

Phase I/II Clinical Study of Pulsed Paclitaxel Radiosensitization for Thoracic Malignancy: A Therapeutic Approach on the Basis of Preclinical Research of Human Cancer Cell Lines¹

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ABSTRACT

Purpose: A Phase I/II clinical study using pulsed low-dose paclitaxel and radiation for thoracic malignancy was conducted. The study was based on preclinical research of the effects of paclitaxel on apoptosis and the cell cycle in human cancer cell lines.

Experimental Design: Three human epithelial cancer cell lines were investigated for preclinical study. Cells were analyzed for apoptosis and cell cycle characteristics after paclitaxel treatment. The Phase I/II clinical trial for non-small cell lung cancer used pulsed low-dose paclitaxel three times/week with the starting dose of 15 mg/m². Daily thoracic radiotherapy was delivered in 1.8 Gy/fraction to 60–65 Gy for gross disease and to 45–58 Gy for microscopic disease. Timing of radiotherapy was delayed to allow for a minimum of 4 h for cell cycle progression.

Results: Forty-one patients have enrolled and 33 completed treatments. Seventeen patients completed the Phase I study, with an average primary tumor shrinkage of 83 ± 8% (95% confidence interval). Tumor response rate was 100% for the Phase I study. Overall local control was 98%, and the survival rate was 46% at 1 year, 33% at 2 years, and 18% at 3 years. Toxicity was low with 3 of 18 patients having grade 3 pneumonitis and 3 of 18 patients having grade 3 esophagitis. There was no grade 4 pneumonitis, esophagitis, or hematological toxicity.

Conclusions: Pulsed low-dose paclitaxel radiosensitization for non-small cell lung cancer resulted in a superior local control rate and comparable survival rate when compared with chemoradiation regimens using systemic dose chemotherapy. The regimen is associated with low toxicity and deserves additional investigation, particularly in patients with poor performance or older age, who cannot tolerate standard chemoradiation regimens.

INTRODUCTION

Paclitaxel is a cell cycle-specific chemotherapeutic agent characterized by its potent effect on microtubule stabilization and its inhibition of normal dynamic reorganization of the microtubule network, which is essential for vital interphase and mitotic cellular functions (1–5). Paclitaxel causes cytokinetic stabilization of the spindle microtubule followed by apoptotic cell death (6–9). The effect on cell arrest at the G₂-M phase of the cell cycle, the most radiosensitive phase, makes paclitaxel a promising radiation sensitizer (10). Many published reports have supported the role of paclitaxel in radiosensitization of human tumor cell cultures of different cell types (11–16).

More than 10 different dose schedules of paclitaxel have been tested in clinical trials where the paclitaxel was given concurrently with radiation for the treatment of human solid tumors (17–21). These clinical trials, which reported different response rates and toxicity profiles, included many Phase I/II clinical trials combining paclitaxel and radiotherapy for lung cancer. The response rates were in the range of 65–86%, but treatment toxicity generally was high, particularly in neutropenia, thrombocytopenia, esophagitis, and pneumonitis (22–26). This is likely because of the radiosensitizing effect of paclitaxel on normal tissues as well. Because cell cycle progression is a dynamic process, most clinical trials using paclitaxel concurrently with radiotherapy may not have fully incorporated the best timing for paclitaxel treatment and irradiation to maximize the G₂-M cell cycle effect for radiosensitization. The optimal dose schedule in balancing the radiosensitization effect with the efficacy of therapy for paclitaxel and concurrent radiation treatment for lung cancer has not been defined.

We present in this article both preclinical research on human cancer cells treated with paclitaxel *in vitro* and clinical data from our Phase I/II study. Based upon our preclinical data, we hypothesized that maximal tumor control could be achieved using pulsed low-dose paclitaxel with radiation if the timing of radiation was synchronized to allow for the maximal cell cycle and apoptotic effects of paclitaxel. Because normal tissue and cancer cells differ in growth rate and growth fractions, we anticipated differential paclitaxel cell cycle effects on the cancer cells and surrounding normal tissues; thus, side effects could be minimized, whereas paclitaxel enhanced the tumoricidal effects of ionizing radiation. A Phase I/II clinical trial using the pulsed

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low-dose paclitaxel dose schedule and daily fractionated radiotherapy for thoracic malignancy was conducted based on the preclinical laboratory data. We present the design of the Phase I/II clinical trial, tumor response rate, tumor control rate, survival rate, and toxicity outcome of pulsed low-dose paclitaxel and radiation treatment for thoracic malignancy.

