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# A phase I feasibility and pharmocokinetic study of intrapleural paclitaxel in patients with malignant pleural effusions

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**To evaluate the feasibility and pharmacology of intrapleural ($IP_L$) administration of paclitaxel, 18 patients with malignant pleural effusions were entered onto a phase I clinical study, 13 were caused by lung cancer. Following an effusion drainage rate of less than 100 ml/24 h and full expansion of the lung, patients were treated with a single instillation of pacilitaxel administered $IP_L$ in 500 ml of normal saline and retained for a maximum of 96 h when tolerated. No systemic chemotherapy or ipsilateral thoracic irradiation was given for 4 weeks before and after the $IP_L$ treatment. The starting dose was 82.5 mg/m$^2$ with the dose escalation schedule of 125, 175, 225 and 300 mg/m$^2$. There were minimal local or systemic toxicities, such as local chest pain or myelosuppression, even when the paclitaxel dose reached 225 mg/m$^2$. The pharmacological advantages of the $IP_L$ administration of paclitaxel were demonstrated by the mean exposure of the pleural cavity (area under the concentration–time curve) to paclitaxel after $IP_L$ delivery exceeding that of the plasma by approximately 370-fold (range 55–684) and by the extraordinarily slow $IP_L$ clearance of paclitaxel (mean ± SE 0.49 ± 0.07 l/m$^2$/day; range 0.08–1.16 l/m$^2$/day) with significant concentrations of paclitaxel persisting within the cavity for more than 48–96 h after a single $IP_L$ instillation. In patients with detectable plasma paclitaxel levels, the plasma levels achieved exceed the minimal concentrations that are required to induce cytotoxic effects *in vitro*. Four patients had progressive dyspnea during $IP_L$ retention of paclitaxel solution because of treatment failure and needed drainage of effusion. One of these patients who was at the dose level of 225 mg/m$^2$ originally had severely chronic obstructive lung disease, developed acute respiratory failure, refused mechanical ventilation support and succumbed to respiratory failure. No further patients were included after this event. Antitumor effect was shown by four of the 15 evaluable patients having no recurrence of effusion on chest radiograph at 1 month. Most of these responders had a good performance status, normal pretreatment pleural pH and/or glucose compared with the non-responders. We conclude that paclitaxel at a dose level of 175 or 225 mg/m$^2$ is feasible for use intrapleurally. It could be considered for incorporation into treatment programs for patients with less advanced thoracic tumors with carcinomatous pleuritis or with $IP_L$ tumors following surgical debulking.**

*Key words*: Intrapleural paclitaxel, malignant pleural effusions, pharmacokinetics.

## Introduction

Malignant pleural effusions occur frequently in patients with locally advanced or disseminated cancer. In almost all patients, it results in symptoms ranging from mild dyspnea to persistent cough and severe shortness of breath.[1] Adequate control of effusions may dramatically improve quality of life.

The leading causes of malignant pleural effusions are cancers of lung and breast.[1] Paclitaxel is an active drug in the treatment of these tumors.[2–5] Paclitaxel is a unique antineoplastic agent that exerts its cytotoxic effect by inducing excessive polymerization of tubulin and dysfunctional microtubules.[6] Phase II studies of paclitaxel demonstrated in lung cancer response rates ranging from 21 to 24%[2,3] and in breast cancer response rates ranging from 56 to 62%.[4,5]

Several features of paclitaxel make it an attractive agent for intracavitary administration in the management of malignant effusions. (i) Its high molecular weight (845 Da) and bulky structure cause retention inside the pleural or peritoneal cavity after intracavitary delivery. This increases the exposure of tumor to paclitaxel in the cavity, and reduces systemic drug uptake and toxicity.[7,8] (ii) Its metabolism in the liver. This further increases the potential for a significant

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therapeutic pharmacological advantage compared with the systemic administration.[9] (iii) Its antimicrotuble and cytotoxic effects which are dependent on both drug concentration and duration of exposure, factors that may be optimized by regional intrapleural ($IP_L$) or intraperitoneal drug delivery.[10]

Recent results of a phase I trial of intraperitoneal paclitaxel showed that it can be delivered by the intraperitoneal route with minimal toxicity and a major pharmacokinetic advantage.[8] However, there are no reports about the feasibility, toxicity and pharmacokinetic study of $IP_L$ paclitaxel therapy. Herein, we report this phase I feasibility and pharmacokinetic study of $IP_L$ administration of paclitaxel in patients with malignant pleural effusions.

