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Toxicity Profile and Pharmacokinetic Study of A Phase I Low-Dose Schedule-Dependent Radiosensitizing Paclitaxel Chemoradiation Regimen for Inoperable Non-Small Cell Lung Cancer (NSCLC)

Yuhchayau Chen, Ph.D., M.D.,

University of Rochester School of Medicine, Department of Radiation Oncology, 601 Elmwood Ave., Box 647, Rochester, NY 14642, Phone: 585-275-5623, Fax: 585-275-1531

Kishan J. Pandya, M.D.,

University of Rochester School of Medicine, Department of Medical Oncology, 601 Elmwood Ave., Box 704, Rochester, NY 14642, Phone: 585-275-9319, Fax: 585-275-5823

Richard Feins, M.D.,

University of North Carolina at Chapel Hill, Division of Cardiothoracic Surgery, 3031 Burnett-Womack Building, C.B. 7065, Chapel Hill, NC 27599-7065, Phone: (919) 966-3381, Fax: (919) 966-3475

David W. Johnstone, M.D.,

Dartmouth-Hitchcock Medical Center, Division of Cardiothoracic Surgery, 1 Medical Center Dr. Lebanon, NH 03756, Phone: (603) 650-8537, Fax: (603) 650-6346

Thomas Watson, M.D.,

University of Rochester School of Medicine, Division of Cardiothoracic Surgery, 601 Elmwood Ave., Box SURG, Rochester, NY 14642, Phone: 585-275-1509, Fax: 585-273-1011

Therese Smudzin, B.S., and

University of Rochester School of Medicine, Department of Radiation Oncology, 601 Elmwood Ave., Box 647, Rochester, NY 14642, Phone: 585-275-7848, Fax: 585-275-1531

Peter C. Keng, Ph.D.

University of Rochester School of Medicine, Department of Radiation Oncology, 601 Elmwood Ave., Box 647, Rochester, NY 14642, Phone: 585-275-6332, Fax: 585-275-1531

Yuhchayau Chen: yuhchayau_chen@urmc.rochester.edu; Kishan J. Pandya: kishan_pandya@urmc.rochester.edu; Richard Feins: richard_feins@med.unc.edu; David W. Johnstone: david.w.johnstone@hitchcock.org; Thomas Watson: thomas_watson@urmc.rochester.edu; Therese Smudzin: therese_smudzin@urmc.rochester.edu; Peter C. Keng: peter_keng@urmc.rochester.edu

Abstract

Correspondence to: Yuhchayau Chen, yuhchayau_chen@urmc.rochester.edu.

CONFLICT OF INTEREST NOTIFICATION

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Purpose—We report the toxicity profile and pharmacokinetic data of a schedule-dependent chemoradiation regimen using pulsed low-dose paclitaxel for radiosensitization in a phase I study for inoperable non-small cell lung cancer (NSCLC).

Methods and Materials—Paclitaxel at escalating doses of 15 mg/m², 20 mg/m², and 25 mg/m² were infused on Monday, Wednesday, and Friday with daily chest radiation in cohorts of 6 patients. Daily radiation (RT) was delayed for maximal G2/M arrest and apoptotic effect, an observation from preclinical investigations. Plasma paclitaxel concentration was determined by High Performance Liquid Chromatography (HPLC).

Results—Dose-limiting toxicities included 3/18 patients with grade 3 pneumonitis and 3/18 patients with grade 3 esophagitis. There was no grade 4 or 5 pneumonitis or esophagitis. There was no grade 3 or 4 neutropenia, thrombocytopenia, anemia or neuropathy. For dose levels I (15 mg/m²), II (20 mg/m²), and III (25 mg/m²), the mean peak plasma level was 0.23 ± 0.06 μM, 0.32 ± 0.05 μM, and 0.52 ± 0.14 μM, respectively; AUC was 0.44 ± 0.09 μM, 0.61 ± 0.1 μM, and 0.96 ± 0.23 μM, respectively; and duration of drug concentration above 0.05 μM ($t > 0.05 \mu\text{M}$) was 1.6 ± 0.3 hr, 1.9 ± 0.2 hr, and 3.0 ± 0.9 hr, respectively.

