Original Article

Phase I Study to Determine MTD of Docetaxel and Cisplatin with Concurrent Radiation Therapy for Stage III Non-Small Cell Lung Cancer

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ABSTRACT

Objective: To evaluate the maximum tolerated dose (MTD) of docetaxel (DCT) and cisplatin (DDP) concurrently with three dimensional (3D) conformal radiotherapy or IMRT for patients with locally advanced non-small cell lung cancer (stage IIIa and IIIb) after 2–4 cycles of induction chemotherapy.

Methods: Fourteen patients with histological/cytological proven stage III non–small-cell lung cancer were eligible. 3D or IMRT radiotherapy (60-70Gy in 30-35 fractions, 6-7weeks, 2 Gy/fraction) was delivered concurrently with cisplatin and docetaxel, 2 cycles during concurrent chemoradiotherapy (CCRT). The level I dosage was composed of 56 mg/m^2 DCT, on day 1 and 28mg/m^2 DDP, on day 1 and day 2. The level II was composed of 60 mg/m^2 DCT, on day 1 and 30 mg/ m^2 DDP, on day 1 and day 2. The level III was composed of 64 mg/m^2 DCT, on day 1 and 32 mg/ m^2 DDP, on day 1 and day 2.

Results: Fourteen patients were allocated and finished concurrent chemoradiotherapy. The dose-limiting neutropenia was at the dose Level III (64 mg/m^2) and occurred in 2 of 5 patients. No dose limiting non-hematologic or hematologic toxicity occurred in the other patients.

Conclusions: Patients with locally advanced non-small cell lung cancer may tolerate 60mg/m^2 docetaxel and 60mg/m^2 cisplatin for 2 cycles during concurrent radiotherapy after 2-3 cycles of induction chemotherapy.

Key words: Non–small-cell lung cancer; Concurrent chemoradiotherapy; Cisplatin docetaxel; Toxicity

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the urban areas of China[1]. About 600 000 people die from lung cancer each year. For locally advanced inoperable lung cancer, concurrent chemo-radiotherapy (CCRT) produced better survival rates than the sequential administration of these two modalities[2-7]. Furuse et al. reported the superiority of concurrent chemoradiotherapy compared with sequential therapy[7] (median survival: 16. 5 vs. 13. 3 months, 5-year survival rate: 15. 5 vs. 8. 9%, respectively). The Radiation Therapy Oncology Group (RTOG) study (RTOG 9410) confirmed the same results[8, 9].

Docetaxel (Taxotere) is a semisynthetic taxane that possesses significant activity in the treatment of patients with non-small-cell lung cancer (NSCLC). Docetaxe increases the rate of microtubule assembly and inhibits the depolymerization of microtubules[10,11]. Due to the unique mechanism of action and an apparent lack of cross-resistance, several clinical trials in combination with other active agents have been studied. Cisplatin remains a key drug for the treatment of NSCLC.

As a chemotherapy regimen, docetaxel combined with cisplatin has been evaluated in large trials in patients with NCSLC. In the combination of cisplatin, docetaxel has been studied in doses ranging from 60 to 100 mg/m^2. Phase I and/or II studies in Japan demonstrated that cisplatin (80 mg/m^2) plus docetaxel (60mg/m^2) therapy should be recommended[12]. However, the dose limiting factor of the chemotherapy is neutropenia and grades 3–4 neutropenia was observed in 80% of the cases[12].

A group of physicians in Korean found 20mg/m^2 docetaxel (TXT) plus 20mg/m^2 cisplatin (DDP) weekly to be the maximum tolerated dose (MTD) for patients with locally advanced NSCLC during 6 weeks of 63Gy radiotherapy[13]. In their study, the DLT was esophagitis.

Given the evidence that aggressive multimodality treatment can improve survival in stage III NSCLC,

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docetaxel and cisplatin, 2 cycles in 6 weeks is close to the standard chemotherapy regimenes, which we hope it could improve the control of tumor with acceptable toxicity. We undertook this phase I study to determine the maximum tolerated dose (MTD).

PATIENTS AND METHODS

Patients

Written informed consent was obtained from each patient before enrollment. All patients had histological proven and unresectable Stage III NSCLC without previous RT. Measurable disease was assessed by radiograph, computed tomography, or magnetic resonance imaging. Other eligibility criteria included: (a)Age ≥18 years; (b) Performance Status of 0 or 1 by the Eastern Cooperative Oncology Group (ECOG) scale in patients ≤70 years old; (c) Negative head computed tomography and bone scan; (d)Weight loss < 10% within the past 6 months of diagnosis; (e) Adequate end organ function as defined by Granulocyte count≥1. 5×10^9/L; (f) Platelet count ≥100×10^9/L; (g) Serum bilirubin level ≤1. 5 × the upper limit of normal; (h) Calculated creatinine clearance ≥30 ml/min; (i) AST and ALT level≤2× the upper limit of normal; alkaline phosphatase level ≤2 ×the upper limit of normal; (j) Forced expiratory volume in 1 second ≥1. 5 L or >50% of the predictive value; (k) No other treatment for cancer in the last month. Women were required to have childbearing potential terminated previously by surgery or menopause or attenuated by the use of an approved contraceptive method.