## Patients and methods

### Patients

Patients with cytologically or histologically documented symptomatic malignant pleural effusions without previous $IP_L$ therapy other than repeated thoracentesis were eligible for entry onto this phase I study. No systemic chemotherapy, hormonal therapy, immunotherapy or ipsilateral thoracic irradiation given for 4 weeks before and after $IP_L$ paclitaxel was allowed. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq 3$, life expectancy $\geq 6$ weeks; white blood cell count $\geq 3000/mm^3$, platelets $\geq 100\,000/mm^3$, total bilirubin $\leq 1.5$ mg% and serum creatinine $\leq 1.5$ mg/dl. Patients with loculated pleural effusions detected by sonography of chest before treatment were excluded. Patients with cardiac conduction system abnormalities or other serious medical problems that would limit full compliance with the study or portend undue risk were also excluded. Written, informed consent was obtained from all patients before entry on study and stated that they were aware of the investigation nature of this treatment program. The study was approved by the institution's Human Investigations Committee.

### Pretreatment evaluation

Patients were required to have a complete history and physical examination to include performance status, height, weight and concurrent non-malignant disease and therapy. Laboratory studies included a hemogram, blood chemistries, electrocardiogram, chest radiograph, and pretreatment pleural fluid pH and glucose values. All tests were performed within 14 days prior to initiation of therapy.

All patients were admitted to the hospital. A 7.8 French, polyethylene-lined pigtail catheter (Meadox Surgimed A/S, Copenhagen, Denmark) was inserted into the pleural cavity under sonographic guiding. The technique for placement of soft small-bore catheters has been described previously.[11] A two-way stopcock was attached to the catheter and extension tubing was used to connect the stopcock to an underwater-seal suction bottle to facilitate rapid evacuation of the fluid. Following suction or gravity drainage, a drainage rate of less than 100 ml/24 h with radiographic evidence of absent or minimal residual effusion and full expansion of the lung were required before $IP_L$ administration of paclitaxel. This chest radiograph was kept and served as a baseline reference for follow-up evaluation of recurrence.

### Treatment plan

The paclitaxel (Taxol®; 6 mg/ml in a 5 ml ampule; Bristol-Myers Squibb, Princeton, NJ) dose was dissolved in a room temperature isotonic saline to a final 500 ml solution and was instilled into the pleural cavity through the catheter in 15 min. Prior to therapy, patients received dexamethasone 20 mg orally 12 and 6 h before paclitaxel, and diphenhydramine 50 mg and cimetidine 300 mg intravenously 30 min before paclitaxel to prevent paclitaxel-associated hypersensitivity reactions.[12] Polyvinyl chloride materials (such as chest tubes, syringes and solution bags) were avoided since cremophor might leach plasticizer from such products. Only glass or polyolefin containers and polyethylene-lined nitroglycerin tubing are recommended for drug administration. After instillation, patients were asked to change positions at 15 min intervals for 2 h to ensure adequate $IP_L$ distribution. Patients' electrocardiograms were monitored continuously at bedside during and after paclitaxel instillation for 1 h. The treatment volume was retained in the pleural cavity for a maximum of 96 h when tolerated and was drained out as completely as possible thereafter. Then, the catheter was removed. All patients received only a single instillation of $IP_L$ paclitaxel therapy. Patients could receive systemic therapy 4 weeks later after treatment or whenever failure to $IP_L$ paclitaxel treatment was documented.

Since paclitaxel was safe at the 25 and 50 $mg/m^2$ dose levels in the phase I intraperitoneal trial,[8] we decided to start $IP_L$ at a dose level of 82.5 $mg/m^2$. At

least three assessable patients were treated at each dose level and were fully evaluated for 21 days (with day 1 indicating the start of therapy) before new patients received the next higher level. After the initial dose level, the following dose escalation schema was used: 125, 175, 225 and 300 mg/m$^2$.

