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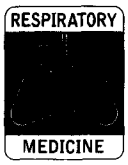

Phase II trial of intrapleural paclitaxel injection for non-small-cell lung cancer patients with malignant pleural effusions

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A phase II clinical trial of intrapleural paclitaxel injection for malignant effusions of non-small-cell lung cancer (NSCLC) was conducted in order to evaluate the efficacy and toxicity profile of paclitaxel pleurodesis in patients with malignant effusions. From February to May of 1996, 15 NSCLC patients with malignant pleural effusions were enrolled on study. After adequate drainage and assurance of lung re-expansion, paclitaxel 125 mg m^{-2} diluted in normal saline was infused through a preinserted pig-tail catheter which was removed 2 h later. Chest radiography and sonography were scheduled 4 days later; depending on whether there remained a significant amount of pleural effusion, further drainage by needle thoracentesis or by a pig-tail catheter was performed.

All patients were assessable for toxicity. Ipsilateral chest and/or shoulder pain, fever, facial flushing and nausea were the most frequent side-effects. Grade 4 neutropenia, grade 3 anaemia, and grade 3 renal impairment occurred in one patient each. Fourteen patients were evaluable for response at the end of the fourth week. Overall response rate of pleural effusion in evaluable patients was 92·9%, with a complete response rate of 28·6%. There was one out of 14 evaluable patients whose measurable tumour lesion decreased by more than 50% (partial response). No disease progression was noted among evaluable patients at the end of the fourth week. It is concluded that paclitaxel is a useful agent for the treatment of malignant pleural effusions. Because of its relatively low systemic toxicity, intrapleural paclitaxel injection in combination with systemic chemotherapy or radiotherapy can be considered in treating NSCLC patients with malignant pleural effusions.

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Introduction

Malignant pleural effusion is a common and significant problem in advanced cancer. Lung cancer is the leading cause of malignant pleural effusion (1–4). When patients with lung cancer are first evaluated, about 15% have a pleural effusion (3,5). During the disease course of lung cancer, at least 50% of patients with disseminated lung cancer develop a pleural effusion (5). The presence of pleural effusion in patients with non-small-cell lung cancer (NSCLC) usually indicates advanced disease and portends a grave prognosis. In contrast to breast cancer or lymphoma, NSCLC is usually refractory to chemotherapy, and thus the most common therapy for these NSCLC patients with malignant pleural effusions is a tube thoracostomy and intrapleural instillation of a sclerosing agent to obliterate the pleural space and to prevent reaccumulation of the effusion. Previously, tetracycline was recommended as the agent of choice for chemical pleurodesis. Because of its unavailability in parenteral form, the derivatives minocycline and doxycycline have been substituted. Other frequently recommended agents are talc, *Corynebacterium parvum*, and the antineoplastic agent bleomycin (6,7).

There has been a recurring interest in using intracavitary chemotherapy for malignant ascites or pleural effusions because of its potential ability to treat the underlying malignancy in addition to providing local control of the effusion. Chemotherapeutic agents that have been administered in the past include nitrogen mustard, doxorubicin, bleomycin, methotrexate, mitoxantrone, 5-fluorouracil, cisplatin, carboplatin, melphalan, mitomycin, cytarabine, etoposide, etc (8–11). Except for cisplatin, most of these chemotherapeutic drugs are ineffective when given for NSCLC.

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Paclitaxel (Taxol), the first of the taxane antimicrotubule agents isolated from the Western Yew, is a new anticancer agent that has demonstrated efficacy in the treatment of ovarian, breast and lung cancer (12–17). It is a novel chemotherapeutic agent which has a single-drug response rate of 21–24% in NSCLC (16,17). Results of a phase I clinical trial of intraperitoneal paclitaxel showed that paclitaxel can be delivered by the intraperitoneal route with minimal toxicity with a major pharmacokinetic advantage (18). The experience with intrapleural paclitaxel chemotherapy has been relatively rare. We previously performed a phase I intrapleural paclitaxel injection trial on patients with malignant pleural effusion, which found that maximal tolerated intrapleural paclitaxel injection dose was 225 mg m^{-2} and dose-limiting toxicity involved the development of severe dyspnoea (19). It was found that taxol 125 mg m^{-2} was effective for pleurodesis in patients who received this level of dosage. This report is of a phase II clinical trial of intrapleural paclitaxel injection (125 mg m^{-2}) to determine the efficacy of effusion control in NSCLC patients with malignant pleural effusion and to determine the toxicity profile of this kind of treatment. The result of this kind of treatment was promising and without severe side-effects.