Conclusion—Pulsed low-dose paclitaxel chemoradiation is associated with low toxicity. Pharmacokinetic data showed that plasma paclitaxel concentration above 0.05 μM for a minimum of 1.6 hours was sufficient for effective radiosensitization.

Keywords

pharmacokinetics; paclitaxel; radiosensitization; non-small cell lung cancer; chemoradiation

INTRODUCTION

Combination chemoradiation therapy has improved survival in patients with stage III inoperable non-small cell lung cancer when compared with radiation treatment alone (1–9). Despite the promising improvement by combined modality therapy, investigations using various chemoradiotherapy combinations have yielded an average 5-year survival of less than 25%. While chemotherapy combinations have reached the plateau for non-small cell lung cancer (10), intrathoracic disease control is even more disappointing with an average low rate of control at 40–50% at best by radiographic criteria (1,4,6), and only 15%–17% control rate by tumor biopsy through post-treatment bronchoscopy (4). Because locoregional failure can serve as a continuous source of distant metastasis, improving chest disease control is critical in the management of locally advanced NSCLC.

We previously conducted preclinical studies of the cell cycle and apoptotic effects of low-dose paclitaxel on human lung cancer cell lines. We found that pulsing low-dose paclitaxel every 48 hours resulted in the restitution of G2/M cell cycle arrest, the most radiosensitive phase of the cell cycle. The cell cycle effect started at approximately 4 hours after drug treatment, and peaked at 24 hours. This was followed by a gradual recovery of G2/M effect after 36 hours, and a return to baseline cell cycle distribution at 48 hours after treatment. In addition, paclitaxel apoptotic effect peaked at 48 hours after in vitro treatment of lung cancer cell lines (12,13). Clinical data from phase II investigation showed a 100% gross tumor response rate at 4 to 6 weeks post-therapy, with an absolute in-field tumor control rate of 97.6%, and a 3-year survival rate of 21% (12,13).

To our knowledge, complete toxicity detail and pharmacokinetic profile using paclitaxel in such a low dose range for radiosensitization has not been reported. The toxicity and pharmacokinetic profiles of low-dose paclitaxel combined with chest irradiation, as well as the clinical implications of this phase I study, will be discussed.

METHODS AND MATERIALS

Phase I Clinical Study of Pulsed, Low-dose Paclitaxel for Radiosensitization

A phase I clinical study of pulsed low-dose paclitaxel with daily fractionated thoracic irradiation for inoperable NSCLC was conducted between 1998 and 2001 through a clinical protocol approved by the University of Rochester Institutional Review Board. All patients had given informed consent for participation. All patients were given standard premedications (cimetidine, dexamethasone, and diphenhydramine) prior to paclitaxel infusion to reduce the risk of hypersensitivity reactions. Low-dose paclitaxel was administered as a one-hour intravenous infusion in the morning on Monday, Wednesday, and Friday. Thoracic radiation (XRT) was given after 4:00 PM on the days when patients received chemotherapy to allow for a minimum of a 4-hour interval for cell cycle progression. On Tuesday and Thursday when there was no paclitaxel treatment, XRT was given any time after 11:00 AM.

The starting dose of paclitaxel was 15 mg/m² with 5 mg/m² increments for dose-escalation. Dose-limiting toxicity was defined as grade 4 hematologic toxicity as well as grade 3 and 4 nonhematologic toxicity. Our initial plan was that escalation would be stopped when three or more dose-limiting toxicities were observed at a dose in 6 patients. We maintained this schema up to the third dose level (25mg/m²), where we found that the rates of tumor response and shrinkage at all dose levels achieved maximum clinical effect in response to radiotherapy.

