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ORIGINAL ARTICLE

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Carboplatin and docetaxel in advanced non-small-cell lung cancer: results of a multicenter phase II study

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Abstract *Background*: To evaluate the efficacy of carboplatin and docetaxel combination in patients with advanced non-small-cell lung cancer. *Methods*: In a phase II study, patients with inoperable stage IIIB or stage IV non-small-cell lung cancer (ECOG performance status of 0 or 1) were treated with the combination of carboplatin AUC 5 mg/ml·min and docetaxel 80 mg/m^2 administered once every 3 weeks. *Results*: A total of 45 patients were accrued to the study. The median age was 62 years and adenocarcinoma was the most common histology. Patients received a median of four cycles of chemotherapy. The objective response rate was 29% with a median survival of 11.9 months among evaluable patients. The 1-year survival rate was 47%. Febrile neutropenia (17%) was the most common hematological toxicity associated with the regimen whereas grade 3 fatigue (4%) was the major nonhematological toxicity. *Conclusions*: The combination of carboplatin plus docetaxel is well tolerated and is effective for the treatment of patients with previously untreated advanced or metastatic non-small-cell lung cancer.

Keywords Docetaxel · Carboplatin · Non-small-cell lung cancer · NSCLC · First-line chemotherapy

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States. About 171,900 new cases of lung cancer were diagnosed in the US in the year 2003 [1]. A majority of the patients have surgically unresectable disease at the time of presentation. With the exception of stage T1N0, more than 50% of patients who undergo surgical resection will develop recurrence of disease [2]. Systemic chemotherapy is the mainstay of treatment for patients with advanced or recurrent disease.

Cisplatin-based chemotherapy provides a modest survival advantage to patients with advanced non-small-cell lung cancer (NSCLC). A meta-analysis demonstrated that cisplatin-based therapy is associated with a 10% improvement in 1-year survival and a 1.5-month increase in median survival over best supportive care in patients with advanced NSCLC [3]. Several randomized clinical trials completed in the past few years have established the efficacy of platinum-based doublet combination chemotherapy in the treatment of patients with advanced NSCLC [4, 5, 6]. Administration of systemic chemotherapy improves quality of life and produces a modest prolongation in survival. As a result, platinum-based doublet chemotherapy is considered the standard of care in the treatment of patients with advanced NSCLC. The combination of carboplatin and etoposide was compared to cisplatin plus etoposide in a clinical trial by Klastersky et al. [7]. The study revealed

no significant difference in overall survival, and a more favorable toxicity profile in the carboplatin arm. In another study, Rossell et al. compared the efficacy of carboplatin/paclitaxel and cisplatin/paclitaxel for patients with advanced NSCLC in a randomized clinical trial. The primary endpoint of the study, the objective response rate, was comparable between the two regimens [8]. Carboplatin has become the preferred platinum compound to treat advanced NSCLC in clinical practice in the US, mainly due to its better therapeutic index.

Docetaxel is an active drug in NSCLC. The combination of docetaxel and cisplatin has been recently approved for use in the first-line treatment of advanced NSCLC. Docetaxel has been associated with single-agent response rates of 19–27% in phase II trials in previously untreated patients with NSCLC [9, 10, 11]. The combination of docetaxel and cisplatin in the treatment of advanced NSCLC results in response rates of 17–32%, as noted in phase II and phase III clinical trials [12, 13, 14, 15]. We conducted a phase II clinical trial to evaluate the efficacy of docetaxel, used in combination with carboplatin, in previously untreated patients with advanced NSCLC. The doses of carboplatin and docetaxel were chosen based on our phase I clinical trial [16].

The first cohort of 33 patients received treatment with carboplatin at a dose of AUC 6 mg/ml·min and docetaxel at 80 mg/m^2 administered every 3 weeks. The results in this cohort of patients have been reported recently [17]. In order to reduce the incidence of febrile neutropenia, the study was amended to reduce the dose of carboplatin to a target AUC of 5 mg/ml·min in the second cohort of patients, while the dose of docetaxel was maintained at 80 mg/m^2. We report the results in the second cohort of patients ($n=45$) and provide an analysis of the outcome for both cohorts of our study.

