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PRECLINICAL AND PILOT CLINICAL STUDIES OF DOCETAXEL CHEMORADIATION FOR STAGE III NON-SMALL CELL LUNG CANCER

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Abstract

Purpose—Local and distant failure rates remain high despite aggressive chemoradiation (CRT) treatment for stage III non-small cell lung cancer (NSCLC). We conducted preclinical studies of docetaxel cytotoxic and radiosensitizing effects on lung cancer cell lines and designed a pilot study to target distant micrometastasis upfront with one-cycle induction chemotherapy, followed by low-dose radiosensitizing docetaxel CRT.

Methods and Materials—Preclinical study was conducted in human lung cancer cell lines NCI 520 and A549. Cells were treated with two concentrations of docetaxel for 3 hours and then irradiated immediately vs. delayed at 24 hours. Clonogenic survival assay was conducted and analyzed for cytotoxic effects vs. radiosensitizing effects of docetaxel. A pilot clinical study was designed based on pre-clinical study findings. Twenty-two patients were enrolled with a median follow-up of 4 years. Induction chemotherapy consisted of 75 mg/m² docetaxel and 75 mg/m² cisplatin on day 1, and rh-GCSF 150 mg/m² on days 2–10. Concurrent CRT started 3–6 weeks later with twice-weekly docetaxel at 10–12 mg/m² and daily delayed radiation in 1.8 Gy fractions to 64.5 Gy for gross disease.

Results—Preclinical study demonstrated potent cytotoxic effects of docetaxel and subadditive radiosensitizing effects. Delaying radiation resulted in more cancer cell death. The pilot clinical study resulted in a median survival of 32.6 months for the entire cohort, with a 3-year and 5-year

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survival of 50% and 19%, respectively, and a distant metastasis-free survival rate of 61% for both 3 and 5 years. Patterns of failure analysis revealed 75% chest failures, and 36% all distant failures. Therapy was well tolerated with grade 3 esophagitis observed in 23% of patients.

Conclusions—One-cycle full-dose docetaxel/cisplatin induction chemotherapy with rh-GCSF followed by pulsed low-dose docetaxel chemoradiation is promising in its anti-tumor activity, low rates of distant failure, and low toxicity, suggesting that this regimen deserves further investigation.

Keywords

Docetaxel; taxotere; chemoradiation; non-small cell lung cancer; radiosensitization

INTRODUCTION

Locally advanced stage III non-small cell lung cancer (NSCLC) has often been considered unresectable. Definitive radiation in combination with chemotherapy, either sequentially or concomitantly, has been reported to yield favorable survival outcome over radiation alone in several phase III studies. However, this result is associated with a disappointingly high rate of intrathoracic failure as well as distant metastasis. The median survival rate has been in the range of 11–16 months in most large studies, with a 5-year survival rate at 6–20% (1–9). The intrathoracic failure rate is quite high, which is approximately 50% by radiographic criteria, and more than 85% by biopsy through bronchoscopy, with the distant failure rate being more than 70% (1,4,5,7).

Findings from two of the phase III studies support that concurrent CRT is superior to sequential CRT. The study by Radiotherapy Oncology Group (RTOG) revealed a median survival of 17.1 months in the CRT arm vs. 14.6 months in the sequential (2), while the Western Japan study showed a median survival of 17 months vs. 13 months respectively (2,4). Combining two modalities concurrently results in better survival but at the price of more grade 3 toxicities, especially the increased risk of pneumonitis and esophagitis (1–9). Therefore, using low-dose sensitizing chemotherapy during CRT may offer clinical advantages without increasing adverse side effects.

Taxanes are known for the cytotoxic effects and radiosensitizing effects. In a preclinical study, we investigated the cell cycle effects of both paclitaxel and docetaxel for radiation sensitization of lung cancer cell lines. Docetaxel demonstrated a G2/M arrest for 72–96 hours while paclitaxel sustained a G2/M arrest for 48 hours of lung cancer cell lines. Docetaxel also demonstrated better subadditive effects with radiation when compared with paclitaxel in preclinical investigations (12,13). Subsequently, a clinical phase I/II study was conducted using a pulsed low-dose paclitaxel radiosensitizing strategy with paclitaxel dosing once every 48 hours, which yielded a 97.6% in-field chest tumor control rate (10,11,14). However, the low-dose pulsed paclitaxel chemoradiation did not appear to further improve the survival result when compared with other large randomized studies using full-dose chemotherapy and radiation. Thus, a therapeutic strategy that will integrate full-dose chemotherapy in combination with low-dose sensitizing chemoradiation is desirable in targeting micrometastasis and in reducing treatment-related toxicities for better chest disease control.