There were 6 to 7 patients treated at each dose level, with at least 5 or 6 patients completing the correlative pharmacokinetic studies. All patients had CT-based treatment planning with lung correction. The average XRT dose was 60–65 Gy to the gross disease and 45–58 Gy to potential mediastinal microscopic disease given at 1.8 Gy daily fractions over 7.5 weeks. In general, radiation portals encompassed gross disease with a 1.5 cm to 2 cm margin of surrounding lung parenchyma.

Response and Toxicity Assessment

Blood counts, chemistry, and treatment related toxicities were monitored weekly during chemoradiation treatment and at each follow-up visit. Toxicity was scored according to National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 2.0 (14). All patients had follow-up chest CT scans at 4 to 6 weeks post-therapy and serial follow-up CT scans at 3-month intervals. Response to therapy was assessed according to two-dimensional radiological tumor measurements. Clinical Complete Response (CR) was defined as complete disappearance of all evidence of tumor. Partial Response (PR) was defined as a tumor decrease by at least 50%. Stable Disease (SD) was defined as no change in measurable disease or changes that were too small to meet the requirements for partial response or progression. Progressive Disease or Relapse was defined as the development of any new areas of malignant disease that were measurable or palpable, or an increase by more than 25% in any pretreatment area of measurable disease.

Pharmacokinetic Measurements

All patients had intravenous catheters inserted in both of their arms. One catheter was used for the infusion of paclitaxel while the other was used for blood sample collection. A total of 17 samples from each patient were collected in green-top, heparinized vacutainers (2.5 mL to 3.0 mL of blood). Blood was collected prior to paclitaxel infusion and at the following time points from the start of infusion: 10 minutes, 15 minutes, 1 hour, 1 hour and 10 minutes, 1 hour and 15 minutes, 1 hour and 30 minutes, 1 hour and 45 minutes, 2 hours, 2 hours and 30 minutes, 4 hours, 6 hours, 8 hours, 16 hours, 24 hours, and 30 hours. Samples were immediately placed on ice and centrifuged at 1,000 × g to produce plasma. Plasma was immediately frozen and stored at –20 °C until assayed for paclitaxel concentration.

Paclitaxel concentration in plasma was determined by HPLC, using modifications of the method by Jamis-Dow, et al (15). Briefly, 0.5 mL of plasma was mixed with 5 μ L of 50 μ M cephalomannine internal standard (Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD) and applied to a Spe-ed C₁₈ solid phase extraction device (Applied Separations, Lehigh Valley, PA), which had been preconditioned with sequential washings of 1 mL acetonitrile and 1 mL distilled water. After application of plasma, the devices were washed with 3 mL distilled water, and paclitaxel and internal standard were eluted from the Spe-ed with 2 mL acetonitrile. The eluates were evaporated to dryness under nitrogen with an N-evap (Organomation Associates, South Berlin, MA). The dried residues were reconstituted in 200 μ L of the mobile phase described below, and 150 μ L were injected onto the HPLC system.

HPLC system included a Hewlett Packard (Palo Alto, CA) 5 μ m Hypersil ODS (100 $\times$ 4.6 mm) column protected with a Brownlee Newguard precolumn cartridge (Applied Biosystems Inc., Foster City, CA). The isocratic mobile phase, which consisted of acetonitrile: distilled, deionized water (45:55, v/v), was delivered at a low rate of 1.0 mL/min with a Waters model 510 pump (Waters Chromatography, Milford, MA). Column effluent was monitored at 230 nm with a Spectroflow 757 absorbance detector (AB1 Analytical, Kratos Division, Ramsey, NJ). Under each peak eluted, the detector signal was processed with a Hewlett Packard model 3396 integrator. Paclitaxel concentration in each sample was calculated by determining the ratio of paclitaxel peak area to that of the corresponding internal standard peak and comparing that ratio to a concomitantly performed standard curve prepared in the appropriate matrix. The lower limit of quantization was 0.010 μ M in human plasma. The assay was linear between 0.010 and 200 μ M paclitaxel. The coefficient of variability for the analysis was $\leq$ 15% with regard to both intra-day analysis of any concentration on the standard curve or inter-day comparison of standard curves.