### Evaluation during treatment, response criteria and statistical analysis

Blood chemistries and hemograms were checked 2 and 4 weeks after therapy. Chest radiographs were followed up at 1, 2, 3, 6 and 12 months after therapy unless treatment failure or death. All toxicities were evaluated and graded according to the ECOG common toxicity criteria.[13] Response was defined as no pleural fluid reaccumulation for at least 1 month as determined by chest radiographs[14] since patients treated by simple thoracentesis and followed for 1 month have a 97% recurrence rate.[15] All others were defined as recurrence. The survival of patients was measured from the time of enrollment on protocol to death from any cause. SAS version 6.10 (SAS Institute Inc., Cary, NC) was used to process and analyze data. Pearson correlation coefficient was used to measure the relation between peak $IP_L$ paclitaxel concentrations and the administered dose levels or total doses. One-tailed non-parametric Wilconxon rank sum test was used to compare peak pleural levels or pleural area under the concentration–time curves (AUCs) of paclitaxel, and pretreatment pleural fluid pH or glucose values between responders and non-responders.

### Pharmacokinetics analysis

To measure paclitaxel concentration, blood and pleural fluid samples were collected whenever possible before drug administration, then 0.5, 1, 2, 4, 5, 6, 24, 48 and 96 h after the end of drug instillation. Samples were collected in tubes containing EDTA, centrifuged and the supernatant was stored at −20°C until assay.

Paclitaxel concentrations in plasma or in pleural effusion samples were previously extracted by ethyl acetate and determined by using a reverse-phase HPLC assay with carbazole as an internal standard. Extraction efficiency was above 82.86%. The HPLC assay equipment used was a Waters chromatographic system (Waters Associates, Milford, MA). The mobile phase (methanol:distilled water = 3:2) was delivered at a flow of 0.8 ml/min through a Waters $\mu$-Bondapak $C_{18}$ column (3.9 mm × 30 cm). Paclitaxel detection was performed at 235 mm. The limit of determination of paclitaxel was 0.13 $\mu$mol/l.

Pharmacokinetic parameters of paclitaxel in the pleural compartment were estimated using a one-compartment open model with first-order absorption kinetics to fit the data base.[8] The data were fitted by the non-linear regression program PCNONLIN (Statistical Consultants, Lexington, KY) which estimated the following kinetic parameters for each clearance curve: the rate constant of elimination and its associated elimination half-life, the volume of distribution, pleural cavity clearance, and the $IP_L$ AUC. The pleural clearance was determined by the rate constant of elimination times the volume of distribution. The $IP_L$ and plasma AUCs from time zero to the last time point were calculated by the trapezoidal method. The pharmacological advantage derived from $IP_L$ drug administration was determined by calculating the $IP_L$:plasma AUC ratio.

## Results

From September 1994 to November 1995, 18 patients were entered onto this pase I study. Patient characteristics are listed in Table 1. There were 10 men and eight women, with a median age of 71

**Table 1.** Patient characteristics

| | |
|---|---|
| No. of patients | 18 |
| Sex | |
| male | 10 |
| female | 8 |
| Median age, years (range) | 71 (43–82) |
| Performance status (ECOG) | |
| 0–1 | 2 |
| 2 | 10 |
| 3 | 6 |
| Primary site | |
| lung | 13 |
| stage $III_b$ | 4 |
| stage IV | 9 |
| ovary | 1 |
| thyroid | 1 |
| unknown | 3 |
| Cell type | |
| adenocarcinoma | 17 |
| carcinoma, poorly differentiated | 1 |
| Previous therapy | |
| no | 13 |
| chemotherapy | 2 |
| thoracic irradiation | 2 |
| operation and $^{131}I$ ablation | 1 |
| Therapy after $IP_L$ paclitaxel | |
| chemotherapy | 7 |
| thoracic irradiation | 1 |

years (range 43–82). Two patients had an ECOG performance status (PS) of 0–1, 10 patients had PS 2 and six patients had PS 3. Thirteen patients had non-small-cell lung cancer, one patient had ovarian cancer, one patient had thyroid cancer and three patients were unknown primary. Histologically, 17 patients had adenocarcinomas and one patient with a lung primary had a poorly differentiated carcinoma. Two patients had previous systemic chemotherapy, two patients had previous thoradic irradiation, while 13 patients did not have therapy before $IP_L$ paclitaxel treatment. Table 2 lists the dose levels tested in this study and the total number of patients at each dose level.