Based upon the superior local tumor effect of radiosensitization by pulsed low-dose paclitaxel, we designed a pilot study for the treatment of stage IIIA and IIIB NSCLC, using one-cycle induction chemotherapy consisting of docetaxel and cisplatin followed by pulsed low-dose sensitizing docetaxel chemoradiotherapy for gross chest tumors. The rationale of using one-cycle induction chemotherapy instead of the conventional 2 to 3 cycles is based

on the hypothesis that delaying local therapy to gross chest disease is detrimental to cancer control (15,16), and that a single cycle of full-dose chemotherapy should suffice in targeting systemic micrometastasis at the beginning of cancer therapy without further delaying local therapy.

MATERIALS AND METHODS

Preclinical study of radiation and docetaxel interactions

Human lung cancer cell lines NCI 520 and A549 were used. Because p53 status may affect radiation sensitivity, the p53 status of these cancer cell lines was assayed in the laboratory and both cell lines were found to have normal p53 status. All cells were grown as monolayer cultures in Eagle Minimum Essential Medium (EMEM) (Life Technologies, Inc. Laboratories, Grand Island, NY) supplemented with 10% fetal bovine serum (Life Technologies, Inc. Laboratories) and 100 units/ml penicillin and streptomycin (Life Technologies, Inc. Laboratories). All cell culture experiments were carried out at 37°C in a humidified 5% CO₂ environment. The cell cultures were initiated with 5×10^5 exponentially growing cells in 75-cm² flasks (Corning Glass Works, Corning, NY) for 2–3 days.

Radiation effect and interaction with docetaxel treatment were conducted using the clonogenic survival assay in monolayer cell cultures. For drug treatments, cells were incubated with two concentrations of docetaxel (25 nM vs. 50 nM for A549, and 50 nM vs. 100 nM for NCI 520) for 3 hours. After drug treatments, the cells were washed with EMEM 3 times and supplemented with 10% fetal bovine serum and 100 units/ml penicillin and streptomycin. Cell cultures were then separated into the early radiation group (3 hours) vs. the delayed radiation group (24 hours) at room temperature (20°C ± 1.5°C) using a Cesium-137 gamma-ray irradiator at a dose rate of 4 Gy per minute. The radiation doses were 2, 6, 8, and 10 Gy in single fractions. Cells were trypsinized after irradiation and plated at different dilutions in 60 mm petri dishes for two weeks for colony-forming measurement. The cell-surviving fraction was determined from the ratio of colony-forming efficiency of irradiated cells to non-irradiated control. The average surviving fraction at each dose was determined from at least three replicated experiments. Survival curves were constructed by plotting the surviving fraction as a function of dose according to the linear quadratic model, $S = \exp(-\alpha D - \beta D^2)$, and the multi-target model using least-squares regression and linear regression, respectively.

Patient eligibility and pretreatment evaluation

This study was fully reviewed and approved by the University of Rochester Institutional Review Board. Table 1 shows the characteristics of patients enrolled in the protocol. Twenty-two patients, with a median age of 62, were enrolled from February 2002 to April 2005. Patients were informed of the investigational nature of this study and gave written informed consent in accordance with institutional and federal guidelines. Patients with proven histological stage IIIa and IIIb NSCLC were eligible for this study, and were staged according to the American Joint Committee on Cancer (AJCC). The eligibility criteria included the following: Age ≥ 18, Karnofsky performance status ≥ 70%, forced expiratory volume in 1 second (FEV₁) ≥ 800 ml, and serum creatinine ≤ 1.5 mg/dl or creatinine clearance > 60 ml/min. Patients with hypersensitivity to docetaxel, myocardial infarction or symptomatic heart disease (including angina, congestive heart failure, uncontrolled arrhythmia) within the previous 6 months were excluded, along with patients with malignant pleural effusion and women who were pregnant or breastfeeding.