Patients and methods

The study was conducted at five institutions in the US in accordance with the guidelines established in the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (IRB) at each participating institution. All patients provided written informed consent prior to any study-related procedures. Between September 1996 and August 1998, 78 patients were registered in this study. The results in the first cohort of 33 patients who were treated with docetaxel 80 mg/m^2 and carboplatin AUC 6 mg/ml·min have been reported previously [17].

Eligibility

Patients were eligible to participate in the study if they met the following criteria: histological/cytological confirmation of NSCLC, inoperable stage IIIB or stage IV disease, no prior chemotherapy, measurable site of disease that had not been irradiated, age >18 years, ECOG performance status (PS) 0 or 1 at the time of screening for the study, estimated life expectancy >12 weeks, adequate bone marrow function (absolute neutrophil count $>1500/mm^3$, platelets $>100{,}000/mm^3$), renal (serum creatinine >1.8 mg/dl) and hepatic function (aspartate aminotransferase and alanine aminotransferase less than 1.5 times the upper limit of normal (ULN) for the institution, serum bilirubin within normal institutional limits and serum alkaline phosphatase less than five times the ULN for the institution). At least 4 weeks should have elapsed since prior radiation therapy and/or major surgery and enrollment in the study. Prior radiation therapy was permitted if the measurable disease was completely outside the radiation portal. Patients with brain metastasis were eligible if they had stable disease after 21 days from completion of radiation therapy for brain metastasis.

Criteria for exclusion from the study were: history of another malignancy within 5 years prior to enrollment (except basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix), grade 2 or greater peripheral neuropathy, meningeal carcinomatosis, inadequate organ function, pregnancy or lactation and history of hypersensitivity to products containing polysorbate 80 (Tween 80).

Treatment plan and response assessment

Pretreatment evaluations included the following: complete history and physical examination, assessment of PS, complete blood count, blood chemistry tests to evaluate hepatic and renal function, pregnancy test (if applicable), electrocardiogram, chest radiograph, bone scan, and computed tomography (CT) scan of the chest and upper abdomen. Imaging of the brain was performed if clinically indicated. Baseline tumor assessments were to be performed not more than 3 weeks before registration and laboratory assessments were to be performed not more than 2 weeks before registration.

Treatment consisted of:

1. Carboplatin AUC 5 {dose = AUC×[creatinine clearance (ml/min) + 25]}. The dose of carboplatin was calculated using the formula of Calvert et al. [18], except that the estimated creatinine clearance was used in place of measured glomerular filtration rate.
2. Docetaxel 80 mg/m^2.Both drugs were administered on day 1 of each 3-week cycle by the intravenous route, and treatment continued until there was evidence of progressive disease or unacceptable toxicity. Premedications included antiemetics (granisetron or ondansetron) and dexamethasone 8 mg administered orally twice a day for three consecutive days starting 1 day prior to each infusion of docetaxel. Prophylactic use of granulocyte colony stimulating factor (G-CSF) was prohibited during the initial cycle. Patients who experienced febrile neutropenia or neutropenia for 7 days or more received G-CSF during subsequent treatment cycles. The dose of docetaxel was subsequently reduced if grade 4 leukopenia or febrile neutropenia occurred despite prophylactic treatment with G-CSF.