MATERIALS AND METHODS

Cell Lines and Culture Conditions. Human cancer cell lines A431, A549, and NCI-H520 were used in the preclinical study. These were all human epidermoid cancer cell lines: A549 and NCI-H520 were derived from human lung cancer, and A431 was derived from human epidermoid cancer. The P53 status of these cancer cell lines was assayed in the laboratory. A549 and NCI-H520 cell lines showed normal P53 status, with inducible expression of P53 protein by either paclitaxel or radiation. The A431 line showed aberrant P53 function, with a baseline overexpression of the P53 protein under normal culture condition. All cells were grown as monolayer cultures in Eagle Minimum Essential medium (Life Technologies, Inc. Laboratories, Grand Island, NY) supplemented with 10% fetal bovine serum (Life Technologies, Inc. Laboratories) and 100 units/ml penicillin/streptomycin (Life Technologies, Inc. Laboratories). All cell culture experiments were carried out at 37°C in a humidified 5% CO₂ environment. The cell cultures used for experiments were initiated with 5×10^5 exponentially growing cells in 75-cm² flasks (Corning Glass Works, Corning, NY) and grown for 2–3 days.

In Vitro Drug Treatments and Cell Cycle Analysis.

Cells in the exponential growth phase were treated with paclitaxel for 3 h. After drug treatments, cells were trypsinized and fixed in 70% ethanol at a concentration of 10⁶ cells/3 ml. Fixed cells were stored at 4°C overnight before staining and flow cytometric measurement. For DNA staining, cells were washed in PBS and suspended in 1 mg/ml RNase (1 ml/10⁶ cells) for 30 min at room temperature. Cells were then spun and resuspended in 10 g/ml propidium iodide (1 ml/10⁶ cells) for DNA analysis. Fluorescence distributions of 10,000 cells/sample were analyzed with a B-D FACSCalibur Flow Cytometer (Becton Dickinson, Palo Alto, CA) using a 15-mW argon laser. Cell cycle distribution was analyzed using the Modfit program (Verity Software House, Inc., Topsham, ME) on a Mac G3 computer. Percentages of G₁, S, and G₂-M cells were determined from two to six experiments.

In Vitro Analysis of Paclitaxel-induced Apoptosis.

At 70–80% confluence of cell growth, paclitaxel, at the concentration of 200 nM, 600 nM, or 2 μM, was added to the culture medium. The paclitaxel-containing medium was removed after 3 h of drug treatment and replaced by fresh culture medium. The cells were then incubated for either 24 or 48 h before fixation for apoptosis analysis. The apoptosis assay was conducted with positive and negative controls using an APO-BRDU assay kit (Phoenix Flow Systems). Cells were fixed in paraformaldehyde containing PBS, washed, and labeled with Br-dUTP. After additional washing, labeled cells were treated with fluorescein-labeled anti-BrdUrd monoclonal antibody. These cells were additionally treated with propidium iodide/RNase solution before flow cytometric analysis for the percentage of apoptosis.

Table 1 Treatment schema

	M	T	W	Th	F
Paclitaxel	X (a.m.)		X (a.m.)		X (a.m.)
XRT	X (p.m.)	X (Anytime after 11:00 a.m.)	X (p.m.)	X (Anytime after 11:00 a.m.)	X (p.m.)

