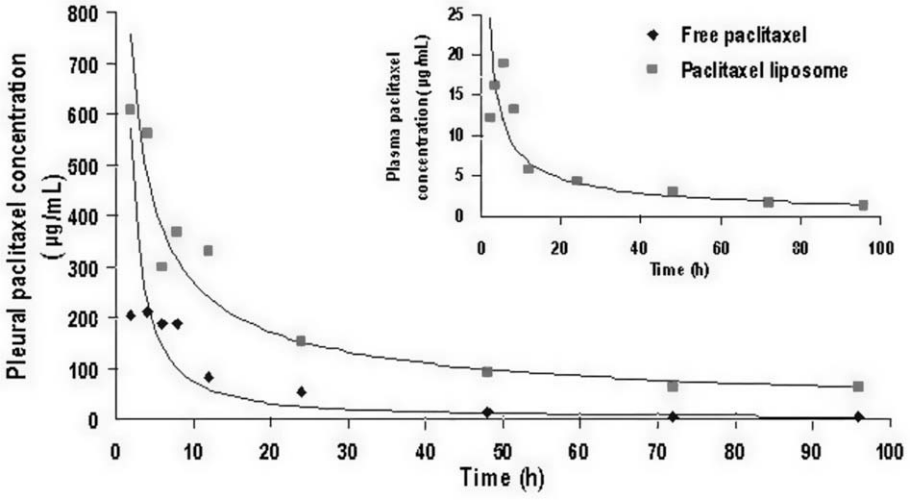


**Fig. 1 – Intrapleural paclitaxel elimination curve for patient no. 5 (paclitaxel liposome) and patient no. 11 (free paclitaxel) who were treated with 125 $mg/m^2$. Inset: plasma concentration for patient no. 5 during the same time period (paclitaxel plasma concentration for patient no. 11 was not detected).**

of paclitaxel liposome were, respectively, 12.89 μg/ml and 778 μg h/ml, however, the mean $C_{max,Pla}$ in the plasma after intrapleural administration of free paclitaxel was 26.41 μg/ml and paclitaxel was eliminated fast from plasma, and $AUC_{0\rightarrow96,Pla}$ could not be calculated because paclitaxel in the samples after 8 h could not be detected. (3) The mean excretory rate of paclitaxel in 24 h from urine were, respectively, 20% and 24% for paclitaxel liposome and free paclitaxel, this result revealed that the excretory speed of free paclitaxel was faster than that of paclitaxel liposome, the excretory rate was defined as % excretory rate = [$M_{24h}$ (excretory content in 24 h from urine)/Mo (total dose)] × 100. (4) The mean $AUC_{0\rightarrow96,IP}$ (17,831 μg h/ml) in the pleural fluid was about 23-fold than that (778 μg h/ml) in the plasma after intrapleural administration of paclitaxel liposome.

## 4. Discussion

Paclitaxel was a novel chemotherapeutic agent which had a single-drug response rate of 21–24% in NSCLC,[13,14] and that it could be delivered by intraperitoneal and intrapleural route had been proved.[9,12] NSCLC became the major cause of malignant pleural effusion. The traditional management of malignant pleural effusion had been focused on the control of the effusion, however, paclitaxel as a intrapleural chemotherapeutic agent had the potential great advantages of controlling the effusion and treating the underlying malignancy. Its efficacy of intrapleural injection for NSCLC patients with malignant pleural effusions had been confirmed.[8] Nevertheless the Cremophor EL as the solvent of free paclitaxel would result in severe anaphylaxis and peripheral nerve toxicity and so on.[15] Therefore it was a good strategy to develop a suitable delivery system for decreasing this toxicity. Liposome had some characteristics of low toxicity, solubilising and delayed release and had been widely acceptable.[16]

In our study, we selected paclitaxel liposome as pharmaceutical preparation to be infused in NSCLC patients with malignant pleural effusions to investigate the feasibility, pharmacokinetics, efficacy and toxicity. The solvent was not Cremophor EL but 5% glucose. Although the efficacy did not show significant difference between paclitaxel liposome and free paclitaxel in this study, the toxicity of paclitaxel liposome was much lower than that of free paclitaxel. Anaphylaxis, peripheral nerve toxicity, nausea and vomiting never occurred in patients treated with paclitaxel liposome. In contrast, anaphylaxis and peripheral nerve toxicity were the major side-effects on patients treated with free paclitaxel. In addition, symptoms of diarrhoea, anaemia, neutropaenia, thrombocytopaenia, hepatotoxicity and chest pain were all mild after intrapleural paclitaxel liposome and were easily controlled, however, all these symptoms became more severe in patients treated with free paclitaxel. Therefore, the low toxicity of paclitaxel liposome would significantly improve the quality of life of NSCLC patients with malignant pleural effusion and lessen the suffering of them.

Pharmacokinetics parameters of intrapleural paclitaxel liposome showed some characteristics of liposome, including delayed release and low systemic toxicity. The mean $T_{1/2}$ and $AUC_{0\rightarrow96,IP}$ in the pleural fluid after intrapleural administration of paclitaxel liposome were, respectively, about 2-fold and over 2.5-fold than those of free paclitaxel. The phenomenon revealed that paclitaxel liposome eliminated more slowly than free paclitaxel from pleural fluid and had delayed release action. The mean $AUC_{0\rightarrow96,IP}$ in the pleural fluid was only about 23-fold than that in the plasma after treatment with paclitaxel liposome, however, the ratio after treatment with free paclitaxel might be larger than it. The reasons might be summarised as follows: (1) After intrapleural administration of free paclitaxel, although the $C_{max,Pla}$ in the plasma was high, paclitaxel was eliminated quickly from plasma and not be detected after 8 h so that $AUC_{0\rightarrow96,Pla}$ could not be calculated. (2) In contrast to this, although the $C_{max,Pla}$ of paclitaxel liposome in the plasma was low, paclitaxel was released slowly and uninterruptedly from pleural fluid into plasma and could be detected at all designated times, resulting that the $AUC_{0\rightarrow96,Pla}$ could be calculated under all designated time points. The result revealed that after treatment with paclitaxel liposome, paclitaxel in plasma kept a steady and low concentration extent during 96 h, indicating the low systemic toxicity of paclitaxel liposome. In contrast, after treatment with free paclitaxel, the concentration of paclitaxel in plasma fluctuated greatly during 96 h, indicating the high systemic toxicity of free paclitaxel. Therefore, the approach of intrapleural administration of paclitaxel liposome could maximise the treatment effect of local disease while minimising systemic toxicity. However, the major shortage of our study was the limited number of patients tested. The phase II study of a large number of patients was recommended to confirm this finding.

In a word, paclitaxel liposome might be a more useful agent than free paclitaxel for the treatment of malignant pleural effusions because of its relatively low toxicity and local efficacy, and distinct pharmacokinetic characteristics.

## Conflict of interest statement

None declared.

## Acknowledgement

The authors greatly appreciate financial support from National 863 Programme (2007AA021201 and 2009ZX09501-015).

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