Treatment was delayed if the ANC was $\leq 1500/mm^3$ or the platelet count was $\leq 100{,}000/mm^3$ on the day of treatment. If recovery was not evident after 2 weeks, the patient was withdrawn from the study. Dose adjustments were made according to the organ system with the greatest degree of toxicity. Patients who experienced grade 3 or worse neurotoxicity were removed from the study; for grade 2 neurotoxicity, the dose of docetaxel was reduced by 25% for subsequent cycles. The dose of docetaxel was reduced by 25% for AST and/or ALT from 1.6 to 5 times the ULN. Docetaxel therapy was withheld for up to 3 weeks for: serum bilirubin above the ULN, ALT, AST or alkaline phosphatase level more than five times the ULN. Patients were removed from further protocol therapy if normalization of serum bilirubin level and reduction in ALT, AST and/or alkaline phosphatase did not return to less than five times the ULN upon withholding therapy for up to 3 weeks.

Tumor assessments (clinical and radiographic) were performed after every two cycles, and at the completion of protocol therapy. Patient response to treatment was categorized as complete response, partial response, stable disease or progressive disease

according to WHO criteria. Complete response, partial response, and stable disease had to be confirmed by two observations performed not less than 4 weeks apart. The duration of complete response was defined as the time from first documentation of complete resolution of disease to first documentation of progressive disease. The duration of partial response was defined as the time from initiation of treatment to the time of disease progression. The time to progression was defined as the interval from the initiation of treatment to the occurrence of progression, or to last contact or initiation of other antitumor therapy. Safety evaluations, including clinical examinations, vital signs, PS assessments and toxicity assessments, were performed prior to therapy and were repeated at each visit. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC 1.0).

Statistical methods

The primary endpoint of the study was the objective response rate. Secondary endpoints included time to progression, overall survival, 1-year survival, and the incidence of toxicity. A two-stage design was used for the study. In the first stage, 20 evaluable patients were enrolled. If at least three responses were observed, an additional 15 evaluable patients were accrued. Primary efficacy analysis was based on evaluable patients. Secondary efficacy intent-to-treat analysis was performed on all treated patients. Safety analysis included all patients who had received at least one dose of study drug. Response rate and duration of response were calculated with a 95% confidence interval. Kaplan Meier estimation was performed for duration of response, time to first response, time to progression and survival.

Table 1 Patient characteristics

	Cohort I Carboplatin AUC 6, docetaxel 80 mg/m^2 *n* (%)	Cohort II (present study) Carboplatin AUC 5, docetaxel 80 mg/m^2 *n* (%)
Number of patients	33	45
Age (years)		
Median	65	62
< 50	4 (12%)	7 (16%)
50–65	10 (30%)	20 (44%)
> 65	19 (57%)	18 (40%)
Sex		
Male	20 (61%)	21 (47%)
Female	13 (39%)	24 (53%)
ECOG performance status		
0	14 (42%)	20 (44%)
1	19 (58%)	24 (53%)
2	0 (0)	1 (2%)
Histology		
Adenocarcinoma	13 (39%)	22 (49%)
Squamous	9 (27%)	8 (18%)
Other	10 (33%)	15 (33%)
Stage		
IIIB	8 (24%)	7 (16%)
IV	25 (76%)	37 (82%)

Results

Patient characteristics

The demographics of the 45 patients enrolled in the study are shown in Table 1. The study included near-equal numbers of male and female patients. Adenocarcinoma was the most common histological subtype. Metastatic involvement of three or more organs was seen in 21 patients. The most frequently involved organs were lung, lymph nodes, liver, bone and adrenal gland. The proportions of patients with ECOG PS 0 and 1 were evenly distributed in the two cohorts. One patient was deemed ineligible as he had an ECOG PS of 2 and a waiver for the protocol deviation was not granted. Ten patients had received prior radiotherapy whereas one patient had received prior surgery. The most common comorbid conditions included cardiovascular (hypertension, coronary artery disease) and pulmonary diseases (chronic obstructive airway disease).