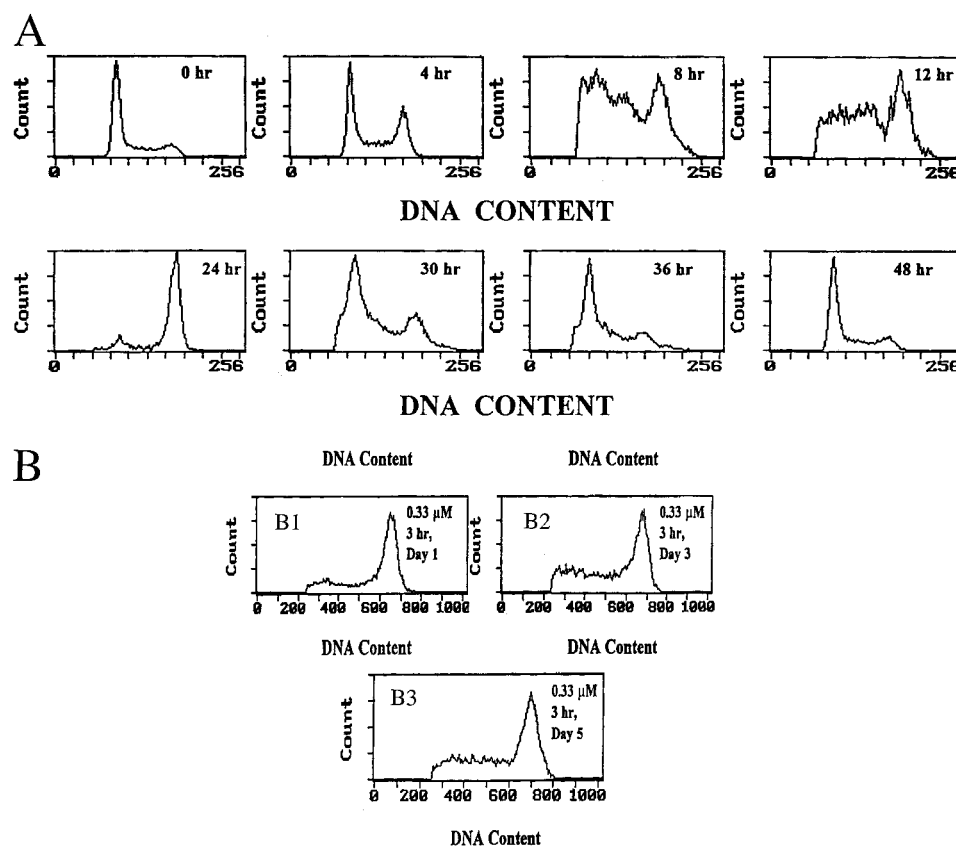
Phase I/II Clinical Trial Using Pulsed Low-Dose Paclitaxel and Radiation.

A clinical trial using pulsed low-dose paclitaxel with daily fractionated thoracic irradiation for thoracic malignancy was conducted based on the preclinical data. All patients had history and physical examinations, electrocardiogram, pretreatment PFT³, chest X-rays and CT, blood work, including complete blood count with differential, and chemistries, including electrolytes and liver enzymes. Low-dose paclitaxel for radiosensitization was administered as a 1-h i.v. infusion in the morning on Monday, Wednesday, and Friday. Thoracic radiation (XRT) was given after 4:00 p.m. on the days when patients received paclitaxel to allow for a minimum of a 5-h interval for cell cycle progression. On Tuesday and Thursday, when there was no paclitaxel treatment, XRT was given any time after 11:00 a.m. Treatment schema is demonstrated in Table 1. The starting dose of paclitaxel was 15 mg/m² with a dose escalation in 5 mg/m² increments. The starting dose was chosen based on previously published results using weekly paclitaxel and radiation for non-small cell lung cancer. Choy *et al.* (17), who delivered weekly paclitaxel with thoracic radiation, established the MTD as 60 mg/m², with the dose limiting toxicity of grade 3 and 4 esophagitis. Aisner *et al.* (23) delivered weekly paclitaxel at 45 mg/m² in conjunction with weekly carboplatin (100 mg/m²) and thoracic radiation. The MTD in this study was determined to be 45 mg/m², with the dose-limiting toxicity of grade 3 neutropenia (23). In our Phase I dose escalation study, we had planned on delivering paclitaxel every 48 h (three times/week dosing) to maximize the cell cycle and apoptotic effects of paclitaxel, and thus the starting dose of 15 mg/m² was chosen by dividing the published lowest MTD of weekly paclitaxel (45 mg/m²) by three.