Materials and Methods

The primary objective of this study was to evaluate the efficacy of paclitaxel pleurodesis, including symptom relief and prevention of reaccumulation of effusions. The second objective was to evaluate the side-effects accompanying this kind of treatment. Whether there exist systemic antitumour effects in addition to pleurodesis was also assessed.

Patients were eligible for this study if they had symptomatic, cytologically proven malignant pleural effusion of NSCLC. No prior intrapleural therapy was allowed. Radiotherapy, systemic chemotherapy and hormonal therapy were also not allowed within 4 weeks prior to trial entry. However, radiotherapy, chemotherapy and/or hormonal therapy can be given 4 weeks after intrapleural paclitaxel treatment. Adequate liver, renal and hematological function were required for study entry. The parameters used for this were (1) total serum bilirubin $\leq 1{\cdot}5$ mg%, (2) serum creatinine $\leq 2{\cdot}0$ mg dl^{-1} and (3) peripheral blood granulocyte count ≥ 1500 mm^{-3} and platelet count $\geq 100{\cdot}000$ mm^{-3}. Patients must be 18 years of age or older. A life expectancy of 2 months or longer and a performance status of 0–2 on the Zubrod scale after effusion drainage were required. This trial was approved by the hospital ethics committee and informed consent was obtained from all patients before study entry

All patients were required to be admitted to the hospital and to have a pig-tail catheter inserted. A chest roentgenogram to confirm lung re-expansion after catheter drainage is needed. This X-ray film after adequate catheter drainage was to serve as the baseline for follow-up evaluation of recurrence of effusion. A drainage rate less than 150 ml ($24\ h^{-1}$) was required. All patients received premedication for paclitaxel treatment, including dexamethasone 20 mg orally 12 and 6 h prior to paclitaxel treatment, diphenhydramine 50 mg intravenous infusion 45 min prior to paclitaxel treatment, and cimetidine 300 mg intravenous infusion 30 min prior to paclitaxel treatment. Then, paclitaxel 125 mg m^{-2} was diluted in normal saline to a concentration of $0{\cdot}6$ mg ml^{-1} (270–320 ml) and instilled into the pleural cavity through the pig-tail catheter. After paclitaxel instillation, the pig-tail catheter was clamped for 2 h and then removed. Patients were asked to change position at 15 min intervals during this 2 h period in order to ensure good dispersion of the drug throughout the pleural space. Chest roentgenography and ultrasonography were done after 96 h to assess the initial response of pleural effusion to treatment. If there was no obvious effusion remaining, no further management was given and the patient was discharged. If there was a small amount of effusion remaining, sono-guided needle aspiration of the remaining fluid was performed. 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, and the tube was removed. The purpose of retention of paclitaxel in the pleural cavity for 96 h or longer was to allow the chemotherapeutic effect to occur by prolonged contact of paclitaxel with pleural space. Patients were evaluated for toxicity during hospitalization, and every 2 weeks after discharge for 8 weeks, and then monthly for 6 months. Thereafter, patients were evaluated every 3 months. Toxicity was graded according to the U.S. National Cancer Institute Common Toxicity Criteria. Chest roentgenograms were obtained monthly to assess reaccumulation of the pleural effusion. A follow-up chest CT scan was performed at 4 weeks after paclitaxel treatment if initial measurable lesions were evaluated by CT scan. Chest ultrasonography was done if reaccumulation of effusion could not be ascertained by chest radiography or loculated effusion was suspected. All the chest X-ray films taken in this study were obtained with the standard posterior–anterior view. All the radiological examinations were performed under the monitoring of a radiologist not involved in the study. The single-blind method was used in follow-up chest radiograph evaluation by physicians and radiologists.

The treatment response of malignant effusion was evaluated according to the following criteria: (1) complete response (CR), no fluid reaccumulation and patients were free of symptoms for at least 4 weeks as determined by chest radiography, ultrasonography and/or CT scan and clinical evaluation; (2) partial response (PR), recurrence of effusion to less than 50% of the original effusion volume, patients were asymptomatic and no need for thoracentesis for symptom relief within 4 weeks after treatment; (3) failure, recurrence of effusion greater than 50% of the original volume, patients were symptomatic and need for thoracentesis to relieve symptoms within 4 weeks of treatment. Objective treatment response of malignant effusion included CR and PR. The criteria for main tumour lesion response to intrapleural paclitaxel treatment were as follows: (1) CR, the disappearance of all known disease for at least 4 weeks after treatment; (2) PR, at least a 50% decrease in total tumour size of the lesions that had been

TABLE 1. Clinical characteristics of patients with non-small-cell lung cancer with malignant pleural effusion