Pharmacokinetic analysis was conducted using the program ADAPTII. A previously described 3-compartment non-linear model was fit to the plasma paclitaxel concentration versus time profile of each patient (16). In this analysis, the model was fit to the data using Bayesian estimation with previously described population means and variances as prior information for each pharmacokinetic parameter estimated by the model as described (16).

RESULTS

Patient characteristics

Seventeen patients completed the 7.5 weeks of chemoradiation, and one patient completed 6 weeks of the planned chemoradiation before evidence of distant disease progression. Patient characteristics are shown in Table 1. The definition of “inoperable” non-small cell lung cancer in this study includes the majority of stage III non-small cell lung cancer, who are not operable due to tumor stage, as well as a smaller population with stage I–II disease deemed inoperable by the thoracic surgeons due to poor pulmonary functions. Specifically, two of the four patients were deemed inoperable for pneumonectomy, which included one patient of stage II disease with a FEV₁ of 1.53 L and the other patient of stage II disease with a FEV₁ of 2.38 L. The other two of the four patients were deemed inoperable for lobectomy, which included one patient of stage I disease with a FEV₁ of 0.75 L and the other of stage I disease with a FEV₁ of 1.03 L.

Toxicity profiles by dose levels

With 6 patients at each dose level, toxicity was recorded and evaluated. When there was $<3/6$ patients with grade 3 and above nonhematologic toxicity, or grade 4 hematologic toxicity, the dose was escalated to the next level. As shown in Table 2, hematologic toxicity was mild, being

either grade 1 or 2. Non-dose limiting grade 3 lymphopenia was seen for all dose levels and is an expected side effect from radiation treatment. Table 3 shows the nonhematologic toxicities for all 3 dose levels. There was no peripheral neuropathy. Nausea/vomiting, fatigue, weight loss, or tachycardia was only grade 1 or 2. There were no grade 4 nonhematologic toxicities. Grade 3 pneumonitis occurred in 3/18 patients with one at each dose level. Grade 3 esophagitis occurred in 3/18 patients with 1 at dose level I, 2 at dose level II, and none at dose level III. Grade 2 alopecia was observed in 3 patients at dose level III but not at dose level I or II. There was no grade 3 and 4 dose-limiting toxicity (DLT) for dose levels I and II, and thus dose escalation continued to level III. At dose level III, 3 patients showed grade 2 alopecia and 2 patients showed grade 3 anemia. By the time the third dose level completed, the tumor response rate was analyzed, which showed equivalent gross tumor shrinkage and response for all dose levels, i.e., 100% response rate and 87% tumor shrinkage for all doses (Table 4). It was deemed of no further benefit to continue dose escalation as the maximal clinical effect of local tumor response to radiotherapy had been achieved.

Gross tumor shrinkage by dose levels

The gross tumor response was measured from chest CT scans obtained at 4 to 6 weeks postchemoradiation and compared with pretreatment tumor dimensions on CT. The overall response rate was 100% with 12% (2/17 patients) complete response, and 88% (15/17 patients) partial response. Although there was difference in stage distribution in term of early stage (stage I and II) of patients of each dose level, but the difference did not impact on the response rate. Dose level I had one stage II patient (1/6 = 17%) and five stage III patients. Dose level II had two stage II, and 1 stage IIB patients (3/6 = 50% for stage I and II) and three stage III patients. Dose level III had all stage III non-small cell lung cancer and no stage I–II patients. Despite the differences in the stage distribution of these stage I–II patients, the degree of tumor shrinkage did not differ, and the overall tumor response rate (CR + PR) was all 100% for all three dose levels, as shown in Table 4.

Pharmacokinetics

Pharmacokinetic analyses were conducted in 7 patients treated at 15 mg/m², 5 patients at 20 mg/m², and 6 patients at 25 mg/m². Figure 1A demonstrates a representative plasma paclitaxel concentration versus time curve of low-dose paclitaxel given as a one-hour intravenous infusion. With dose escalation there was an increase in the peak plasma concentration (Figure 1B), the area under the plasma paclitaxel versus time curve (AUC) (Figure 1C), and the duration for which paclitaxel concentration was above 0.05 µM (Figure 1D). Table 5 summarizes the pharmacokinetic profiles of the 3 dose levels.