For the Phase I dose escalation portion of the protocol, a minimum of three patients and a maximum of six patients were assigned at each dose level, according to the recommendation of our biostatistician. As the study proceeded, there were five to six patients treated at each dose level to allow for collection of blood samples from a sufficient number of patients for a separate correlative laboratory study. All patients (Phase I and II) had received standard premedication before paclitaxel infusion to reduce the risk of hypersensitivity reactions. For the first dose of paclitaxel treatment, patients received i.v. premedication 30 min before paclitaxel treatment (which included 20 mg of dex-

³ The abbreviations used are: PFT, pulmonary function test; CT, computed tomography; XRT, radiotherapy; MTD, maximally tolerated dose; CR, complete response; PR, partial response; CI, confidence interval.

Fig. 1 A, human epidermoid cell line A431 culture was exposed to 1.0 μM paclitaxel for 3 h. After 3 h, the drug-containing medium was removed and replaced with fresh culture medium. At different time intervals, cells were analyzed for cell cycle progression. Data show that treatment with paclitaxel caused $\text{G}_2\text{-M}$ arrest at ~ 4 h posttreatment and maximized at 24 h. This was followed by a timely reversal of $\text{G}_2\text{-M}$ arrest to the baseline level by 48 h. **B**, cells were treated with paclitaxel for 3 h using pulsed dose schedules: drug treatment with 0.33 μM on day 1 (B1); or day 1 and day 3 (B2); or day 1, day 3, and day 5 (B3). Drug containing culture medium was removed after treatment and replaced with fresh maintenance medium. The cells were analyzed for cell cycle distribution at 24 h after drug removal. Data show that treatment with pulsed paclitaxel three times a week using one-third of the initial dose sustained the $\text{G}_2\text{-M}$ cell cycle effect.



amethasone, 50 mg of diphenhydramine, and 300 mg of cimetidine). If the patient did not develop an allergic reaction to the first dose of paclitaxel, subsequent dosing of paclitaxel was preceded by oral dosing of 4 mg of dexamethasone, 50 mg of diphenhydramine, and 300 mg of cimetidine 2 h before paclitaxel infusion.

All patients (Phase I and II) 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 microscopic disease given at 1.8 Gy daily fractions over 6–7.5 weeks. In general, radiation portals encompassed gross disease with a 1.5- to 2-cm margin of radiographically normal lung. Mediastinal irradiation was included for most patients with adequate pretreatment PFT and excluded for those with poor pretreatment PFTs. The treatment schema is shown in Table 1. Treatment related toxicity was closely monitored during the treatment and follow-up visits. Toxicity was scored according to National Cancer Institute Common Toxicity Criteria version 2.0 and Radiation Therapy Oncology Group Radiation Acute Toxicity Scale (27, 28). All patients had follow-up CT scans of the chest at 4–6 weeks after therapy and serial CT scans at 3-month intervals. Response to therapy was assessed according to three dimensional radiological tumor measurements. Clinical CR was defined as complete disappearance of all evidence of tumor. PR was defined as a tumor volume decrease by at least 50% in the sum of the products of the perpendicular diameters of measurable lesions in the radiation ports. Stable disease was defined as no change in

measurable disease or changes that were too small to meet the requirements for PR 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 $>25\%$ in any pretreatment area of measurable disease.

Statistics. Tumor response was assessed in the Phase I study by three-dimensional CT scan measurement. Average tumor shrinkage was calculated with a 95% CI. Overall survival was defined as the interval between the start of therapy to death or to the last follow-up visit. Survival statistics were analyzed using Kaplan-Meier methods (29).

RESULTS

Paclitaxel Cell Cycle Effects. The cell cycle effect of paclitaxel was investigated in human cancer cell lines A431, A549, and NCI-H520. Fig. 1A demonstrates the cell cycle progression of cell line A431 after a 3-h treatment with 1 μM paclitaxel. $\text{G}_2\text{-M}$ accumulation is appreciated at ~ 4 h after drug treatment. Additional cell cycle progression to $\text{G}_2\text{-M}$ phase is observed and is followed by a dynamic redistribution of cell cycle to return to the baseline. Fig. 1B shows that by pulsing paclitaxel on alternate days using one-third of the concentration (0.33 μM) of paclitaxel, there is sustained cell cycle arrest in $\text{G}_2\text{-M}$ phase.