Characteristic	Number of patients	%
Sex		
Male	8	53·3
Female	7	46·7
Age (years)	Mean 64·1, range 47–78	
Performance status		
1	4	26·7
2	10	66·7
3	1	6·6
Histology		
Adenocarcinoma	13	86·6
Epidermoid carcinoma	1	6·7
Carcinoma, poorl differentiated	1	6·7
Stage		
IIIB	10	66·7
IV	5	33·3
Prior treatment		
No	7	46·7
Radiotherapy	3	20
Repeated thoracentesis	5	33·3

measured before treatment at 4 weeks after intrapleural chemotherapy and, in addition, there must be no appearance of new lesions, progression of any other lesion or failure of effusion treatment; (3) minor response (MR), a 25–50% decrease in total tumour size of the lesions that had been measured before treatment at 4 weeks after intrapleural chemotherapy and, in addition, there may be no appearance of new lesions, progression of any lesion or failure of effusion treatment; (4) stable disease (SD), a 25% decrease in tumour size cannot be established, nor is a 25% increase in the size of one or more measurable lesions demonstrated at 4 weeks after treatment; (5) progressive disease (PD), at least a 25% increase in size of at least one measurable lesion or the appearance of new lesions.

Results

From February 1996 to May 1996, 15 NSCLC patients with malignant pleural effusions were enrolled on study. There were eight men and seven women. The average age was 64 years (range, 47–78 years). The clinical characteristics of these 15 patients are shown in Table 1. The majority of patients had an initial performance status scale of 1 or 2. Adenocarcinoma was the most common cell type and was seen in 13 patients. One patient had epidermoid carcinoma and another poorly differentiated carcinoma that could not be further characterized. All patients were chemotherapy naive. Only three patients received prior radiotherapy for control of primary NSCLC lesions. Five of 15 patients had a history of repeated thoracentesis.

Pig-tail drainage of effusion was done in all patients before intrapleural paclitaxel injection. From 3 to 14 days (median 7 days) drainage was needed before paclitaxel could be given. After intrapleural paclitaxel injection for 96 h, there were five patients who needed pig-tail reinsertion. Four patients received thoracentesis only. The remaining six patients received no further management because chest radiography and sonography showed no evidence of obvious residual effusion (Table 2). Three patients had follow-up effusion cytology on day 5 and the results were negative for malignant cells in two patients and marked degeneration of tumour cells in one patient. Five patients had effusion cell count and differential count follow-up on day 5 and all showed a marked increase in neutrophil count with a reversal of lymphocyte predominance to neutrophil predominance.

All patients were assessable for toxicity. The toxicities are shown in Table 3. Seven patients (46·7%) suffered from ipsilateral chest or shoulder pain which could be relieved by non-steroid anti-inflammatory drugs or codeine. It usually occurred several hours after intrapleural paclitaxel injection and subsided 3 or 4 days later. Alopecia occurred only in one (6·7%) patient. Grade 1 or 2 nausea occurred in seven patients (46·7%). Grade 2 vomiting occurred in only one (6·7%) patient. Fever occurred in five patients. Among these five patients, four patients had no evidence of infection and the remaining patient suffered from febrile neutropenia. The duration of fever was 1–5 days with a median of 2 days. Concerning myelosuppression, only one patient suffered from grade 4 neutropenia (neutrophils $<500\ \mu\ l^{-1}$). There was also one patient who suffered from grade 2 thrombocytopenia, two patients had grade 1 anaemia and one patient had grade 3 anaemia (haemoglobin between 6·5–7·9 g dl^{-1}). One patient suffered from grade 3 renal function impairment (serum creatine between 3·1 and 6·0 times normal range) and grade 2 liver function impairment. This patient, who suffered from renal and liver function impairment, deteriorated rapidly and died on the 14th day after

TABLE 2. Effusion management at 96 h after intrapleural paclitaxel treatment

	Pig-tail reinsertion	Thoracentesis	No further management
Patient number	5	4	6
Amount drained, mean (range)		480 (150–1060)	
Days on pig-tail, mean (range)	6 (2–12)		

TABLE 3. Toxicity in patients with non-small-cell lung cancer with malignant pleural effusion after paclitaxel intrapleural therapy

Type of toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Chest and/or should pain	6·7	40	0	0
Alopecia	6·7	0	0	0
Nausea	33·3	13·3	0	0
Vomiting	0	6·7	0	0
Fever				
Without neutropenia	0	26·7	0	0
With neutropenia	0	6·7	0	0
Myelosuppression				
Neutropenia	0	0	0	6·7
Thrombocytopenia	0	6·7	0	0
Anaemia	13·3	0	6·7	0
Renal	0	0	6·7	0
Hepatic	0	13·3	0	0