There were four patients who had progressive dyspnea during the 4 day $IP_L$ retention of paclitaxel solution. One of these patients was at the dose level of 125 mg/m$^2$, one at the dose level of 175 mg/m$^2$ and two at the dose level of 225 mg/m$^2$. Urgent chest radiographs showed rapid reaccumulation of effusions without obvious lung parenchymal changes in all four patients. After unclamping of the catheters and draining of effusions, three patients had symptomatic improvement. One of the patients at the dose level of 225 mg/m$^2$ originally had severely chronic obstructive lung disease, developed acute respiratory failure, refused mechanical ventilation support and succumbed to respiratory failure. No further patients were included at the 225 mg/m$^2$ dose level and further dose escalation was ceased after this event.

## Toxicity

To evaluate the local toxicity of treatment, a chest pain score was used (Table 3), which was modified from the abdominal pain scoring in the phase I trial of intraperitoneal paclitaxel.[8] At the dose level of 225 mg/m$^2$, the majority of patients had mild to moderate chest pain only (Table 4).

Nausea and/or vomiting were mild and were easily controlled by antiemetics whenever needed. Nausea, vomiting or local chest pain usually occured 24–48 h later after $IP_L$ paclitaxel. Myelosuppression was also mild (Table 5). Only one patient had grade 3

**Table 2.** Number of patients at $IP_L$ paclitaxel dose level tested

| Dose (mg/m$^2$) | No. of patients |
|---|---|
| 82.5 | 3 |
| 125 | 6 |
| 175 | 5 |
| 225 | 4 |

**Table 3.** Chest pain score[a]

| 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 alangesia 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 |

[a]Modified from abdominal pain scoring of the phase I trial of intraperitoneal paclitaxel.[8]

**Table 4.** Local toxicity associated with $IP_L$ paclitaxel

| Dose level (mg/m$^2$) | No. of patients | Chest pain grade | | |
|---|---|---|---|---|
| | | 0–1 | 2 | 3 |
| 82.5 | 3 | 3 | 0 | 0 |
| 125 | 6 | 3 | 2 | 1 |
| 175 | 5 | 4 | 0 | 1 |
| 225 | 4 | 1 | 2 | 1 |

**Table 5.** Number of patients with hematologic toxicity by dose level

| Toxicity grade | Dose level (mg/m$^2$) | | | | Total |
|---|---|---|---|---|---|
| | 82.5 | 125 | 175 | 225 | |
| No. of evaluable patients | 3 | 6 | 5 | 3 | 17 |
| WBC count | | | | | |
| 0–1 | 3 | 5 | 4 | 3 | 15 |
| 2 | 0 | 1 | 0 | 0 | 1 |
| 3 | 0 | 0 | 1 | 0 | 1 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| Hemoglobin | | | | | |
| 0–1 | 3 | 4 | 3 | 3 | 13 |
| 2 | 0 | 1 | 1 | 0 | 2 |
| 3 | 0 | 1 | 1 | 0 | 2 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| Platelets | | | | | |
| 0–1 | 3 | 6 | 5 | 3 | 17 |
| 2 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 |

leukopenia. Two patients had grade 3 anemia and received blood transfusions. No patient had thrombocytopenia. One patient experienced asymptomatic transient bradycardia during paclitaxel instillation and one patient had transient hypotension after paclitaxel instillation. No other cardiac complications, hypersensitivity reactions or peripheral neuropathy were observed.

## Efficacy

Of the 18 patients, 15 were evaluable for response at 1 month. Of the unevaluable patients, one (dose level 125 mg/m$^2$) had trapped lung after drainage of effusion and was excluded for efficacy analysis, one (dose level 125 mg/m$^2$) did not return for follow-up chest radiographs and one (dose level 225 mg/m$^2$) died early. Four of the 15 patients had no recurrence of effusion by a chest radiograph at 1 month (response rate = 27%) (Table 6). The remaining 11 patients all had evidence of recurrent effusion by 1 month. Six of these 11 non-responders at 1 month did not receive further thoracocentesis or pleurodesis because the amount of recurrent efffusion was less than 50% of the original volume and they were not symptomatic. The other five non-responders received repetitive thoracocentesis and/or pleurodesis with bleomycin.

