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ORIGINAL ARTICLE

Phase II study of carboplatin combined with weekly docetaxel in patients with advanced non-small cell lung cancer

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Abstract
Purpose This phase II study is performed to evaluate the safety, efficacy and tolerability of carboplatin combined with weekly docetaxel in patients with advanced non-small cell lung cancer (NSCLC).
Patients and methods All patients were treated with the combination of docetaxel 35 mg/m^2 by IV infusion over 30–60 min weekly, on days 1, 8, and 15, for 3 weeks followed by 1 week of rest, with intravenous carboplatin (AUC 6) administered immediately afterward on day 1. Cycles were repeated every 28 days.
Results Forty-seven (95.9%) of the 49 patients were assessable for response, one case of complete response and 17 cases of partial response were confirmed, giving an overall response rate of 36.7% (95% CI 23.2–50.2%). The median time to progression and overall survival (OS) for all patients were 5.2 months (95% CI 4.1–6.3 months) and 10.4 months (95% CI 7.3–13.5 months), respectively. The estimate of OS at 12 months was 37.6% (95% CI 24.0–51.2%). The most severe hematologic adverse event was anemia, which occurred with grade 3/4 intensity in 7 (14.9%) patients. Neutropenia occurred with grade 3 intensity in 4 (8.5%) patients. However, no grade 4 neutropenia was observed. Grade 3 nausea/vomiting, diarrhea, asthenia, nail changes, and skin reaction were observed in 6 (12.8%), 3 (6.4%), 2 (4.3%), 2 (4.3%) and 1 (2.1%) patients. Yet, no grade 4 non-hematologic toxicity was observed.
Conclusions The combination of carboplatin with weekly docetaxel is a tolerated treatment modality with encouraging activity and survival outcome in previously untreated patients with advanced NSCLC.

Keywords Advanced non-small cell lung cancer · Docetaxel · Carboplatin · Weekly

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Introduction

Non-small cell lung cancer (NSCLC) is diagnosed at an advanced stage in approximately 40% of the patients [1]. Systemic chemotherapy is the primary treatment modality for advanced-stage NSCLC [2]. The platinum-based combination regimens are considered the 'standard of care' for patients with advanced NSCLC. One of these platinum compounds, cisplatin, requires hydration to prevent renal damage and is therefore not indicated in the treatment of outpatients. To alleviate the renal toxicity of cisplatin, carboplatin was developed as a second generation platinum compound. In NSCLC, the antitumor effect of carboplatin was found to be almost equal to that of cisplatin [3], although meta-analyses suggested that cisplatin was slightly superior to carboplatin, at least in terms of response [4, 5]. Because carboplatin does not induce renal damage or emesis, it is suitable for outpatient-based chemotherapy.

Docetaxel has been associated with single agent response rates of 19–27% in phase II trials in previously untreated patients with NSCLC [6–8]. The commonly used

dose and schedule of docetaxel is 60–100 mg/m^2 every 3 weeks; however, moderate to severe neutropenia is frequently observed [3, 7–11]. Several studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12, 13]. Carboplatin and docetaxel have different mechanisms of antitumor action, and most of their toxicities do not overlap. In addition, because docetaxel and platinum compounds do not have cross-tolerance, their combination may have higher efficacy than either alone [14–16]. Based on these favorable results, we conducted the present phase II study to evaluate the safety, efficacy and tolerability of carboplatin combined with weekly docetaxel in patients with advanced NSCLC.

Materials and methods

Patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for the study. Each patient was required to meet the following criteria: clinical unresectable stage IV or IIIB, an Eastern Cooperative Oncology Group performance status (PS) of 0–2, no prior chemotherapy or radiotherapy, measurable lesions, adequate hematological function [white blood cell count (WBC) 4,000–12,000 per mm^3; neutrophils $\geq$2,000 per mm^3; platelets $\geq$100,000 per mm^3; hemoglobin $\geq$9.0 g/dl], adequate hepatic function (total bilirubin <1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase <60 IU/l), and adequate renal function (creatinine $\leq$1.2 mg/dl, creatinine clearance $\geq$60 ml/min). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy and pleural and/or pericardial effusion requiring drainage were excluded. The institutional review board of authors' institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Patient evaluation

The pretreatment evaluation consisted of complete blood cell count, differential count, routine chemistry measurements, a chest radiograph, a chest computed tomography (CT) scan, abdominal ultrasound or CT scan, whole brain magnetic resonance imaging or CT scan, and an isotope bone scan. Complete blood cell count, differential, count and routine chemistry measurements were carried out at least twice a week during the first course of chemotherapy.