TABLE 4. Chest radiographic findings of 14 evaluable patients before and 4 weeks after intrapleural paclitaxel therapy

Findings*	Number of patients (%)			
Before drainage	Before paclitaxel injection	96 h after paclitaxel injection	4 weeks later	
Massive amount of effusion	11 (78·6)			
Moderate amount of effusion	3 (21·4)		1 (7·1)	
Small amount of effusion		3 (21·4)	3 (21·4)	3 (21·4)
Costophrenic angle blunting	10 (42·9)	4 (28·6)	7 (50)	
Localized loculated effusion				5 (35·7)
Multiple loculated effusion		1 (7·1)	5 (35·7)	6 (42·9)
Interlobar effusion		1 (7·1)	2 (14·3)	2 (14·3)

*Massive amount of effusion, volume of effusion more than half of hemithorax with mediastinal shift; moderate amount of effusion, volume of effusion between one-third and one-half of hemithorax; small amount of effusion, volume of effusion less than one-third of effusion and more than only costophrenic angle blunting.

treatment owing to disease progression. Facial flushing occurred in six patients (40%) and five were women. The facial flushing occurred within 24 h and subsided within 72 h after paclitaxel treatment. Paclitaxel fluid leakage into the subcutaneous space of the chest wall occurred in one patient. This patient was the only patient who suffered from grade 4 neutropenia with fever. Tumour seeding along the pig-tail tunnel with moderate pain occurred in one patient. The most frequent late effect or complication of intrapleural paclitaxel injection was pleural thickening with loculated effusion which occurred in 11 of 14 patients (78·6%) in follow-up chest CT scan, radiography and/or sonography 4 weeks after intrapleural paclitaxel injection (Table 4). The loculated effusions were usually complex, septated effusions with marked thickening of pleura, found by sonography and/or CT scan.

Fourteen of the 15 patients were assessable for response of effusion control at the end of the 4th week (Table 5). The remaining patient died of progressive disease during the first 4 weeks after entry on study. This early death did not seem to be related to the intrapleural chemotherapy. Four patients had a CR and nine patients had a PR at 4 weeks for an overall initial objective response rate of 86·7% of effusion control (13 of 15; 95% confidence interval, 69·5–100%). Among the 14 patients assessable at 4 weeks, this represents an effusion control rate of 92·9% (13 of 14; 95% confidence interval, 79·4–100%). This also meant that 92·9% of patients had their dyspnoea improved after intrapleural paclitaxel treatment. Fourteen patients were assessable for response at 2 months after treatment. Among them, four patients had a CR and six patients had a PR for an overall

TABLE 5. Response of malignant pleural effusion after paclitaxel intrapleural therapy

Months	No. of evaluable patients	CR (%)	PR (%)	Overall response (%)	Failure (%)
1	14	4 (28·6)	9 (64·3)	13 (92·9)	1 (7·1)
2	14	4 (28·6)	6 (42·8)	10 (71·4)	4 (28·6)
3	13	4 (30·8)	5 (38·4)	9 (69·2)	4 (30·8)

objective response rate of 71·4% of effusion control in 14 assessable patients. Overall response rate of effusion control in 13 evaluable patients at 3 months after treatment was 69·2% (Table 5).

Regarding tumour response to intrapleural paclitaxel treatment, one patient had a PR of his measurable lesion at 4 weeks, and three patients had an MR. Among 14 assessable patients, no progressive disease of tumour lesions was noted at 4 weeks after treatment.

Discussion

Malignant pleural effusions are recognized as a distressing common problem of advanced cancer. Lung cancer is the leading cause of malignant effusions. The presence of a malignant pleural effusion in lung cancer indicates at least locally advanced disease (stage IIIb, IV). The prognosis of these patients is poor.