Pretreatment evaluation included a detailed medical history, physical examination, and performance status. Blood work included a Complete Blood Count with differential, platelet

count, electrolytes, serum glutamic pyruvic transaminase (SGPT), total protein, albumin, calcium, inorganic phosphorus, glucose, blood urea nitrogen (BUN), uric acid, creatinine, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, and serum glutamic oxaloacetic transaminase (SGOT). Creatinine clearance was required if serum creatinine was >1.5 mg/dl. Chest X-ray and computerized tomography (CT) scans of the chest (including liver and adrenal glands) were done within 4–6 weeks of registration. CT scans of the brain and either a positron emission tomography (PET) or a radionuclide bone scan were required to rule out distant metastasis. Electrocardiogram (EKG) and pulmonary function tests including FEV1, vital capacity (VC), and diffusion lung capacity for carbon monoxide (DLCO) were required.

Protocol treatment

Beginning 24 hours before docetaxel, patients were given 8 mg dexamethasone orally twice daily for 3 days. A 16 mg dose of ondansetron was administered intravenously before treatment, and 8 mg twice daily was taken orally for 3 days following treatment. All patients received one cycle of induction chemotherapy consisting of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 given sequentially over a one hour IV infusion, and rh-GCSF 150 mg/m^2 on days 2–10. Cisplatin infusion was given according to the University of Rochester's institutional policy of hydration and diuresis. Patients received 2 liters of normal saline with added potassium. Magnesium was given separately. Polyantiemetics were given on day 1. After cisplatin infusion, an additional 1000 ml of hydration fluid was given over 2 hours. For 12 hours afterward, inpatients were given an additional 2 liters of fluid intravenously, while outpatients were encouraged to drink as much liquid as possible overnight.

Concurrent chemoradiation started 3–6 weeks after the induction chemotherapy. Given the longer duration of G2/M effect up to 72–96 hours by docetaxel in the preclinical investigation of lung cancer cell lines, sensitizing docetaxel at 12 mg/m^2 was delivered on Monday and Thursday mornings, with IV over 15–30 minute infusion, and daily radiation. The dose of 12 mg/m^2 docetaxel twice weekly was chosen based on the maximum tolerated dose of twice weekly dosing previously reported at 15 mg/m^2 (17), but subsequently was reduced to 10 mg/m^2 due to the high rate of grade 3 esophagitis. Concurrent chemoradiation schema is shown in Table 2. At least a 4 hour delayed RT interval was required between RT and docetaxel to allow for progression to the G2/M phase, the most radiosensitive phase of the cell cycle. Patients were given 10 mg dexamethasone IV prior to the low-dose docetaxel. One 150 mg dose of ranitidine daily during concurrent chemoradiation was recommended.

Radiation therapy

Radiation treatment was delivered using conformal CT guided radiation plans. Gross disease was defined as visible primary disease and enlarged lymph nodes (≥ 1 cm) on CT scans. Microscopic disease was defined as no grossly visible mediastinal and supraclavicular lymph nodes on CT scans. The radiation portal included the gross disease and prophylactic mediastinal radiation. Radiation therapy began on the Tuesday after the first dose of sensitizing docetaxel given on Monday. Treatment volume included the gross disease with a 2 cm margin. All gross disease received 60–65 Gy. Regional lymphatics with potential microscopic disease received 45–58 Gy. Daily fraction was 1.8 Gy. Contralateral hilum was not included unless it was suspicious for disease involvement (N3) on CT scan or pathologic documentation. The spinal cord dose was kept below 50 Gy. Supraclavicular region(s) were treated prophylactically for microscopic disease for upper lobe lesions or high mediastinal nodal involvement. The total dose to the supraclavicular fosse did not exceed 50.4 Gy for microscopic disease. For grossly enlarged supraclavicular fossa lymph nodes, electron boost

after 50.4 Gy to the final dose of 60 Gy was allowed. An example of the radiation plan is shown in Figure 1.

Chemotherapy dose modifications

There was dose modification in the induction phase as there was only one cycle. The sensitizing docetaxel dose was reduced to 10 mg/m² after the tenth enrolled patient because of the high incidence of grade 3 dysphagia or esophagitis.

Evaluation of toxicity and response

All treated patients were followed at 6–8 weeks post therapy and then once every 3 months in the first two years, once every 6 months from year 3 to year 5, and once a year after the 5th year. Physical examinations, vital signs and a chest CT scans were done at each follow-up visit. Toxicity was assessed by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) by National Cancer Institute (NCI). Response to therapy by CT scan was assessed according to 2D radiological tumor measurements by the following criteria: complete Response (CR) - complete disappearance of all tumor evidence; partial Response - at least 50% of measured area; stable Disease (SD) – stable disease; progressive Disease (PD) - development of any new areas of malignant disease that were measurable or palpable, or by a $\geq 25\%$ increase in any pretreatment area of measurable disease.