Treatment schedule and modification

All patients were treated with the combination of docetaxel 35 mg/m^2 by IV infusion over 30–60 min weekly, on days 1, 8, and 15, for 3 weeks followed by 1 week of rest, with intravenous carboplatin (AUC 6) administered immediately afterward on day 1. Cycles were repeated every 28 days. The carboplatin dose was calculated using the Calvert formula, with creatinine clearance estimated by the Cockroft–Gault equation. Before administration of anticancer agents, each patient received antiemetic agents consisting of 8 mg of dexamethasone and a 5-HT3 antagonist intravenously. No prophylactic granulocyte colony-stimulating factor or prophylactic antibiotic support was planned.

Dose adjustments at the start of a new cycle were based on the worst toxicity observed during the previous cycle. Toxicities were assessed at the end of each cycle according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The dose of docetaxel was reduced to 80% if grade 4 myelosuppression or febrile neutropenia was present, and if myelosuppression or febrile neutropenia persisted an additional reduction of docetaxel dose to 60% was required. If there was a third such episode docetaxel was discontinued. In the case of grade $\geq$2 non-hematologic toxicity, treatment was delayed until recovery but not for more than 2 weeks. The dose was reduced in the case of severe non-hematologic toxicity that was not controllable with usual measures, and treatment was discontinued if the patient experienced a significant hypersensitivity reaction or unacceptable toxicity (e.g., grade 4 stomatitis or diarrhea, grade $\geq$3 peripheral neuropathy, severe and persistent skin/nail changes). Docetaxel administration could be omitted if one of the following toxicities was noted on day 8 or day 15: grade $\geq$2 hematologic or non-hematologic toxicities, fever $\geq$38°C, diarrhea of any grade, or a decreased PS. Dose reduction in subsequent cycles was permitted in cases of carboplatin reduced to AUC 5 with grade 4 neutropenia lasting 4 days, febrile neutropenia <1,000 per mm^3, thrombocytopenia <20,000 per mm^3 or the need for platelet transfusion, or if a major non-hematological toxicity of at least grade 3, excluding anorexia or nausea.

It was intended that all patients would receive at least four cycles unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after this study were not restricted by the protocol.

Treatment assessment

After every two cycles of treatment, response was evaluated using RECIST criteria. Of the lesions observed prior to treatment, a maximum of five measurable lesions from each metastasized organ up to a total of ten lesions were selected as target lesions. In cases of partial or complete response (CR), a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles.

Statistical analysis

The current trial used a two-stage optimal design, as proposed by Simon, with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis [17]. The current trial was designed to detect a response rate of 40% as compared to a minimal, clinically meaningful response rate of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The time to progression (TTP) and overall survival (OS) analyses were all estimated using the Kaplan–Meier method. The TTP was calculated from the initiation of chemotherapy to the date of disease progression, while OS was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, IL, USA).

Results

Patient characteristics

From July 2005 to August 2007, a total of 49 patients were enrolled in the current study from five centers. The characteristics of the patients are summarized in Table 1. The median age was 58 (range 32–79) years, with 35 males and 14 females. Twenty-eight (57.1%) patients had a metastatic disease, while 21 patients had a recurrent disease after surgical resection (pulmonary resection) of the primary tumor. No patients had received prior chemotherapy or radiotherapy.