Sustained $\text{G}_2\text{-M}$ arrest by pulsing paclitaxel at lower doses was also observed in A549 and NCI-H520. For A549 cell line,

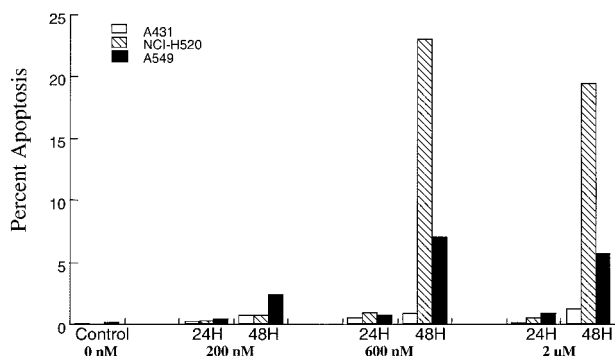


Fig. 2 Human cancer cell lines A431, A549, and NCI-H520 were treated with paclitaxel at 200 nM, 600 nM, or 2 μ M concentrations. Cells were analyzed for apoptosis using Tunnel assay at 24 h as well as 48 h after drug treatment. Data showed that apoptosis was more prominent at a higher drug concentration, and it was observed primarily at 48 h after drug treatment.

the baseline G_2 -M fraction is 10.5% without paclitaxel treatment. Pulsing paclitaxel (0.66 μ M) on days 1, 3, and 5 results in sustained G_2 -M arrest of 61.9, 68.8, and 57% on days 2, 4, and 6, respectively. The baseline G_2 -M fraction of NCI-H520 is 12.0%. Pulsing paclitaxel (0.66 μ M) on days 1, 3, and 5 results in G_2 -M arrest of 57.5, 58.7, and 55.2% on days 2, 4, and 6, respectively.

Paclitaxel Apoptotic Effect. Paclitaxel induced apoptosis was investigated in three human cancer lines: A431, A549, and NCI-H520. As shown in Fig. 2, the percentage of apoptotic cells varied among these three cell lines. Common observations were made, however, in that higher doses (600 nM and 2 μ M) of paclitaxel caused more apoptosis than the lowest dose (200 nM). It was also observed that more apoptosis occurred at 48 h after drug treatment than at 24 h.

Patient Characteristics. Forty-one patients were enrolled (23 for Phase I study and 18 for Phase II study) and 33 completed treatments. Eight patients did not complete protocol treatments because of acute allergic reactions in 3, distant disease spread during therapy in 3, and 2 intercurrent deaths unrelated to therapy. Stage distributions of non-small cell carcinoma for patients completing therapy were: 2 stage I, 1 stage IIB, 15 stage IIIA, and 22 stage IIIB. One patient had stage II mesothelioma.

Local Tumor Response and In-Field Tumor Control Rate. Tumor response was assessed in the Phase I study (Table 2). Mean tumor shrinkage was 82 ± 14 , 84 ± 16 , and $84 \pm 27\%$ for dose levels I, II, and III, respectively, with an average primary tumor shrinkage at 4–6 weeks posttherapy of $83 \pm 7\%$ (95% CI). The overall locoregional tumor response rate was 100% [2 of 17 (12%) CR and 15 of 17 (88%) PR]. Fig. 3A demonstrates an example of radiographic tumor shrinkage after treatment in a patient with stage III non-small cell lung cancer. This was documented as a CR. Fig. 3B demonstrates an example of radiographic tumor shrinkage after treatment in a patient presenting with malignant mesothelioma, which in general was considered resistant to either chemotherapy or radiation treatment. The posttreatment CT scan showed only residual fibrotic bands of the pericardium and the pleura.