Statistical analyses

Overall survival, progression-free survival, and distant metastasis-free survival were calculated using the Kaplan-Meier life table methods. Disease recurrence was defined as the time between the first day of therapy until the first notation of clinical progression or relapse. The time of survival was defined as time from treatment start to death or last date known alive.

RESULTS

Radiation and docetaxel interaction in lung cancer cell lines

Figure 2 shows the clonogenic survival of human lung cancer cell lines NCI 520 and A549 after irradiation at 2, 4, 6, and 8 Gy with sham irradiation. For both cell lines, there was a marked decrease of surviving lung cancer cell fractions after docetaxel treatment by more than one log as shown on Y-axis comparing control and drug treated groups at 0 Gy radiation (Figure 2). This reduction of surviving fractions was directly attributed to cytotoxic effects of docetaxel on lung cancer cells without radiation effects. When comparing the controls and drug treated groups in response to increasing radiation doses, there was an additional reduction of surviving fractions with increasing radiation doses for all, although in some cases the slope of the curves in the drug treated groups appeared shallower than the control. Despite such observations, the surviving fractions of drug treated groups were much less than the control, thus consistent with a subadditive effect of docetaxel and radiation rather than a synergistic effect.

In the A549 cell line, the delayed radiation treatment groups (24 hours) resulted in more cell death than immediate radiation (3 hours) in both the 25 nM and the 50 nM docetaxel concentration groups. Likewise, for NCI-520 cell line, the delayed radiation groups resulted in more cell death for both the 50 nM docetaxel group and the 100 nM docetaxel group. Delaying radiation after drug treatment appeared to be the preferred strategy to enhance radiation cytotoxicity, and therefore this observation was integrated into the timing of radiation of this phase II clinical trial.

Tumor response

Overall response rate was 69% [50% (11/22) PR and 19% (4/22) CR]. Of the 22 patients enrolled in the study, 6 received partial protocol treatment for the following reasons: 4 of the 6 received the induction chemotherapy without subsequent CRT due to hypersensitivity reactions to docetaxel (acute flushing, increased heart rate, and grade 3 hypoxia), intermittent condition, or progressive disease. Two of the 6 completed induction chemotherapy and initiated concurrent CRT but did not complete the latter due to progressive disease in one and progressive intolerance to docetaxel during CRT in the other.

Treatment toxicity

Grade 3 and 4 toxicities are listed in Table 3. There was no grade 3 or 4 neutropenia, which is likely due to the built-in rh-GCSF injection in the protocol. Five patients had grade 3 infections without neutropenia (4 had pneumonia and 1 had a groin infection). Chemotherapy-related nausea/vomiting was observed in 6 patients. Esophagitis/dysphagia was observed in 5 patients during chemoradiotherapy. Other grade 3 toxicities were fatigue (4/22), loss of appetite (4/22), dyspnea/chest pain (2/22), lymphocytopenia (13/22), and allergic reactions (2/22). One patient had grade 4 headaches, and one had grade 4 bone pain due to the neupogen injection. There was one grade 4 AV heart block due to a change in blood pressure medication as well as a previously undiagnosed cardiac condition.

Patterns of failure

We have analyzed the pattern of failure of patients treated in the protocol with a minimum of follow up of 4 years: 45% failure in the radiation ports, 75% all chest failures, and 36% all distant failures which included 23% brain failures.

Survival outcome

Figure 3 shows the Kaplan-Meier survival outcome for all patients enrolled. The 3-year and 5-year overall survival rate was 50% and 19%, respectively. The progressions -free survival rate at 3 and 5 years was the same at 23%. The distant metastasis-free survival rate was 61% for both 3 and 5 years.