DISCUSSION

Improving chest disease control can improve survival of patients with stage III NSCLC. The best example is the randomized phase III study incorporating low-dose sensitizing cisplatin to chest radiation conducted by Schaake-Koning et al (1). There were three treatment arms of this European study: radiotherapy alone, radiotherapy with weekly cisplatin (30 mg/m²), and radiotherapy with daily cisplatin (6 mg/m²). There was no treatment arm administering systemic doses of cisplatin; thus the improved survival outcome of this study is through improving chest tumor control by enhanced radiation effect. We report that the daily cisplatin and radiotherapy arm yielded the best survival rate, supporting the idea that improving chest disease control will improve survival. In recent years, many other chemotherapeutic agents have been delivered as sensitizing agents to improve radiation effect, including the taxanes, gemcitabine, vinorelbine, and topoisomerase (17,18). Among these, paclitaxel has been a favored drug due to its ability to arrest cells at the G2/M interphase in the cell cycle. While several different dose schedules of paclitaxel chemoradiation regimens in the treatment of

inoperable NSCLC have been reported, the optimal schedule in delivering paclitaxel chemoradiation combination remains unclear.

The pharmacokinetics of full-dose paclitaxel at much higher concentrations of 135 mg/m², 175 mg/m² and 225 mg/m² was previously investigated by Gianni et al (16). These investigators reported important pharmacokinetic characteristics and the impact on bone marrow suppression by the differences of drug concentrations and infusion time. It was found that the infusion time affected the peak plasma concentration as well as the duration of the peak concentration of the drug. The shorter infusion time of 3 hours in their study resulted in a higher plasma peak concentration of paclitaxel, which was followed by a rapid decline of plasma drug concentration. The longer infusion time of 24 hours resulted in a relatively lower plasma peak concentration, but a much longer duration of a plateau during this time period. They found that the 24-hour infusion time with a longer plateau concentration above 0.05 μM ($t > 0.05 \mu\text{M}$) resulted in higher incidences of neutropenia than the 3-hour infusion, thus the duration of plasma paclitaxel concentration that was higher than 0.05 μM ($t > 0.05 \mu\text{M}$) was directly proportional to the risk of neutropenia.

We report the details of the toxicity profile with low-dose paclitaxel delivered in a pulsed schedule every 48 hours, and the pharmacokinetic properties of radiosensitizing paclitaxel in the very low dose range of 15 mg/m² to 25 mg/m². We chose the one hour infusion time with the intention of applying low-dose paclitaxel primarily for radiosensitization, thus an immediate peak level in rendering cancer cells into the G2/M phase of the cell cycle followed by a rapid decline would be ideal and would be at low risk of hematologic toxicity.

The response rate of our study was compared with chemoradiation using full-dose chemotherapy (13). From the perspective of radiosensitization, the clinical outcome of our phase I/II study was quite satisfactory with a 100% response rate and a 97.6% chest disease control rate. This is a significant improvement when compared with other reported studies for locally advanced NSCLC, where local control is less than 50% at best.