Table 2 Tumor shrinkage at 4–6 weeks after completion of therapy

Pulsed paclitaxel dose level	Tumor shrinkage	Response rate	
		CR	PR
I, 15 mg/m ² (n = 6)	$82 \pm 14\%$	2	4
II, 20 mg/m ² (n = 6)	$84 \pm 16\%$	0	6
III, 25 mg/m ² (n = 4)	$84 \pm 27\%$	0	4
Average	$83 \pm 7\%$ (95% CI)	14%	86%

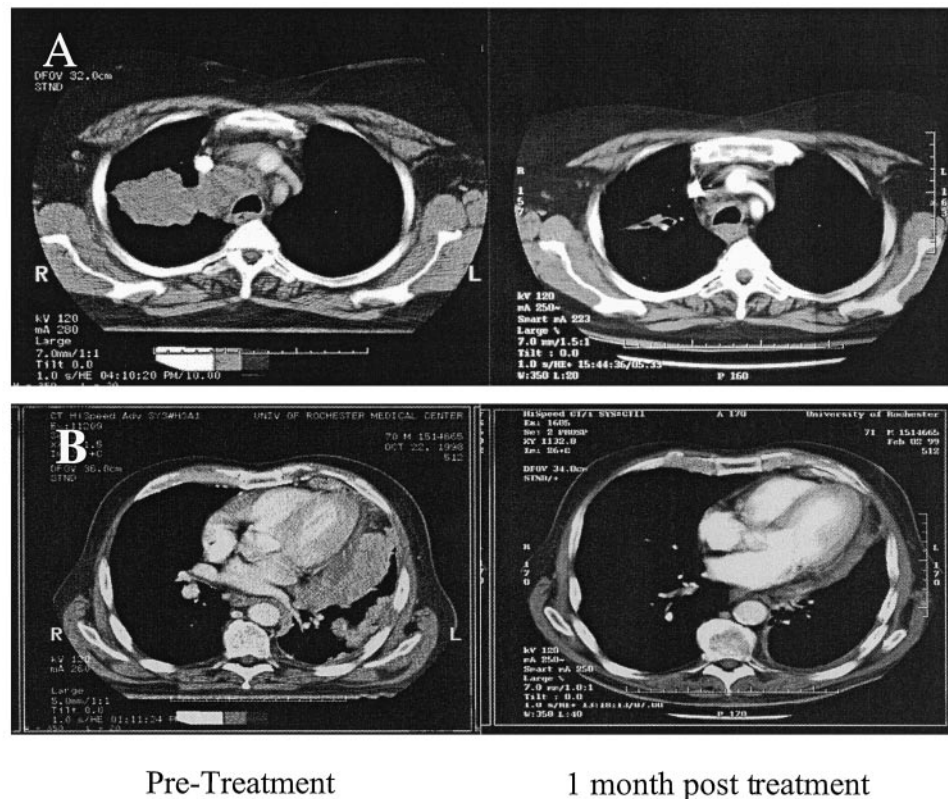
Local control for those patients who completed radiotherapy in both Phase I and II was 98%, with a median follow up of 11 months. Survival analysis, as demonstrated in Fig. 4, shows the Kaplan-Meier cumulative survival estimate of patients in both the Phase I and Phase II studies. For all patients enrolled, the survival probability was 46% at 1 year, 33% at 2 years, and 18% at 3 years (Fig. 4A). For patients who did not complete the 7.5-week protocol treatment, the survival was dismal. For those completed the protocol treatment, the survival estimate was 52% at 1 year, 40% at 2 years, and 21% at 3 years (Fig. 4B).

Toxicity and MTD. There was no treatment interruption from side effects of therapy. Toxicity was assessed for all patients in the Phase I study, including the 1 patient who received only two-thirds of the total radiation dose. Three of 18 patients (17%) experienced grade 3 pneumonitis and 3 of 18 (17%) experienced grade 3 esophagitis. No patients experienced grade 4 pneumonitis or esophagitis. Additionally, no patients experienced grade 3 or 4 neutropenia, thrombocytopenia, neuropathy, or cardiac arrhythmia. At the highest dose level of 25 mg/m², 2 of 6 patients developed tachycardia with a heart rate in the range of 120–140 beats/min, as well as mild to moderate alopecia. These patients were not symptomatic clinically, and the electrocardiogram showed sinus tachycardia. Because of the observed increase in toxicity, and yet no additional gain in tumor response rate (Table 2), we felt it was not in the best interests of patients to continue dose escalation to reach MTD. The degree of tumor shrinkage was similar for all three dose levels; thus, the data support 15 mg/m² as the minimal effective dose.