The most practical approach today for the clinician to treat a patient with a symptomatic malignant effusion is still controversial. The traditional management of malignant pleural effusions has been focused on the control of the effusion for the palliation of symptoms. Many agents have been used and no single agent has been proved to be entirely satisfactory. They include the intrapleural administration of talc, *C. parvum*, tetracycline, tetracycline derivatives, bleomycin, mechlorethamine, doxorubicin, cisplatin, cytarabine, etoposide, fluorouracil, mitomycin-C, interferon, interleukin-2, OK-432 etc (6,8,10,11, 20–34). Tetracycline has emerged as the agent of choice because it is at least as effective as all the others and is easily available and inexpensive (6,8,9,32). However, parenteral tetracycline has become unavailable owing to more stringent manufacturing requirements. Minocycline and doxycycline, with success rates of more than 70%, appear to be effective tetracycline-replacement agents in recent studies (6,26). Because of the lack of a large-scale randomized study, difficulties with study design and inconsistencies in evaluation of patients in different studies, none has been clearly proved superior to other agents. Doxycycline, bleomycin, and talc are effective sclerosing agents most frequently used in recent years (35–37). It was found that bleomycin is superior to or as effective as tetracycline in previous randomized trials (30,35,38). In two small randomized studies comparing the efficacy of talc with either tetracycline or bleomycin, it was found that talc appeared to be more effective than tetracycline and bleomycin (39,40). A phase II clinical trial with multiple arms including talc, tetracycline and bleomycin also showed significant superior response in talc treatment compared with tetracycline and bleomycin. In this study, it was found that 97% patients had a successful pleurodesis at 30 days and 95% at 90 days. It was 64% and 70% in 30 days and 90 days respectively in the bleomycin group. It was only 33% and 47% in 30 days and 90 days respectively in tetracycline-treated patients (41). The expected response rate for freedom from recurrence of a symptomatic effusion 1 month after treatment is 84%, 69% and 96% for bleomycin, tetracycline and talc respectively (36). However, the administration of talc is considered to be more complicated and with a higher incidence of morbidity than simple pleurodesis with bleomycin or tetracycline (35,36). When comparing with our studies, it was found that paclitaxel-treated patients had a 92·9% response rate 1 month after treatment. This response rate was better than the expected response rate of bleomycin and tetracycline. However, it was still lower than that for talc treatment.

The use of intrapleural chemotherapy has the potential advantage of treating the underlying malignancy and controlling the malignant effusion. The drug level in the pleural cavity can be many-fold higher than the systemic level. In theory, such an approach could maximize the treatment effect of local disease while minimizing systemic toxicity. However, it has several limitations. It requires good dispersion throughout the whole pleural cavity and it can penetrate into the tumour to a distance of only a few millimeters (8,9,11). Patients who have bulky tumours or intrapleural adhesions are unlikely to benefit from this treatment modality. Bleomycin is an effective sclerosing agent with few side-effects, but it does not have good antineoplastic activity in the malignancies that commonly cause pleural effusion (8,9,27,30,35). As more effective anti-cancer drugs have been found in recent years, there is an increasing interest in using drugs that are thought to act primarily by cytotoxicity rather than by sclerosis.

Paclitaxel is a new chemotherapeutic agent with activity in NSCLC. From our data, paclitaxel is highly effective in controlling malignant effusion from NSCLC. This result is most likely better than previous reports involving intrapleural chemotherapy, including bleomycin (6,8,32,33). In addition, no patient suffered from progression of disease during 4 weeks follow-up after paclitaxel treatment. More importantly, there was one out of 14 patients who had more than 50% primary tumour lesion shrinkage. This means that intrapleural paclitaxel injection still had a systemic anti-tumour effect. The exact mechanisms of pleurodesis caused by paclitaxel on malignant pleural effusion of NSCLC were not clear. Intrapleural paclitaxel treatment probably had both anti-cancer effect and sclerosing effect.

The anti-tumour effect was supported by disappearance or marked degeneration of malignant cells from the effusion after paclitaxel treatment in patients who had effusion cytology follow-up. The sclerosing effect was supported by the observation that paclitaxel can cause chest pain after instillation and produce pleural thickening and adhesions.

The toxicities of paclitaxel treatment seen in this study are somewhat different from those found when it is administered systematically. Facial flushing, chest and/or shoulder pain and fever are more commonly seen than in those patients receiving systemic paclitaxel treatment. However, no serious adverse reactions were seen. Another problem concerning intrapleural paclitaxel treatment is that the cost is much higher in patients receiving paclitaxel treatment than chemical pleurodesis alone, such as minocycline or doxycycline.

When considering cost-effectiveness, paclitaxel is expensive at a cost of approximately $1200 for a 70 kg person of normal surface area. This cost is higher than those of doxycycline or minocycline pleurodesis. The cost will be even higher when the hospitalization fee is also considered. Therefore, use of paclitaxel for the purpose of pleurodesis only has a cost disadvantage. However, the major shortcoming of our study is the limited number of patients tested. Given the small number of patients tested, it needs to be more cautious when drawing the conclusions.

Overall, paclitaxel appears to be a useful agent for the treatment of malignant pleural effusions. Because of its low systemic side-effects and high local efficacy, it can be considered to be used in combination with systemic chemotherapy or radiotherapy in managing NSCLC patients with malignant pleural effusions.

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