Table 1 Patient characteristics

Characteristics	Number of patients *n* (%)
Patients enrolled	49
Sex	
Male	35 (71.4)
Female	14 (28.6)
Age at diagnosis (years)	
Median (range)	58 (32–79)
Histologic type	
Adenocarcinoma	29 (59.2)
Squamous cell carcinoma	15 (30.6)
Large cell carcinoma	5 (10.2)
ECOG performance status	
0	34 (69.4)
1	11 (22.4)
2	4 (8.2)
Disease stage	
Stage IIIB/recurrent	21 (42.9)
Stage IV/metastatic	28 (57.1)

ECOG Eastern Cooperative Oncology Group

Efficacy and survival

Forty-seven (95.9%) of the 49 patients were assessable for response, of the two patients not assessable, both were lost to follow-up after the second cycle of the treatment. All efficacy data are reported using the intent-to-treat patient population. One case of CR and 17 cases of partial response (PR) were confirmed, giving an overall response rate of 36.7% (95% CI 23.2–50.2%) (Table 2). Of 18 responses, 3 (16.7%) were observed after three cycles, 11 (61.1%) after four cycles and 4 (22.2%) after six cycles. The median follow-up period was 13.5 months. The median TTP for all patients was 5.2 months (95% CI 4.1–6.3 months). Thirty-two patients had died at the time of the present evaluation. The estimated median OS was 10.4 months (95% CI 7.3—13.5 months) (Fig. 1). The estimate of OS at 12 months was 37.6% (95% CI 24.0–51.2%).

Table 2 Tumor response (intention-to-treat analysis, $n = 49$)

Response	*n* (%)
Overall response rate (ORR)	18 (36.7)[a]
Complete response (CR)	1 (2.0)
Partial response (PR)	17 (34.7)
Stable disease (SD)	19 (38.8)
Progressive disease (PD)	10 (20.4)
Not assessable	2 (4.2)

[a] 95% Confidential interval (CI) = 23.2–50.2%

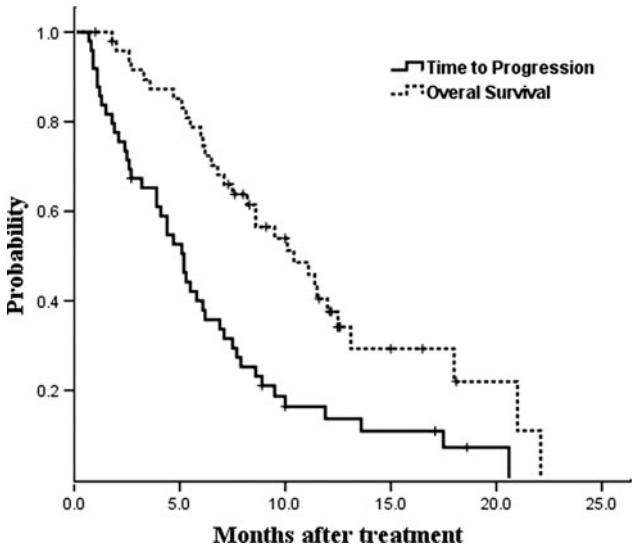

Fig. 1 Time to disease progression and overall survival for all patients

Table 3 Adverse reactions (by patients, $n = 47$)

	Grade[a] *n* (%)			
	1	2	3	4
Hematologic				
Anemia	13 (27.7)	12 (25.5)	6 (12.8)	1 (2.1)
Neutropenia	6 (12.8)	11 (23.4)	4 (8.5)	0 (0)
Thrombocytopenia	7 (14.9)	4 (8.5)	0	0
Non-hematologic				
Nausea/vomiting	14 (29.8)	9 (19.1)	6 (12.8)	0
Diarrhea	6 (12.8)	5 (10.6)	3 (6.4)	0
Asthenia	5 (10.6)	11 (23.4)	2 (4.3)	0
Edema	5 (10.6)	1 (2.1)	0	0
Neuropathy	12 (25.5)	0	0	0
Nail changes	3 (6.4)	1 (2.1)	2 (4.3)	0
Skin reaction	8 (17.0)	5 (10.6)	1 (2.1)	0
Pneumonia	3 (6.4)	1 (2.1)	0	0
Elevated transaminase	1 (2.2)	1 (2.2)	0	0
Elevated creatinine	2 (4.3)	1 (2.2)	0	0