Of the four responders, one patient had a PS 1 and three patients had PS 2. None of the patients who had PS 3 were responders. Three of the four responders had carcinomas of lung and the other one patient had a tumor of unknown primary. Only one of the four responders had a low pretreatment pleural pH (less than 7.30) whereas five of the 11 non-responders had a low pretreatment pleural pH. The mean pretreatment pleural fluid pH value ± SE of the four responders was 7.42 ± 0.06 (range 7.27–7.56) and 7.28 ± 0.04 in the 11 patients with recurrence (range 7.08–7.55) ($p = 0.039$). Five of the 11 non-responders had a low pretreatment pleural fluid glucose (less than 60 mg/dl) compared with the four responders. The mean pretreatment pleural fluid glucose value ± SE of the four responders was 147 ± 19 mg/dl (range 119–202) and 63 ± 15 mg/dl in the 11 patients with recurrence (range 4–121) ($p = 0.007$). There was no significant difference of peak pleural levels or pleural AUCs of paclitaxel between responders and non-responders ($p > 0.05$).

Of the 18 patients, seven patients received systemic chemotherapy and one patient received thoracic irradiation at least 4 weeks later after $IP_L$ paclitaxel treatment (Table 1). No patient is still alive. The median survival time of the patients was 3 months (range 0–17).

**Table 6.** Efficacy

| Dose level (mg/m$^2$) | No. of patients | Responders[a]/ evaluable patients | | | |
|---|---|---|---|---|---|
| | | 1[b] | 2[b] | 3[b] | 6[b] |
| 82.5 | 3 | 1/3 | 1/3 | 1/2 | 0/0 |
| 125 | 6 | 2/4 | 1/4 | 1/2 | 1/1 |
| 175 | 5 | 1/5 | 1/4 | 1/3 | 0/1 |
| 225 | 4 | 0/3 | 0/1 | 0/1 | 0/1 |
| Total | 18 | 4/15 | 3/12 | 3/8 | 1/3 |

[a]Defined as patients having no recurrence of effusion for at least 1 month by chest radiographs.
[b]Months.

## Pharmacokinetics analysis

Pleural and plasma samples were obtained from all 18 patients and pharmacokinetic parameters for individual patients are listed in Table 7. Peak $IP_L$ paclitaxel concentrations were achieved at either the 30 or 60 min sampling times and ranged from 186 to 925 μmol/l. There were wide interindividual differences in peak $IP_L$ concentrations. The peak $IP_L$ concentrations have no significant correlation with the administered dose level ($r = 0.32$) or the total dose ($r = 0.31$).

The mean volume of distribution ± SE was low (0.56 ± 0.07 l/m$^2$; range 0.15–1.01 l/m$^2$), which suggested that the initial drug distribution was confined principally to the pleural cavity. The intrapleural clearance of paclitaxel was extremely slow (mean $IP_L$ clearance ± SE, 0.49 ± 0.07 l/m$^2$/day; range 0.08–1.16 l/m$^2$/day) and the pleural exposure to paclitaxel, as expressed by AUC, ranged from 4167 to 43 754 (μmol/l) h. The elimination of paclitaxel from the pleural compartment was described optimally by a monoexponential model with a mean half-life ± SE of 24.2 ± 4.1 h that indicated that approximately 50% of the $IP_L$ dose on average was cleared from the pleura during a 24 h period. A representative $IP_L$ elimination curve is depicted in Figure 1.

Detectable plasma paclitaxel levels were noted in six of 18 patients. Peak plasma concentrations were variably achieved from 0.5 to 6 h and ranged from less that 0.13 (unmeasurable) to 8.55 μmol/l. The mean peak plasma concentration did not correlate well with administered dose, possibly suggesting