DISCUSSION

Progress made in the recent years has established the new standard of treatment for non-small cell lung cancer. Several randomized clinical trials have demonstrated better survival results with combination chemoradiation than with radiation alone for the treatment of locally, advanced, stage III non-small lung cancer (30–35). Both sequential chemotherapy followed by radiation and concurrent chemoradiation have proved to be more effective than radiation therapy alone. A recent report from Radiation Therapy Oncology Group 94–10 also showed that, although concurrent chemoradiation is superior to sequential chemotherapy followed by radiotherapy, the concurrent approach is associated with worse treatment related acute side effects (36). Many issues remain unclear: among these, the optimal chemotherapeutic agents; the sequence; and the dosing schedule in balancing treatment toxicity with the therapeutic gain. Paclitaxel and radiation treatment for inoperable non-small cell lung cancer has been popular because of the effect of

Fig. 3 Tumor response by CT scans. *A* showed a large lesion of non-small cell lung cancer in the right middle lobe of the lung and a large pretracheal lymph node. Four weeks after therapy, the lesion had completely disappeared. *B* shows pericardial and pleural based lesions of mesothelioma. Six weeks after pulsed paclitaxel radiation therapy, there was significant shrinkage of the lesions, with what appeared to be fibrotic bands along the pleura.



Pre-Treatment

1 month post treatment

paclitaxel on the G₂-M phase of the cell cycle, the most radiosensitive phase. Being a cell cycle-specific agent, it is theoretically possible that the paclitaxel effect can be optimized with timing of radiation to allow for radiation injury occurring at the G₂-M phase of cancer cells. There are several different dose schedules of paclitaxel-based chemoradiation regimens in the treatment of lung cancer (17–20, 22, 23). These include concurrent radiation with continuous infusion of paclitaxel, daily paclitaxel, twice weekly paclitaxel, weekly paclitaxel, and once every 3–4-week paclitaxel infusion. These clinical trials reported different response rates and toxicity profiles. Again, the optimal dosing schedule in integrating chemotherapy with radiation remains unclear.

In this study, we hypothesize that maximum tumor control can be achieved by strategic optimization of the timing of low-dose paclitaxel treatment and the timing of daily irradiation. On the basis of the preclinical data, this regimen theoretically should result in maximum apoptosis of cancer cells as well as offering maximal radiosensitization through the G₂-M cell cycle arrest of low-dose paclitaxel. We report results of a chemoradiation schedule in the Phase I/II trial using pulsed low-dose paclitaxel and daily radiation for inoperable non-small lung cancer. The dose and schedule of the paclitaxel and radiation were based on the cell cycle and apoptotic effect of low-dose paclitaxel to allow for maximal radiosensitizing effect and apoptosis of cancer cells. We were encouraged by the gross tumor response rate of 100% and the locoregional tumor control rate of 98%. When our results were compared with large randomized

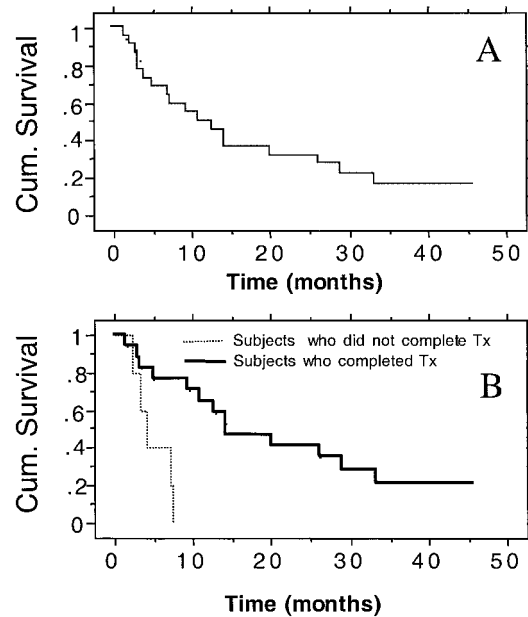


Fig. 4 Kaplan-Meier analysis of survival of patients treated in the Phase I/II clinical trial using pulsed low-dose paclitaxel and radiation treatment. For all patients enrolled, the survival probability was 46% at 1 year, 33% at 2 years, and 18% at 3 years (A). For patients who did not complete the 7.5-week protocol treatment, the survival was dismal. For those who completed the protocol treatment, the survival estimate was 52% at 1 year, 40% at 2 years, and 21% at 3 years (B).