DISCUSSION

A regimen that can improve both local disease control and reduce distant metastasis is necessary to overcome the dismal outcome of inoperable NSCLC. Two different mechanisms can contribute to the improvement of survival of patients from chemoradiation treatment over radiation alone for locally advanced NSCLC. One is the potential cytotoxic effect of chemotherapeutic agents in targeting distant subclinical micrometastasis. The other is the radiosensitization effect of chemotherapy in improving the locoregional disease control by sensitizing radiation effects, thereby controlling the primary source for distant cancer spread. The randomized phase III study by the European Organization for Research and Treatment of Cancer (EORTC) employing weekly low-dose cisplatin (30 mg/m² per week) or very low daily dose cisplatin (6 mg/m² per day) resulted in a significant improvement of survival in stage III NSCLC compared to radiotherapy alone (9). Such low doses of chemotherapy are not expected to render significant cytotoxic effects on cancer cells. Thus, this type of finding supports that the improved survival using very low doses of chemotherapy concurrently with radiation is due to the radiosensitizing benefit of low-dose chemotherapy on improving locoregional disease control (9, 10, 11, 14).

Full-dose chemotherapy can improve survival by targeting subclinical micrometastasis at its earliest stage of cancer diagnosis. A regimen consisting of two cycles of full-dose induction chemotherapy followed by chest radiotherapy has been common practice in many large

clinical trials and has demonstrated prolongation of median survival times when compared with radiation alone for locally advanced NSCLC (1,3,8). Similarly, concomitant chemoradiotherapy using full-dose chemotherapeutic agents has been found superior to radiotherapy alone in phase III studies for stage III NSCLC (18,19). Furthermore, when concomitant chemoradiotherapy and induction chemotherapy were compared directly in randomized phase III trials, the concomitant chemoradiation approach demonstrated better survival outcome than induction chemotherapy followed by chest radiotherapy (2,4,20–23). Unfortunately, the clinical gain from concomitant chemoradiation treatment has been associated with higher rates of grade 3 and 4 toxicities during concurrent chemoradiation, thus lowering treatment tolerability among many patients.

While the sequence of chemoradiotherapy appears to favor concurrent approach, there are still unresolved issues related to sequence and dose intensity of chemotherapy and radiation. The Cancer and Leukemia Group B (CALGB) published the first phase III trial to assess the benefit of induction chemotherapy in the context of concomitant chemoradiotherapy for stage III NSCLC (22). Both arms of the clinical study had concomitant chemoradiation, and one of the two arms had induction chemotherapy. The result showed a trend in improving median survival time favoring patients receiving induction chemotherapy followed by concomitant chemoradiation. This trend disappeared when adjusted for weight loss exceeding 5%. One major concern with the induction chemotherapy approach is that delaying chest radiotherapy for 2–3 months during induction chemotherapy may adversely affect local disease control and compromise ultimate treatment success. Chemotherapy alone is known not effective for gross tumor control of NSCLC with an average response rate of approximately 20% irrespective of the type of chemotherapy combinations for NSCLC (24). Thus we question prolonged chemotherapy for 2–3 months in the induction phase and the delay of starting radiotherapy may adversely affect the survival outcome. Indeed, in a study of a cohort of 23 patients treated by prolonged induction chemotherapy (mean interval before radiation treatment was 80.3 days for stage III NSCLC, it was found that 41% of potentially curable patients became incurable during the chemotherapy period before the start of radiation (15,16).

Our study design is a one-two punch approach by delivering only one cycle of induction chemotherapy to target distant micrometastasis, which avoided delaying local therapy beyond 4–6 weeks. The one-cycle chemotherapy targeted the subclinical disease at distant sites, while the subsequent low-dose chemotherapy with concurrent radiation improves radiation efficacy for gross tumors in the chest through radiosensitization, while minimizing toxicities during chemoradiation by not using full-dose chemotherapy during radiation. Our rationale and hypothesis is that distant microscopic cancer cells bear only minimal tumor burden, thus one cycle of induction chemotherapy should suffice in eliminating the potentially subclinical cancer cells, while allowing treatment of the chest disease sooner than after the traditional 2–3 cycles of chemotherapy. Given the marrow suppressive potential of cisplatin and docetaxel, the rh-GCSF treatment during the induction chemotherapy phase has helped to avoid the unnecessary delay of chest radiotherapy from chemotherapy-induced neutropenia. Our results showed no grade 3 or 4 neutropenia for delaying chest radiotherapy after induction chemotherapy, likely due to rh-GCSF benefit.