Treatment administration

A total of 235 cycles were administered as part of the study. Patients received a median of 4 cycles (range 1–16 cycles) of chemotherapy. Forty-six per cent of the patients received ≥ 5 cycles. The planned dose of docetaxel was administered in 90% of the treatment cycles. Modification to the dose of carboplatin was necessary in four patients. Seven cycles were delayed due to hematological toxicity for three patients and two cycles were delayed for nonhematological toxicity for two patients. Treatment was discontinued after one cycle in three patients due to progression of disease. One patient who experienced a hypersensitivity reaction to docetaxel was removed from the study. Four patients discontinued treatment due to adverse events attributable to the treatment. The median cumulative doses of carboplatin and docetaxel were 2598 mg and 322 mg/m^2, respectively.

Efficacy

The efficacy data are shown in Table 2. Of the 45 patients, 38 were evaluable for response. One patient had a complete response and ten had a partial response for a combined response rate of 29% (95% CI 16–43%), and 26% of the patients had stable disease. The response rate for the intent to treat population was 24%. Of 11 responding patients, 9 were female. Five of the responders had an ECOG PS of 0, and eight had stage IV disease. Six of the responders had adenocarcinoma and three had squamous cell histology. The median duration of response was 29 weeks. Five patients were censored as of September 2001, because their responses were ongoing. The estimated 1-year survival for patients was 47% (Fig. 1). The median number of cycles administered before maximal response was five.

Safety

Overall, the combination of docetaxel and carboplatin was well tolerated. The hematological toxicities

Table 2 Response to chemotherapy

Parameter	Intent to treat patients		Evaluable patients	
	Cohort I $n=33$	Cohort II $n=45$	Cohort I $n=28$	Cohort II $n=38$
Response				
CR (%)	1 (3)	1 (2)	1 (4)	1 (3)
PR (%)	12 (36)	10 (22)	12 (43)	10 (26)
SD (%)	9 (27)	10 (22)	9 (32)	10 (26)
Not evaluable	5 (15)	7 (16)		
Response rate (CR + PR) (%)	39	24	46	29
95% CI	23–55	13–37	28–63	16–43
Median number of cycles until maximal response	3	5	3	5
Median survival (months)	14.1	10.0	13.5	11.9
Estimated 1-year survival (%)	55	42	54	47
95% CI	37–69	31–62	34–69	31–62
Median TTP (weeks)	18.2	6.4	18.2	6.4
Median duration of response (weeks)	20.9	29.1	20.9	29.1

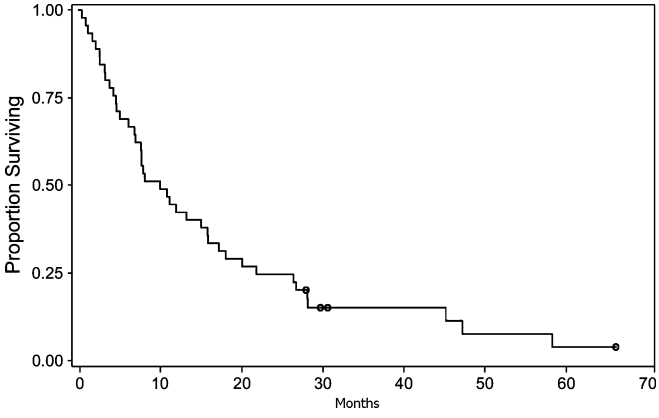

Fig. 1 Kaplan-Meier curve for overall survival

Table 3 Grade 3 and 4 toxicities (NCI-CTC) as number (percent) of patients

Toxicity	Cohort I		Cohort II	
	$n=33$		$n=45$	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematological				
Leukopenia	16 (49)	9 (27)	23 (51)	7 (16)
Neutropenia	2 (6)	27 (82)	4 (9)	32 (71)
Thrombocytopenia	3 (9)	1 (3)	3 (7)	2 (4)
Anemia	5 (15)	3 (9)	5 (11)	0
Nonhematological				
Asthenia	8 (24)	0	2 (4)	0
Nausea	1 (3)	0	3 (6)	0
Diarrhea	1 (3)	1 (3)	2 (4)	0
Vomiting	1 (3)	0	1 (2)	0
Neurosensory	0	0	2 (4)	0