**Table 7.** Phamacokinetic parameters of paclitaxel administered $IP_L$

| Patient no. | Dose ($mg/m^2$) | Total dose (mg) | Peak $IP_L$ level ($\mu$mol/l) | $V_d$ ($l/m^2$) | $T_{1/2}$ (h) | $IP_L$ clearance ($l/m^2$/days) | AUC $IP_L$ [($\mu$mol/l) h] | Peak plasma level ($\mu$mol/l) | AUC plasma [($\mu$mol/l)h] | AUC $IP_L$ AUC plasma |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 82.5 | 117 | 239 | 0.59 | 24.8 | 0.40 | 8539 | < 0.13 | – | – |
| 2 | 82.5 | 137 | 644 | 0.15 | 10.8 | 0.23 | 9990 | < 0.13 | – | – |
| 3 | 82.5 | 140 | 497 | 0.19 | 4.6 | 0.69 | 33216 | < 0.13 | – | – |
| 4 | 125 | 174 | 776 | 0.19 | 38.5 | 0.08 | 42709 | 4.34 | – | – |
| 5 | 125 | 188 | 204 | 0.72 | 57.8 | 0.21 | 17061 | 1.38 | – | – |
| 6 | 125 | 200 | 255 | 0.47 | 11.4 | 0.69 | 4221 | < 0.13 | – | – |
| 7 | 125 | 210 | 186 | 0.79 | 17.3 | 0.76 | 4646 | < 0.13 | – | – |
| 8 | 125 | 195 | 196 | 0.74 | 23.1 | 0.53 | 6516 | < 0.13 | – | – |
| 9 | 125 | 144 | 647 | 0.22 | 11.6 | 0.32 | 10790 | < 0.13 | – | – |
| 10 | 175 | 240 | 209 | 0.97 | 13.9 | 1.16 | 4167 | < 0.13 | – | – |
| 11 | 175 | 252 | 542 | 0.37 | 31.5 | 0.19 | 24989 | < 0.13 | – | – |
| 12 | 175 | 270 | 208 | 0.97 | 21.6 | 0.75 | 6611 | < 0.13 | – | – |
| 13 | 175 | 294 | 200 | 1.01 | 21.7 | 0.78 | 6202 | < 0.13 | – | – |
| 14 | 175 | 252 | 282 | 0.72 | 13.6 | 0.88 | 5549 | < 0.13 | – | – |
| 15 | 225 | 300 | 570 | 0.56 | 22.2 | 0.42 | 14955 | 5.49 | 272 | 55 |
| 16 | 225 | 324 | 881 | 0.48 | 25.5 | 0.31 | 20263 | 0.34 | 53 | 382 |
| 17 | 225 | 315 | 510 | 0.64 | 73.3 | 0.14 | 43754 | 8.55 | 64 | 684 |
| 18 | 225 | 405 | 925 | 0.24 | 13.2 | 0.30 | 21092 | 0.24 | – | – |
| Mean | | – | – | 0.56 | 24.2 | 0.49 | – | – | – | 374 |
| SE | | – | – | 0.07 | 4.1 | 0.07 | – | – | – | 182 |

Abbreviations: $V_d$, volume of distribution; $T_{1/2}$, elimination half-life; AUC, area under the concentration–time curve.

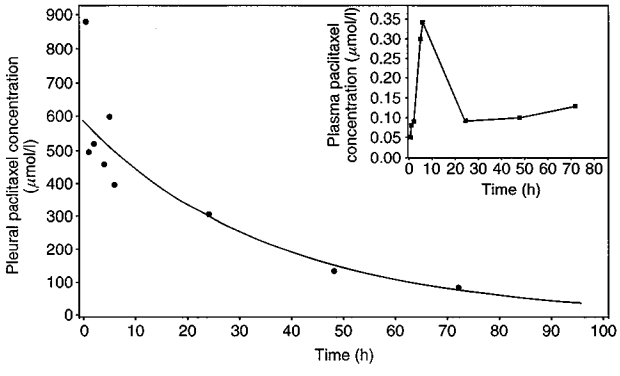


**Figure 1.** $IP_L$ paclitaxel elimination curve for patient no. 16 who was treated with 225 $mg/m^2$. Inset: plasma concentration for patient no. 16 during the same time period.

wide interindividual variability in absorption and significant anatomical differences.

In this study, the limit of detection of paclitaxel was 0.13 $\mu$mol/l. Only patients at the 225 $mg/m^2$ dose level were most of the plasma concentrations detectable. There were considerable differences between paclitaxel concentrations in the pleural fluid and plasma from 1 to 96 h after drug administration at this dose level of patients. Minimal mean $IP_L$: plasma paclitaxel concentration ratios ± SE were 8026 ± 5190 (range 102–17 795) at 1 h; 6322 ± 5907 (range 415–12 229) at 4 h; 6264 ± 2411 (range 1169–11 197) at 6 h; 6902 ± 3523 (range 3378–13 948) at 24 h; 4654 ± 2774 (range 425–12 609) at 48 h; and 1403 ± 1074 (range 329–2477) at 96 h post-treatment. Furthermore, when the plasma AUCs were compared with those for the pleural compartment, pleural exposures were calculated that were 55 to 684 times greater than systemic exposures (mean ± SE 374 ± 182) (Table 7).