Patients were excluded from the study if they had documented distant metastases; malignant pleural effusion; preexisting cardiac, pulmonary, neurological, or other diseases that the investigator judged to be clinically significant; active infectious processes; severe malnutrition or intractable emesis; previous or concurrent malignancy except inactive non-melanoma skin cancer, in-situ carcinoma of the cervix. Pregnant and/or lactating women were also excluded from participation.

Pretreatment Evaluation

Before enrollment into the trial, all patients were staged clinically with history and physical examination, general condition, history, performance status, blood tests and radiographic studies. Blood tests included complete blood cell count (CBC), serum aspartate aminotransferase (AST), calcium, alkaline phosphatase and bilirubin levels. Electrocardiograph, chest radiograph, chest computed tomography (CT) scan, abdominal ultrasound and/or CT scan and brain CT or MRI and isotope bone scan were performed in all cases.

Treatment Plan

This was an open-label, single-center, non-randomized Phase I dose escalation study of docetaxel and cisplatin given with radiotherapy, after 2-4 cycles of induction chemotherapy.

The concurrent chemotherapy consisted of 2 cycles of docetaxel and cisplatin in 6 weeks; doses were given concomitantly with thoracic RT. Docetaxel was given first, and then cisplatin was given after hydration. The cisplatin and docetaxel dose started at 56 mg/m^2, and the increments are 4 mg/m^2 (Table 1). To prevent a hypersensitivity reaction, 7.5 mg of dexamethasone was given twice daily before chemotherapy. Standard docetaxel premedication, including 5–10 mg dexamethasone orally, 20 mg diphenhydramine hydrochloride intramuscularly, and 20–40 mg ranitidine intravenously, was used. Appropriate antiemetics and 250 ml of intravenous normal saline were administered before chemotherapy. Docetaxel was reconstituted in 250 ml of normal saline and given i.v. over 1 h at least 4 h before radiotherapy at the same day.

Table 1. The dose escalation schedule of docetaxel

Level	Number of patients	Dose (mg/m^2)	Days per cycle	Cycles in all
A	3	56	21	2
B	6	60	21	2
C	5	64	21	2

Conformal or IMRT radiotherapy was given using 10 MV or 6 MV photons at a dose of 60-70 Gy. The daily fraction was 2 Gy, administered 5 days a week for 6-7 weeks. Radiotherapy targets were defined according to the International Commission on Radiation Units and Measurements Report Nos. 50 and 62. The target volume and all critical structures were then drawn on the scans. Radiotherapy with a combination of anterior, posterior and oblique fields or any combination of these (even if they were not coaxial) was used. The treatment volumes included the primary disease site with a margin of 1.0-1.5 cm around the mass and the mediastinal lymph nodes of short diameter larger than 1cm. And the normal tissue doses are limited as follows: the spinal cord dose<45 Gy, the esophagus dose<56 Gy and lung V20<30%.

Dose Limiting Toxicity, MTD and Response Evaluation

An evaluation for toxicity was performed on a weekly basis according to the National Cancer Institute's Common Toxicity Criteria [14]. All patients underwent a complete blood count weekly, and blood chemistry analysis, including liver function tests, blood urea nitrogen, and creatinine, every week during the treatment for evaluation of their response and toxicity.

Dose limiting toxicity (DLT) was defined as any non-hematologic toxicity of Grade 3 or higher; persistent Grade 4 vomiting despite the use of antiemetics; Grade 4 neutropenia persisting for 4 days or neutropenic fever; Grade 3 thrombocytopenia or thrombocytopenia with either a bleeding tendency or requirement for transfusion of platelets. Patient accrual and evaluation at certain dose levels were not performed simultaneously because of the required 3 weeks of observation before moving on to the next dose level, and hence the number of patients at each dose level could not be exactly the same as planned. The MTD was defined as the dose of cisplatin and docetaxel

that caused drug-related Grade 3 to 4 non-hematologic or Grade 4 hematological toxicity in less than 1 of 3 patients, or 2 of a 6-patient cohort.

Patients who completed both cycles of chemotherapy and received thoracic RT were considered assessable for the end-point evaluation. Local-regional responses to therapy were determined based on CT scans of the chest performed 1 month after the end of CCRT. Complete response (CR) was defined as the complete clinical and radiographic disappearance of the tumor. Partial response (PR) was defined as a reduction of at least 30% of the products of the longest perpendicular diameters of the largest tumor mass in the radiation field. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for PD below, taking as reference the smallest perpendicular diameters since the treatment started. Progressive disease (PD) was defined as an increase of the longest diameters of the indicator lesion by 20% or the appearance of new lesions.