Our survival data was very encouraging with a median overall survival of 32.6 months for all patients enrolled with acceptable toxicity rates. While the 32.6 month median survival seemed exceptionally good (25), it remained unclear if it was due to our unique study design, potential skewed patient population in a pilot study, or if it was due to combination docetaxel and cisplatin induction chemotherapy. Coincidentally, a study by Kocak et al also reported exceptionally long median survival of 29.9 months for patients treated with docetaxel (75 mg/m²) and cisplatin (75 mg/m²) induction chemotherapy followed by

radiation with concurrent low-dose sensitizing docetaxel (30mg/m²) and cisplatin (20 mg/m²), although the numbers of cycles differed between our study (1 cycle) and Kocak's study (3 cycles)(26). While two to four cycles of induction chemotherapy have been reported in the literature for the treatment of locally advanced NSCLC, there is no literature evidence in demonstrating the optimal number of cycles of induction chemotherapy. Theoretically, longer periods of induction chemotherapy may allow for higher cumulative doses of chemotherapy, while at risk for delaying local radiation treatment.

In conclusion, our trial results show that one-cycle full-dose docetaxel/cisplatin chemotherapy with rh-GCSF followed by pulsed low-dose docetaxel chemoradiation is associated with promising anti-tumor activity, resulting in encouraging survival outcome for locally advanced NSCLC. We acknowledge the potential bias from a pilot study of 22 patients. We'd like to emphasize the translational nature of our study design, which was based on the pre-clinical study and also on a novel hypothesis that one-cycle induction chemotherapy should suffice for targeting distant subclinical disease. Given the promising findings, this type of study design combining a shortened course of induction chemotherapy with radiosensitizing chemoradiation should be considered for further investigation in larger cohorts of patients. We are currently planning a follow-up study comparing the one cycle induction chemotherapy with two cycles of induction chemotherapy and may be able to demonstrate support for our hypothesis in the future.

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References

1. Arriagada R, Le Chevalier T, Quoix E, et al. ASTRO Plenary: Effect of chemotherapy on locally advanced non-small cell lung carcinoma: a randomized study of 353 patients. *Int J Radiat Oncol Biol Phys.* 1991; 20:1183–1190. [PubMed: 1646194]
2. Curran WJ Jr, Scott C, Langer C. Phase III comparison of sequential vs. concurrent chemoradiation for PTS with unresected stage III non-small cell lung cancer (NSCLC): initial report of Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol.* 2000; 19:1891.
3. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high dose radiation versus radiation alone in stage III non-small cell lung cancer. *N Engl J Med.* 1990; 323:940–945. [PubMed: 2169587]
4. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol.* 1999; 17:2692–2699. [PubMed: 10561343]
5. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb non-small cell lung cancer. A meta-analysis. *Cancer.* 1995; 76:593–601. [PubMed: 8625152]
6. Mattson K, Holsti LR, Holsti P, et al. Inoperable non-small cell lung cancer: radiation with or without chemotherapy. *Eur J Cancer Clin Oncol.* 1988; 24:477–482. [PubMed: 2838288]
7. Morton RF, Jett JR, McGinnis WL, et al. Thoracic radiation therapy alone compared with combined chemotherapy for locally unresectable non-small cell lung cancer. *Ann Int Med.* 1991; 115:681–686. [PubMed: 1656827]
8. Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000; 117:358–364. [PubMed: 10669675]

9. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. *N Engl J Med*. 1992; 326:524–530. [PubMed: 1310160]
10. Chen Y, Pandya K, Keng P, et al. Schedule dependent pulsed low-dose paclitaxel radiosensitization for thoracic malignancy. *Am J Clin Oncol*. 2001; 24:432–437. [PubMed: 11586091]
11. Chen Y, Pandya K, Keng PC, et al. Phase I/II clinical trial using pulsed low-dose paclitaxel radiosensitization for thoracic malignancies: a therapeutic approach based on preclinical research of human lung cancer cells. *Clin Cancer Res*. 2003; 9:969–975. [PubMed: 12631594]
12. Keng P, Chen Y, Okunieff P. Comparative analysis of docetaxel and paclitaxel: cell cycle and radiosensitization effects in human cancer cell lines. *Proc Am Soc Clin Oncol*. 2000; 19:662a.
13. Keng PC, Okunieff P, Chen Y. Low dose taxol/taxotere radiosensitization for human lung cancer cells is schedule dependent. *Int J Radiat Oncol Biol Phys*. 2000; 48:272.
14. Zhang H, Hyrien O, Pandya KJ, et al. Tumor response kinetics after schedule-dependent paclitaxel chemoradiation treatment for inoperable non-small cell lung cancer: A model for low-dose chemotherapy radiosensitization. *J Thorac Oncol*. 2008; 3:563–568. [PubMed: 18520792]
15. El Sharouni SY, Kal HB, Battermann JJ. Accelerated regrowth of non-small-cell lung tumors after induction chemotherapy. *Br J Cancer*. 2003; 89:2184–2189. [PubMed: 14676792]
16. El Sharouni SY, Kal HB, Battermann JJ. Tumor control probability of stage III inoperable on-small cell lung tumors after sequential chemo-radiotherapy. *Anticancer Res*. 2005; 25:4655–4661. [PubMed: 16334157]
17. Koukourakis MI, Giatromanolaki A, Schiza S, et al. Concurrent twice-a-week docetaxel and radiotherapy: a dose escalation trial with immunological toxicity evaluation. *Int J Radiat Oncol Biol Phys*. 1999; 43:107–114. [PubMed: 9989521]
18. Jeremic B, Shibamoto Y, Acimovic L, et al. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. *J Clin Oncol*. 1995; 13:452–458. [PubMed: 7844608]
19. Jeremic B, Shibamoto Y, Acimovic L, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. *J Clin Oncol*. 1996; 14:1065–1070. [PubMed: 8648358]
20. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 2005; 23:5883–5891. [PubMed: 16087941]
21. Pierre F, Maurice P, Gilles R. A randomized phase III trial of sequential chemoradiotherapy versus concurrent chemoradiotherapy in locally advanced non-small cell lung cancer (NSCLC) GLOT-GFPC NPC 95-01 study). *Proc Am Soc Clin Oncol*. 2001; 20:312a.
22. Vokes EE, Herndon JE 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol*. 2007; 25:1698–1704. [PubMed: 17404369]
23. Zatloukal P, Petruzella L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer*. 2004; 46:87–98. [PubMed: 15364136]
24. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med*. 2002; 346:92–98. [PubMed: 11784875]
25. Farrar D, Mirkovic N, Albain KS. Multimodality therapy for stage III non-small cell lung cancer. *J Clin Oncol*. 2008; 23:3257–3269. [PubMed: 15886313]
26. Kocak M, Ozkan A, Mayadagli A, et al. Induction chemotherapy and chemoradiation therapy for inoperable locally advanced non-small-cell lung cancer: A single institution review of two different regimens. *Clinical Lung Cancer*. 2009; 10:124–129. [PubMed: 19362956]

Figure 1.
A representative radiation treatment plan from a patient who received conformal radiation treatment for stage IIIa disease is demonstrated.

Figure 3. Kaplan-Meier overall survival (solid black line), progression-free survival (dashed gray line), and distant metastasis-free estimates (solid gray line) for patients in the clinical trial.

Table 1

Patient Characteristics (n=22)

Histology	Adenocarcinoma	6 (27%)
	Squamous	8 (36%)
	NSCLC	6 (27%)
	Adenosquamous	2 (9%)
TNM Stage	T1-4 N2M0 (IIIa)	9 (41%)
	T1-3N3M0 (IIIb)	8 (36%)
	TxN3M0 (IIIb)	2 (9%)
	T4N1-2 (IIIb)	3 (14%)
Race	White	19 (86%)
	Black	2 (9%)
	Asian	1 (5%)
Gender	Male	15 (68%)
	Female	7 (32%)
Age	Median (range)	59 (41–76)

Table 2

Weekly chemoradiation treatment schema

	M	T	W	Th	F
Docetaxel	X (AM)			X (AM)	
Radiation	X (PM)	X (PM)	X (PM)	X (PM)	X (PM)

Table 3

Grade 3 and 4 Toxicities

	Toxicity*	
	Grade 3	Grade 4
Fatigue	18% (4/22)	0
Appetite Loss	18% (4/22)	0
Infection with normal ANC	23% (5/22)	0
Dyspnea/chest pain	9% (2/22)	0
Nausea/vomiting	27% (6/22)	0
Dysphagia/esophagitis	23% (5/22)	0
Headache	0	5% (1/22)
Lymphocytopenia	59% (13/22)	0
Allergic reaction	9% (2/22)	0
Bone pain (due to neupogen	0	5% (1/22)

* Note: One grade 4 AV heart block (due to change in blood pressure medicine and an undiagnosed pre-existing cardiac condition)