## Discussion

The most common treatment of recurrent, symptomatic malignant pleural effusions is usually a tube thoracotomy and the $IP_L$ instillation of a sclerosing agent in an attempt to produce pleurodesis and prevent fluid reaccumulation. Among the sclerosing agents, tetracycline was the most popular agent because of its efficacy (success rate around 67%), ease of administration, low cost and relative lack of side effects.[16] Unfortunately, injectable tetracycline has not been available since mid-1991.[17] The tetracycline substitutes, minocycline and doxycycline, either have had insufficient testing (minocycline[18])

or required multiple treatment to attain similar response rates (doxycycline[19–21]). Although expensive, bleomycin became more popular because in the only controlled tiral of sufficient size, bleomycin was found to be superior to tetracycline.[14] In that study, Ruckdeschel and colleagues reported a recurrence rate at 30 days of 36% after the $IP_L$ instillation of 60 IU bleomycin and 67% after the $IP_L$ instillation of 1 g tetracycline. Reported side effects were similar in the two groups. There has been a resurgence in the use of talc owing to the recent availability of talc in a sterile preparation. Two small randomized studies have suggested that talc is more effective than bleomycin or tetracycline for the control of malignant pleural effusion.[22,23] However, until recently, talc has required intraoperative instillation, which may be difficult for patients with late stage cancer and/or a poor performance status. Bedside instillation of a talc suspension via a chest tube is reported to be effective in the management of malignant pleural effusion without the extreme pleural pain that accompanies poudrage application.[24]

More recently, soft small-bore catheters have been used as a means of reducing the overall morbidity of the procedure.[25,26] Whether soft catheters will replace chest tubes is not yet resolved. The reason we used soft small-bore catheters in this study was to avoid cremophor leaching of plasticizer from polyvinyl chloride materials, such as chest tubes. Video-assisted thoracic surgery is a well-tolerated procedure and has become more widely used, and affords excellent visualization of the entire pleural surface, lysis of adhesions and minimal instrumentation. Pleurodesis may be performed by pleurectomy, mechanical abrasion or talc sclerosis, whenever less invasive measures fail to achieve the clinical management goals.[27]

$IP_L$ chemotherapy for malignant pleural effusions has the potential advantage of treating the underlying malignancy in addition to providing local control of the effusion. Many chemotherapeutic drugs have been tried in the past including mechlorethamine (nitrogen mustard), thiotepa, doxorubicin, bleomycin, cisplatin, etoposide, fluorouracil and mitomycin C.[16] The mechanism of action of most of the chemotherapeutic agents used for treatment of malignant pleural effusions is due to their sclerosant effect.[28] Except for bleomycin, none is satisfactory due to low response rates or severe toxicity, including local chest pain, fever, nausea, vomiting and/or myelosuppression.[16] Bleomycin has few side effects. Whether the mechanism of action of bleomycin is due to a fibrogenic effect or a chemotherapeutic effect is still controversial.[29,30] There is a relative paucity of data on true $IP_L$ chemotherapy for malignant pleural effusions.

Recent evaluations of paclitaxel suggest that it is one of the most exciting cytotoxic agents to enter clinical trials in the past decades.[6] Markman and colleagues[8] evaluated the feasibility of intraperitoneal paclitaxel (25–200 mg/m$^2$ every 3–4 weeks) in 24 heavily pretreated ovarian cancer patients with malignant ascites. The dose-limiting toxicity was the development of abdominal pain at paclitaxel doses more than 175 mg/m$^2$. Moderate leukopenia (white blood cell count below 2 000/mm$^3$) was observed at intraperitoneal doses of 175 mg/m$^2$ or greater. The exposure of the peritoneal cavity (peak levels and AUC) to paclitaxel after intraperitoneal delivery exceeded that of the plasma by approximately 1000-fold. Significant concentrations of paclitaxel persisted within the peritoneal cavity for more than 24–48 h after a single intraperitoneal instillation. Antitumor responses, including control of malignant ascites, were documented clinically and by exploratory laparotomies.