The radiation dose required to control human epithelial tumors larger than 5 cm in diameter is approximately 80 to 100 Gy (19). As for inoperable NSCLC, it was suggested that the radiation dose required for a 50% probability of tumor control was approximately 85 Gy (20,21). For patients treated with definitive radiation for small T1 and T2 inoperable tumors of NSCLC, the local control rates were only 30% to 60% with radiation dose at approximately 60 Gy (22–24). Normal tissue tolerance of the esophagus, trachea, bronchi, lung parenchyma, and heart is a primary dose-limiting factor for chest radiotherapy, thus the radiation doses for inoperable NSCLC have been kept below 70 Gy to avoid complications. Most patients in this phase I study had large, inoperable tumors and received only 60 Gy to 65 Gy radiation to gross tumor, yet the tumor shrinkage was very encouraging (82% to 84%), supporting the fact that schedule-dependent pulsed paclitaxel chemoradiation is an effective radiosensitizing regimen. Furthermore, the lack of dose response of sensitizing paclitaxel supports that pushing for dose-limiting toxicity may not be the optimal goal for radiosensitization chemotherapy. The long-term follow-up data showed that there was one in-field local tumor failure in patients treated at dose level I in the phase I study of this regimen. There was no in-field gross tumor failure at dose level II and level III. Because every follow-up chest CT scan was reviewed personally by the investigator and the medical oncologist, we could comment that there was, however, chest failure presenting as separate pulmonary nodules in other lobes or other lung (outside of initial radiation ports). These were discrete pulmonary nodules in other lobes or contralateral lung, thus were metastatic nodules and not local failure. A separate manuscript has been prepared to address the pattern of failure of this regimen, and these points will be discussed in detail.

The pharmacokinetic study revealed important characteristics of sensitizing paclitaxel. The short infusion time of one hour resulted in a short peak plasma level of paclitaxel, while achieving the effective radiosensitization. Our data support that a short interval (between 1.5 hours and 3 hours) of plasma drug concentration between 0.05 μ M and 0.23 μ M and a very low concentration of paclitaxel is sufficient for effective radiosensitization. Since our chemoradiation schedules were designed to deliver radiation during cell cycle arrest, it is not clear that will be seen without an appropriate delay of 4 hours on the days chemotherapy is administered. The clinical finding was consistent with our preclinical in vitro observation of lung cancer cell lines in that a relatively short duration of exposure of cancer cells to low doses of paclitaxel was sufficient for radiosensitization (12,13). The toxicity profile of this phase I study is compatible with published pharmacokinetic information of full-dose paclitaxel (16) in that the risk of grade 3 and 4 neutropenia in our study was low because of the 1.5 to 3 hour duration of plasma paclitaxel concentration above 0.05 μ M ($t > 0.05 \mu$ M). We saw no grade 2 neutropenia and thrombocytopenia, without any grade 3 or 4 hematologic toxicities. Grade 3 anemia was only seen in 3 patients at the level III dosing of 25 mg/m². The peak plasma level, AUC and $t > 0.05 \mu$ M increased with dose-escalation. The increase in magnitude of these parameters was small, and there did not appear to be any significant increase in the in the risk of nonhematologic toxicity such as grade 3 pneumonitis and esophagitis. The overall rates of grade 3 pneumonitis and esophagitis for all patients in this phase I study were much lower than reports using other dose schedules of paclitaxel and radiation (17,25,26). One may argue that the 4 patients with stage I–II diseases might have been treated with smaller radiation ports, which might have contributed to the low rates of esophagitis and/or pneumonitis. We reviewed the radiation ports of these 4 patients and did not find major differences in the size of radiation ports. These patients were treated during the era when prophylactic mediastinal irradiation had been a common practice for stage III and some stage II patients. Our review showed that the 2 stage II patients had radiation ports encompassing the lung lesion, the ipsilateral hilar and the mediastinum. The 2 stage I patients (both at dose level II) had central lesions and had radiation ports encompassing the lung lesion, the ipsilateral hilar region, and the adjacent mediastinal region due to the proximity of the primary lesions to the mediastinum. Our data in these patients did not show a significant variation in the radiation field size of stage I/II patients vs. stage III patients, thus the data could not reflect the impact on the risk of esophagitis or pneumonitis in relation to radiation field size.

In summary, schedule-dependent pulsed low-dose paclitaxel chemoradiation is an effective regimen for improving local tumor control and is associated with very low rates of toxicity. We found that all three of the dose levels resulted in a similar degree of tumor shrinkage while there appeared to be a trend of increasing toxicity with dose-escalation. The pharmacokinetics, clinical efficacy, and toxicity demonstrated in this trial suggest that effective radiosensitization may be achieved with sensitizing chemotherapy at lower dose levels than previously published.