Table 4 Grade 3 and 4 hematological toxicities (NCI-CTC) as number (percent) of cycles

Toxicity	Cohort I		Cohort II	
	$n=152$		$n=211$	
	Grade 3	Grade 4	Grade 3	Grade 4
Leukopenia	58 (38)	11 (7)	56 (27)	16 (8)
Neutropenia	32 (21)	73 (48)	38 (18)	78 (37)
Thrombocytopenia	5 (3)	1 (1)	5 (2)	1 (1)
Anemia	9 (6)	3 (2)	8 (4)	0 (0)

experienced are detailed in Tables 3 and 4. Grade 4 neutropenia was the most common adverse effect experienced by patients. Eight episodes (3.7%) of febrile neutropenia occurred in eight patients (17.8%). All patients who experienced febrile neutropenia had received full doses of docetaxel and carboplatin. The median duration of the nadir was 8 days. Treatment-related infections concurrent with neutropenia were reported in six patients (13%). All of these infections were grade 1 or 2 in severity. The main nonhematological toxicity reported was grade 3 fatigue, which occurred in two patients (Table 3). No treatment-related deaths were reported. Other toxicities that were less than grade 3 in severity included: neurosensory (22%), alopecia (53%), nausea (44%), vomiting (18%), stomatitis (18%) and fever (22%).

Discussion

Several important advances have been made in the treatment of patients with advanced NSCLC in the past few years. Recently completed randomized clinical trials have established the efficacy of platinum-based doublet combination chemotherapy in improving the survival and quality of life for patients with advanced NSCLC [5, 6]. Until the efficacy of non-platinum combination therapies is proven comparable or superior, platinum will continue to be an essential component of combination chemotherapy regimens in advanced NSCLC. The choice of the second agent in the combination is, however, variable. Several of the available second- and third-generation chemotherapy

agents that have been evaluated in clinical trials in combination with platinum have demonstrated comparable efficacy. Hence the choice of the second agent is largely dictated by the therapeutic index of the drug. The efficacy of docetaxel in combination with cisplatin in advanced NSCLC has been evaluated in phase II clinical trials [14, 15]. This combination was also included as one of the experimental arms in the ECOG 1594 trial [5]. We performed a multicenter phase II study to evaluate the efficacy of docetaxel in combination with carboplatin in the treatment of patients with previously untreated advanced NSCLC, the results of which are reported here.

The first cohort of our study included 33 patients who received carboplatin at a dose of AUC 6 and docetaxel at 80 mg/m^2. Since febrile neutropenia occurred in 24% of the patients in this cohort, the dose of carboplatin was reduced to AUC 5 for 45 patients who were subsequently enrolled in the study. While the study was neither a randomized trial nor was it designed to compare cohorts I and II, we noted some interesting differences in results between the two groups. The results from the first cohort of patients are also included in the Tables 1, 2, 3 and 4 to illustrate the differences in baseline characteristics and outcome for patients in the two cohorts. There were minor differences in the baseline characteristics of the patients in the two cohorts. Cohort I consisted of more males and a higher percentage of patients with age above 65 years. The majority of patients in both cohorts had stage IV NSCLC. Patients in cohort II who received a lower dose of carboplatin had an overall response rate of 24% with a median survival of 10 months. The estimated 1-year survival was 42%. This was lower than the response rate of 39% and a median survival of 14.1 months reported in the first cohort of patients. Patients in cohort II also had a shorter median time to progression. Relatively fewer hematological toxicities occurred in cohort II, with a lower incidence of grade 3/4 neutropenia and thrombocytopenia. The incidence of febrile neutropenia was also lower, occurring in 17.8% of the patients in cohort II and in 24.2% in cohort I.