In our study, we demonstrated that after $IP_L$ administration of paclitaxel the drug was principally confined to the pleural cavity with minimal local or systemic toxicities. The pharmacological advantage of the $IP_L$ administration of paclitaxel consisted of an increased exposure of the pleural cavity to paclitaxel [AUC ranged from 4167 to 43 745 ($\mu$mol/l) h] without increasing the exposure of systemic circulation [measurable AUC ranged from 53 to 272 ($\mu$mol/l) h]. The exposure of the pleural cavity (AUC) to paclitaxel after $IP_L$ delivery exceeded that of the plasma by approximately 370-fold (mean $\pm$ SE 374 $\pm$ 182; range 55–684) at the dose level of 225 mg/m$^2$. The $IP_L$ clearance of paclitaxel was extraordinarily slow and significant concentrations of paclitaxel persisted within the pleural cavity for more than 48–96 h after a single $IP_L$ administration. In theory, these pharmacologic characteristics could maximize the chemotherapeutic treatment of local disease while minimizing systemic toxicity and is especially important for the treatment of slowly growing neoplasms with cell-cycle specific agents in which cytotoxic activity is related to the duration of exposure.[7,8,31] Meanwhile, in some patients, plasma paclitaxel levels produced exceed the minimal concentrations (above 0.1 $\mu$mol/l) that are required to induce microtubule bundling and other pertinent cytotoxic effects *in vitro*,[10] and are compatible to the plasma levels that are achieved when paclitaxel is administered intravenously during a 3 h period.[32] Thus, in reality, the tumor is exposed via its capillary

blood supply to a concentration equivalent to what would be achieved by direct intravenous administration and on the pleural surface to concentrations 1–3 logs higher.

In this study, we believe the action of $IP_L$ administration of paclitaxel is due to a chemotherapeutic effect rather than a sclerosing effect, based on exploratory laparotomies showing the absence of significant intra-abdominal adhesions in a phase I trial of intraperitoneal paclitaxel.[8] Although efficacy was not a major end-point of this study, our study showed four of the 15 evaluable patients having no recurrence of effusion by a chest radiograph at 1 month for a response rate of 27%. Several reasons can be made to explain this relatively low response. First, in order to avoiding prolong retention of a catheter to cause pleural infection, patients received only a single instillation of $IP_L$ chemotherapy. Repetitive treatment might be better. Second, when tumors metastasize to the pleura, tumor cells may be seeded on the mesothelial surface or may invade the subserous layer.[33] Since the depth of penetration of the drug in effective concentrations may be only a few millimeters,[7,31] tumor nodules in the subserous layer and covered with pleura are not directly exposed to $IP_L$ drug. Also, multiple tumor masses and pleural adhesion may be present and adversely affect fluid distribution. Thirdly, the mean pretreatment pleural fluid pH of the four responders in our study was 7.42, compared with 7.28 of the 11 patients with recurrence ($p < 0.05$), and the mean pretreatment pleural fluid glucose of the four responders was 147 mg/dl, compared with 63 mg/dl of the 11 patients with non-responders ($p < 0.01$). It has been reported that low pleural fluid pH (below 7.30) and/or low glucose (below 60 mg/dl) at diagnosis have diagnostic, therapeutic and prognostic implications.[34,35] Such patients have extensive pleural tumors and fibrosis, and the end products of glucose metabolism, $CO_2$ and lactic acid, cannot escape at a normal rate from the pleural space.[36] In this group of patients, the mean survival time is low and the response to pleurodesis is unsatisfactory.

Four of our patients had progressive dyspnea during $IP_L$ retention of paclitaxel solution. Based on chest radiographs showing rapid fluid reaccumulation without parenchymal changes in all these patients and symptoms being relieved by drainage of fluid, the dyspnea was due to treatment failure but not local toxicity of $IP_L$ paclitaxel. Unfortunately, one patient who had severely chronic obstructive lung disease succumbed to respiratory failure. If the patient received mechanical ventilation during respiratory failure, the outcome might be not so ominous.

## Conclusions

From our phase I study of $IP_L$ paclitaxel, we conclude that it is feasible to use paclitaxel at a dose level of 175 or 225 mg/m$^2$ $IP_L$. For patients with malignant pleural effusions, the treatment results appear to be better in patients with normal pleural pH, glucose and a good performance status. When compared with using bleomycin or tetracycline derivatives for the management of malignant pleural effusions, $IP_L$ paclitaxel may not be cost-effective. The intrapleural administration of paclitaxel can be applied for treatment of patients with less advanced tumors or $IP_L$ tumors following surgical debulking, as used in patients with malignant mesothelioma. It may also be useful in lung cancer patients with carcinomatous pleuritis found at thoracotomy and in conjunction with systemic chemotherapy.

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