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Figure 1. Pharmacokinetics of low-dose paclitaxel

1A: Plasma paclitaxel concentration versus time. 1B: Peak plasma level-- relationships of drug concentration and pharmacokinetic properties. 1C: Area under the curve (AUC). 1D: Duration of plasma drug concentration above 0.05 μ M ($t_{>0.05\mu M}$). There is a proportionate increase in peak plasma level, AUC, and $t_{>0.05\mu M}$ with paclitaxel infusion from dose level I to level III.

Table 1

Patient Characteristics

	Patient Number	%
Sex		
Male	11	61
Female	7	39
Age		
Median (range)	70 yr (53–87)	
Zubrod Performance		
0	3	17
1	15	83
Histology		
Squamous	3	17
Adenocarcinoma	9	50
NSCLC, Nos	5	28
Other	1	6
Stage		
I-IIIB	4	22
IIIA	10	56
IIIB	4	12
Weight Loss	4	22

Table 2

Hematologic Toxicity				
Level I: 15 mg/m ² (n=6)	Grade 1	Grade 2	Grade 3	Grade 4
anemia	1	2	0	0
neutropenia	1	0	0	0
thrombocytopenia	2	0	0	0
lymphopenia	0	0	6	0
Level II: 20 mg/m ² (n=6)				
anemia	4	1	0	0
neutropenia	0	0	0	0
thrombocytopenia	1	0	0	0
lymphopenia	0	0	6	0
Level III: 25mg/m ² (n=6)				
anemia	3	1	2	0
neutropenia	1	0	0	0
thrombocytopenia	0	0	0	0
lymphopenia	0	0	6	0

Table 3**Non-hematologic Toxicity**

Level I: 15 mg/m² (n=6)	Grade 1	Grade 2	Grade 3	Grade 4
pneumonitis	0	0	1	0
esophageal	2	3	1	0
nausea/vomiting	0	1	0	0
weight loss	1	0	0	0
fatigue	1	3	0	0
tachycardia	1	0	0	0
alopecia	0	0	0	0
neuropathy	0	0	0	0
Level II: 20mg/m² (n=6)				
pneumonitis	0	0	1	0
esophageal	0	4	2	0
nausea/vomiting	1	0	0	0
weight loss	0	1	0	0
fatigue	1	4	1	0
tachycardia	0	1	0	0
alopecia	0	0	0	0
neuropathy	0	0	0	0
Level III: 25mg/m² (n=6)				
pneumonitis	0	0	1	0
esophageal	2	4	0	0
nausea/vomiting	0	0	0	0
weight loss	1	0	0	0
fatigue	2	3	0	0
tachycardia	1	0	0	0
alopecia	0	3	0	0
neuropathy	0	0	0	0

Table 4

Tumor shrinkage at 4–6 weeks after completion of therapy

Paclitaxel dose levels	Tumor shrinkage	Response	
		CR	PR
I, 15 mg/m ² (n=6)	82% ± 14%	2 (33%)	4 (67%)
II, 20 mg/m ² (n=6)	84% ± 16%	0	6 (100%)
III, 25 mg/m ² (n=6)	84% ± 27%	0	4 (100%)

Table 5Summary of pharmacokinetic characteristics of paclitaxel (mean $\pm$ S.D.)

Dose levels	Peak Concentration (μM)	AUC ($\mu\text{M} \times \text{hr}$)	T > 0.05 μM (hr)
Level I (15 mg/m ²)	0.23 $\pm$ 0.06	0.44 $\pm$ 0.09	1.56 $\pm$ 0.27
Level II (20 mg/m ²)	0.32 $\pm$ 0.05	0.61 $\pm$ 0.1	1.86 $\pm$ 0.21
Level III (25 mg/m ²)	0.52 $\pm$ 0.14	0.96 $\pm$ 0.23	2.94 $\pm$ 0.94