All patients were given an ethics committee approval letter clearly identified with protocol title and study specific consent form, and signed an informed consent. Any serious adverse events will be reported to the ethics committee.

We did not do statistical analysis in this study for the nature of the Phase I trial and the small number of patients.

RESULTS

Patient Characteristics

Between 1 October 2006 and 26 April 2010, 12 men and 2 women were enrolled in this study. The median age of the patients was 60 years (range 50–70 years). The performance status of all patients was 0 or 1. Five patients had stage IIIA disease, and nine patients had stage IIIB disease. Nine were squamous cell cancer, five had adenocarcinoma. Each patient gave a written informed consent and voluntarily agreed to participate in this trial.

Toxicity of Treatment

Toxicity grade at each level, non-hematological toxicity (Table 2) and hematological toxicity (Table 3) were carefully monitored. Toxicity that occurred within 90 days of RT was termed acute.

Table 2. Non-hemotological toxicity

DL	NP	Fatigue				Fever				Esophagitis				Nausea				Vomiting				Cough				Dyspnea				pneumonitis			
		Grade (NCI Toxicity criteria)																															
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	3	-	2	-	-	-	-	-	-	2	1	-	-	2	-	-	-	2	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-
2	6	2	2	-	-	-	-	-	-	2	1	-	-	2	-	-	-	2	-	-	-	2	1	-	-	-	-	-	-	-	-	-	-
3	5	2	2	-	-	-	-	-	-	3	1	-	-	2	1	-	-	2	1	-	-	2	1	-	-	-	-	-	-	-	-	-	-

DL: Dose level, 1: level I, 56mg/m^2; 2: level II, 60mg/m^2; 3: level III, 64 mg/m^2 NP: number of patients

Table 3. Hemotological toxicity

Dose number of level patients		leukocytes				Neutrophils				Hemoglobin				platelets			
		Grade (NCI Toxicity criteria)															
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	3	-	1	-	-	-	1	-	-	1	-	-	-	-	1	-	-
2	6	1	2	3	-	1	2	3	-	2	-	-	-	1	-	-	-
3	5	-	-	3	2	-	-	3	2	2	-	-	-	-	2	-	-

Dose level, 1: level I; 2: level II; 3: level III

None of the 3 patients in level I (patients who received 56 mg/m^2 of cisplatin and docetaxel dose during CCRT) had toxicity greater than grade 2. None of the limitations designated for the MTD were met for level II. Grades II acute radiation esophagitis happened in one patient and 2 patients developed Grades III neutropenia. As for the level III, one of the first three patients developed Grades VI neutropenia. More patients were recruited, but one new patients developed Grades VI neutropenia. So this level was stopped. And we continued to include further 3 patients in the level II, none of the limitations designated for the MTD were met in this level.

Acute radiation pneumonitis grades II was found in 1 case. The symptome included fever, cough, short of breath. The patient who suffered from acute radiation pneumonitis recovered after treatment with antibiotics, dexamethasone and vitamins. Three patients suffered from grades I and IIradiation oesophagitis, which disappeared after treatment.

Response

The responses of concurrent chemoradiotherapy were evaluated with CT scans 1 month after the end of concurrent treatment. Eleven out of 14 (78.6%) patients had a PR, and 3 out of 14 (21.4%) patients had a SD. No patients had PD or CR.

DISCUSSION

To the best of our knowledge, this is the first phase I trial of dose escalation of a 3-week cycle with docetaxel and

cisplatin concurrent with radiotherapy for patients with locally advanced non-small cell lung cancer after two or four cycles of induction chemotherapy. According to the result of our study, administration of docetaxel (60 mg/m^2) and cisplatin (60 mg/m^2) with concomitant RT appears feasible. DLT was neutropenia in our study.

Furuse et al. reported a superior response rate and median survival duration in patients treated in the concurrent arm compared with those receiving sequential therapy in a Phase III study using the chemotherapeutic agents of cisplatin, vindesine, and mitomycin and thoracic RT[7]. Another phase III study was conducted by the Radiation Therapy Oncology Group comparing two concurrent chemotherapy and thoracic RT regimens with a standard sequential chemotherapy and thoracic RT approach. Their preliminary results showed a promising median survival rate for the concurrent platinum-based chemotherapy and RT arm[10].