[a] NCI CTC version 2.0

Toxicity

A total of 198 cycles were administered in 47 patients assessable for toxicity, with a median of four cycles per patient (range 1–6 cycles). The occurrence and the incidence of the hematologic and non-hematologic toxicities are shown in Table 3. The most severe hematologic adverse event was anemia, which occurred with grade 3 intensity in 6 (12.8%) patients and grade 4 in 1 (2.1%) patients. Neutropenia occurred with grade 3 intensity in 4 (8.5%) patients. However, no grade 4 neutropenia was observed. Nausea/vomiting, diarrhea, and asthenia were the most common non-hematological toxicities. Grade 1/2 nausea/vomiting, diarrhea, and asthenia were observed in 23 (48.9%), 11 (23.4%), and 16 (34.0%) patients, respectively. And grade 3 nausea/vomiting, diarrhea, asthenia, nail changes, and skin reaction were observed in 6 (12.8%), 3 (6.4%), 2 (4.3%), 2 (4.3%) and 1 (2.1%) patients. Yet, no grade 4 non-hematologic toxicity was observed. Overall, treatment was delayed or the dose reduced in 34 (17.2%) and 22 (11.1%) cycles, respectively. Five patients were hospitalized because of treatment toxicities (three because of infections and two because of general weakness). There were no treatment-related deaths during this study.

Second-line treatment

Salvage treatment was not specified in the protocol. Palliative radiotherapy was given to seven patients with symptomatic progression in lung, bone, or brain. We offered second-line chemotherapy to 32 patients after failure. Second-line therapy after docetaxel plus carboplatin was mostly non-platinum therapy: 10 patients received gemcitabine-based therapy, 6 patients received irinotecan, 16 patients were treated with gefitinib or erlotinib. Ten patients received third-line treatment.

Discussion

In this study, we performed a phase II trial of carboplatin combined with weekly docetaxel for patients with advanced NSCLC. We observed an overall response rate of 36.7%, a 1-year survival rate of 37.6%, median TTP and OS of 5.2 and 10.4 months, respectively. In previous phase II studies using triweekly docetaxel plus carboplatin, the overall response rates were 35.0–44.0%, the 1-year survival rates were 52.0–61.7%, and the median OS was 12.0–15.0 months [14, 15, 18–20]. Moreover, in a phase II trial of biweekly docetaxel combined with carboplatin for patients with advanced NSCLC, the overall response rate of 30%, a 1-year survival rate of 50%, and an median OS of 11.8 months [21]. Therefore, the efficacy and the survival results of our regimen of carboplatin with weekly docetaxel were comparable with those used in earlier studies.

The use of weekly, rather than traditional 3-weekly, administration of smaller doses of chemotherapy agents has been investigated as a means of reducting toxicity (in particular, myelosuppression) in elderly patients [22]. Results from a phase II study of weekly versus 3-weekly single agent docetaxel in 96 chemonaive elderly and/or poor PS patients with advanced NSCLC suggest that hematologic toxicity is lower with the weekly schedule [23]. Another phase II study involving 33 chemonaive elderly (>75 years) patients treated with docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2, both administered as weekly infusions, reported acceptable tolerability with no grade 4 toxicity [24]. Weekly administration of docetaxel may produce less myelotoxicity than 3-weekly administration. A recent literature-based meta-analysis selected six randomized clinical trials (three phase III, two phase II, 1,018 patients) and confirmed that there was a significant advantage of weekly docetaxel with respect to grade 3/4 neutropenia (absolute benefit of 15–19%, without a survival improvement) [25]. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed [26].

Hematological toxicities were mild and acceptable in our study. The compliance to treatment was in general good. Triweekly docetaxel plus carboplatin induced neutropenia in about 70% of patients and febrile neutropenia in 3–15% [14–16]. In contrast, we observed grade 3 or 4 neutropenia in 8.5% of patients and no incidents of febrile neutropenia,

suggesting that our weekly regimen has a safer toxicity profile. Our tolerability data confirm the previous observations that weekly docetaxel is advantageous in terms of hematological toxicity with respect to 3-weekly schedule [27, 28]. Non-hematological toxicities were mostly mild to moderate and manageable. The incidence of grade 3 or 4 non-hematological toxic effects was rare in this study (12.8% nausea/vomiting, 6.4% diarrhea, 4.3% asthenia, 4.3% nail changes, and 2.1% skin reaction). In contrast to previous findings, we did not observe any incidents of severe pulmonary toxicity [29].

In conclusion, the combination of carboplatin with weekly docetaxel is a tolerated treatment modality with encouraging activity and survival outcome in previously untreated patients with advanced NSCLC.

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Conflict of interest statement The authors declare no conflicts of interest.

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