Table 3 Outcome of clinical trials for locally advanced, stage III non-small cell lung cancer treated with combination chemotherapy and radiation

Chemoradiation Trials	2-year survival	3-year survival	Local control
<i>Chen et al.</i> : pulsed Taxol and RT ^a			
All patients	33%	18%	N/A
Patients completed Rx	40%	21%	98%
Schaake-Koning <i>et al.</i> (European Organization for Research and Treatment of Cancer; Ref. 30)			
Chemoradiation arm	26%	16%	30% ^b
RT arm	13%	2%	19%
Furuse <i>et al.</i> (Japanese; Ref. 31)			
Concurrent chemo arm	35%	22%	
Sequential chemo arm	27%	15%	
Dillman <i>et al.</i> (Cancer and Leukemia Group B; Ref. 32)			
Chemoradiation arm	26%	23%	
RT arm	13%	11%	
Arriagada <i>et al.</i> (French; Ref. 33)			
Chemoradiation arm	21%	11%	17% ^c
RT arm	14%	5%	15%
Sause <i>et al.</i> (RTOG8808; Ref. 34)			
Chemoradiation arm	32%	17%	
RT arm	22%	11%	
Morton <i>et al.</i> (NCCT; Ref. 35)			
Chemoradiation arm	21%		46% ^d
RT arm	16%		45%

^a RT radiotherapy; NCCT, North Central Cancer Treatment Group.

^b Actuarial local control at 2 years.

^c Local control at one year.

^d Local control at time of first relapse.

clinical trials for locally advanced non-small cell lung cancer, it was evident that pulsed paclitaxel radiation resulted in superior local tumor response and tumor control (Table 3). In addition, when survival outcome was assessed, the pulsed paclitaxel/radiation regimen resulted in comparable or better results than most large randomized trials using combination chemoradiation.

In our study, the degree of tumor shrinkage was impressive for all three dose levels (Table 2). We noticed a lack of dose response with increasing paclitaxel doses, in that, even with the lowest dose of paclitaxel at 15 mg/m², the tumor shrinkage was similar to the higher doses of 20 and 25 mg/m². The concept of minimally effective dose is contradictory to the traditional strategy of systemic chemotherapy in achieving MTD. Our data, however, support that when low-dose chemotherapy is used as a radiation sensitizing agent, escalating the dose may not achieve higher local sensitizing effects but may increase toxicity of therapy. Thus the concept of minimally effective dose is appropriate in the context of radiosensitization. It has been reported that paclitaxel enhances tumor response to radiation by improving reoxygenation of radioresistant hypoxic cells (37). More recently, small and frequent dosing of chemotherapeutic agents has been shown to suppress tumor growth through the mechanism of antiangiogenesis in animal tumor models (38, 39). The remarkable tumor shrinkage and local control in our study may be attributed to the combination of cell cycle effects, the apoptotic effect, tumor reoxygenation effect, and antiangiogenic effect of pulsed low-dose paclitaxel and radiation treatments.

When using low-dose chemotherapy with radiation, one may be concerned that the systemic dose of chemotherapy is insufficient to target distant metastatic disease. Our survival data in fact was comparable or better than most published large studies using standard systemic doses of chemotherapy with radiation therapy. In our experience, our regimen was much better tolerated than other chemoradiation regimens using systemic doses of chemotherapy concurrently with radiation. Our toxicity data were also much more favorable than the other regimens. In the context of balancing the toxicity of therapy and the quality of life of patients in the management of inoperable non-small cell lung cancer, pulsed low-dose paclitaxel/radiation offers a tolerable regimen for patients with poor performance or older age, who cannot tolerate combination chemoradiation using standard regimen.

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