The lower response rate and survival noted with the cohort of patients who received the lower carboplatin dose raises the question as to whether a relationship between carboplatin dose and response exists in the combination of carboplatin and docetaxel. Patients in the second cohort received a cumulative dose of carboplatin of 2598 mg (per patient) compared to 2970 mg in the first cohort. The cumulative dose of docetaxel received by the patients in the second cohort was also lower (322 mg/m^2 vs 396 mg/m^2). However, the median docetaxel dose intensity per week was similar in the two groups (26.7 mg/m^2). For carboplatin, the median dose intensity per week was 221 mg for the first cohort and 192 mg for the second cohort.

Jodrell et al. performed a retrospective analysis to determine the relationship between tumor response and carboplatin AUC in patients with ovarian cancer [19]. The analysis included 1028 patients with advanced ovarian cancer who received single-agent chemotherapy with carboplatin. The study showed an increasing likelihood of tumor response with an increase in carboplatin dose, up to an AUC of 7. When the carboplatin dose increased beyond AUC 7, there was an increase in toxicity without any appreciable increase in response. In a prospective Danish study in which two different dose levels of carboplatin (AUC 4 and AUC 8) were evaluated in patients with advanced ovarian cancer, an improvement in response with the higher dose of carboplatin could not be demonstrated [20]. In another study that analyzed the effect of carboplatin dose in patients with testicular cancer, Childs et al. showed that the proportion of treatment failure was higher among patients who received carboplatin at a dose less than AUC 5 [21]. While based on the results of our study, it is not possible to draw any conclusions on the association between the lower dose of carboplatin and the inferior therapeutic response, it is an interesting observation that warrants consideration in future trials when the use of a lower dose of carboplatin is contemplated.

Other investigators have also evaluated the combination of docetaxel and carboplatin in advanced NSCLC (Table 5). Zarogoulidis et al. reported the results of a phase II study of docetaxel and carboplatin in the treatment of inoperable NSCLC [22]. About one-third of patients in their study had stage IIB and IIIA NSCLC and patients above the age of 70 years were excluded. Treatment consisted of carboplatin at a dose of AUC 6 and docetaxel at 100 mg/m^2 administered every 4 weeks up to a maximum of eight cycles. There were 5 complete

Table 5 Phase II studies of docetaxel/carboplatin administered every 3 weeks as first-line treatment for advanced NSCLC

Reference	Number of patients	Regimen	Overall response rate (%)	Median survival (months)
23	30	Docetaxel 90 mg/m^2 day 1; carboplatin AUC 5 day 1	30	13.2
25	45	Docetaxel 75 mg/m^2 day 1; carboplatin AUC 6 day 1	37	Not reported
26	20	Docetaxel 75 mg/m^2 day 1; carboplatin AUC 6 day 1	45	12
27	25	Docetaxel 60 mg/m^2 day 1; carboplatin AUC 6 day 1	35	10.4
28	20	Docetaxel 80 mg/m^2 day 1; carboplatin AUC 6 day 1	55	Not reported

responders and 49 partial responders, for an overall response rate of 44%. The median survival was 12 months with a 1-year survival of 26.6%. Schuette et al. used carboplatin at a dose of AUC 5 mg/ml·min in combination with docetaxel 90 mg/m^2 and observed a response rate of 30% in a study that included 30 patients [23].

The results of a large randomized clinical trial in which the efficacy of docetaxel in combination with cisplatin or carboplatin was compared with that of the control arm of cisplatin and vinorelbine were reported recently [24]. The carboplatin dose was AUC 6 mg/ml·min in combination with docetaxel 75 mg/m^2. This was associated with the most favorable toxicity profile and the efficacy was similar to that of the control arm of cisplatin/vinorelbine. Thus the recommended dose of carboplatin is AUC 6 mg/ml·min when administered with docetaxel. In conclusion, our study, along with data presented from similar studies, established the efficacy of the combination of carboplatin and docetaxel in the first-line treatment of patients with advanced NSCLC.

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