Theoretical benefits of concomitant chemoradiotherapy include improved locoregional control and early eradication of micrometastatic disease. In particular, concurrent treatment has the advantage of the simultaneous delivery of two cytotoxic treatment modalities, a reduction in overall treatment time, and most importantly, radiosensitization by the chemotherapeutic agents[11,12]. Although there were some clinical gains with combined chemoradiotherapy for advanced NSCLC, the survival rates remained low because local recurrence and distant metastasis were still common.

There are many controversies about chemotherapy regimens combined with radiotherapy. NSCLC patients treated with concurrent chemoradiotherapy with standard dose of chemotherapy were usually at high risk of severe toxicity of radiation pneumonitis, oesophagitis and neutropenia. Some studies strongly support the benefit of cisplatin-based chemotherapy with RT for Stage III NSCLC[13]. Some investigators focused on chemoradiotherapy with multiple low doses of chemotherapy[14].

The taxane class has a mechanism of action that leads to the increased formation and stabilization of microtubules. Extensive in vitro and in vivo data have demonstrated the radiation-sensitizing effect induced by docetaxel in human tumor cells. And also, many clinical groups have reported the use of docetaxel either alone or in combination with radiation for the treatment of NSCLC[11-13].

Choy et al. reported dose-limiting esophagitis with mild neutropenia in a Phase I trial of concurrent weekly paclitaxel with RT for NSCLC. Both esophagitis and neutropenia were found to be the DLT in a Phase I study of docetaxel in a 3-week cycle with concomitant thoracic RT. Choy et al. also conducted a Phase I study to determine the DLT and MTD of docetaxel and carboplatin with concurrent thoracic RT[15-18]. The DLT was esophagitis, and the MTD of docetaxel was 20 mg/m2/wk with weekly carboplatin (AUC 2).

Raja et al. evaluated an escalating dose of weekly docetaxel with fixed cisplatin (25 mg/m^2) and concurrent radiation therapy in the treatment of patients with locally advanced, unresectable NSCLC[19]. The MTD of weekly docetaxel in this combination was found to be 25 mg/m^2/week, and the DLT to be esophagitis. The average survival of the stage IIIA patients at last follow-up was 13.6 months and the median has not been reached. Stage IIIB patients had a median survival of 6.7 months.

Hiroshi et al. reported a phase II study of bi-weekly docetaxel and carboplatin with concurrent radiation therapy followed by consolidation chemotherapy with docetaxel plus carboplatin. All the patients received docetaxel 30 mg/m^2 and carboplatin at an AUC of 3 every 2 weeks for six courses–four courses were given during concurrent chemo-radiotherapy performed to a total dose of 60 Gy and two courses following completion of radiotherapy. The overall response rate was 91%, serious side effects were generally limited to grade 3 neutropenia in 6%, grades 3 and 4 pulmonary toxicity in 6% and 3%, and grade 3 esophagitis in 3% of patients[20].

Paal et al. conducted a phase I/II study to evaluate weekly docetaxel with concomitant radiotherapy in patients with stage III unresectable NSCLC[21]. The results from the Phase I of the study showed docetaxel to be well tolerated when administered at a dose of 30mg/m^2 with concurrent 50Gy radiotherapy. Dose-limiting toxicity was grade 3-4 esophagitis. The Phase II part evaluated docetaxel at 30mg/m^2 (considered recommended dose). All patients except one experienced asymptomatic grade 3-4 lymphopenia; four patients (9.5%) had grade 3-4 esophagitis. The overall response rate was 45.5%, with eight (24.2%) complete responses.

A group of physicians in Korean found 20mg/m^2 docetaxel (TXT) plus 20mg/m^2 cisplatin (DDP) weekly to be the maximum tolerated dose (MTD) for patients with locally advanced NSCLC during 6 weeks of 63 Gy radiotherapy[22]. In their study, the DLT was esophagitis. Although the primary goal of our phase I study was not to evaluate the efficacy.The patients in the trial did have benefit from this schedule, although the number of the patients in the trial was limited. The overall responses (PR) were 78.3% (9/11). These are similar to the results reported by Choy et al[15,16] and Zhu et al[14].

Concurrent treatment has the advantage of the simultaneous delivery of two cytotoxic treatment modalities, a reduction in overall treatment time, and most importantly, radiosensitization by the chemotherapeutic agents[11,12,16]. NSCLC patients treated with CCRT with nearly full dose of chemotherapy were usually at high risk of severe toxicity of radiation pneumonitis, oesophagitis and neutropenia. CCRT with relartively low dose chemotherapy can benefit patients with NSCLC in sensitization of lung cancer cells and with promising both short and long term efficacy as reported by Choy et al[18,19] and Zhu et al[14].

Generally speaking, benefits of concomitant chemo-radiotherapy include improved locoregional control and early eradication of micrometastatic disease. But there are many controversies about chemotherapy regimens combined with radiotherapy. Our preliminary study showed CCRT regimens with docetaxel and cisplating was tolerable and promising.

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