

## Docetaxel and Carboplatin as First-line Therapy in Advanced Non-small Cell Lung Carcinoma: A Phase II Study

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**Abstract.** *Background:* Taxanes have been widely used against advanced non-small cell lung cancer (NSCLC), alone and in combination with platinum agents. In order to develop a tolerable palliative regimen, we combined carboplatin with low dose docetaxel. *Patients and Methods:* Chemotherapy-naïve patients, with Stage IIIB or IV NSCLC and an ECOG performance status  $\leq 2$ , were enrolled. Treatment consisted of docetaxel 60 mg/m<sup>2</sup> and carboplatin AUC 6 every 21 days. Therapy continued for 1 year or 6 months beyond best response, whichever was greater. *Results:* Twenty-five patients were enrolled. Most patients (80%) had Stage IV disease. The partial response rate was 16%. Response duration ranged from 6 to 115 weeks. Median survival was 55 weeks. Toxicity was generally limited to grade 3 or 4 neutropenia. There was 1 septic death. *Conclusion:* Survival compared favorably to other similar trials employing higher doses of docetaxel. Additionally, a hematologic toxicity advantage was seen compared to regimens containing higher doses of docetaxel.

Most patients with non-small cell lung cancer (NSCLC) present with either locally advanced or metastatic disease (Stage III inoperable or Stage IV). With chemotherapy, newly diagnosed advanced NSCLC patients have an expected median survival of 6 to 8 months (1,2).

Current treatment goals in this patient population are to break this survival barrier and reduce disease and

treatment-related adverse effects. Platinum and taxane doublets are the accepted regimen based on safety and efficacy profiles. Although paclitaxel is more commonly used in NSCLC, docetaxel has shown single-agent activity at doses ranging from 60 to 100 mg/m<sup>2</sup> in chemotherapy-naïve patients (3-6), as well as in patients failing previous cisplatin-based regimens (7-9). At the time this study was initiated, docetaxel had exhibited promising activity and acceptable toxicity when combined with cisplatin or carboplatin in phase I and phase II trials in NSCLC (10). Additionally, it was approved in 2002 for first-line treatment of locally advanced or metastatic NSCLC in combination with cisplatin.

When choosing a platinum agent, carboplatin is more appealing in the clinic setting and to the patient compared to cisplatin. As an analogue of cisplatin, carboplatin shows similar efficacy in the NSCLC population with less emetogenicity, neurotoxicity and ototoxicity, while its lower nephrotoxicity allows administration without additional hydration therapy.

### Patients and Methods

*Patient population.* Chemo-naïve adult patients, with histologically or cytologically proven Stage IIIB (with malignant pleural effusion) or Stage IV NSCLC, were eligible for this open-label, non-randomized, multicenter trial. Patients with measurable or evaluable disease, Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , no previous or concurrent malignancy (except *in-situ* carcinoma of cervix or non-melanoma skin cancers), were enrolled. All patients were required to have adequate renal, hepatic and bone marrow function. The protocol was reviewed and approved by the Institutional Review Boards (IRBs) of the participating study centers. All patients signed a written informed consent before treatment was initiated.

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Table I. Summary of baseline characteristics.

Characteristics	Patients
Number of patients	25
Male/female	16/9
Median age (range), years	67 (51-80)
ECOG performance status (%)	
0	12 (48%)
1	10 (40%)
2	3 (12%)
Stage (%)	
IIIB	5 (20%)
IV	20 (80%)
Histological subtype (%)	
Adenocarcinoma	15 (60%)
Squamous cell carcinoma	4 (16%)
Large cell carcinoma	2 (8%)
Adenosquamous	1 (4%)
Papillary	1 (4%)
Large cell squamous	1 (4%)
Bronchioalveolar adenocarcinoma	1 (4%)
Prior radiation	5 (20%)

ECOG: Eastern Co-operative Oncology Group

**Treatment plan.** Docetaxel (Taxotere® - Aventis Pharmaceuticals, Bridgewater, NJ, USA) was administered intravenously (*i.v.*) at a dose of 60 mg/m<sup>2</sup> over 1 hour. Carboplatin (Paraplatin® - Bristol Meyers, Princeton, NJ, USA) was dosed to an AUC of 6 mg/mL/min by Calvert's formula (11). Estimated creatinine clearance, calculated by the Jelliffe formula, was substituted for measured glomerular filtration rate (12). Carboplatin was administered *i.v.* immediately after the docetaxel infusion. Treatment was given every 3 weeks.

Patients took dexamethasone 8 mg orally twice daily for 3 days starting the day before chemotherapy and antiemetics were administered at the discretion of the investigator. The prophylactic use of granulocyte colony stimulating factors (G-CSF) was not permitted during the first cycle.

Toxicities were graded using the NCI Common Toxicity Criteria and appropriate dose reductions for toxicity were permitted. Patients with afebrile grade 4 neutropenia or leukopenia for longer than 7 days or grade 4 neutropenia or leukopenia associated with fever were re-treated with the same dose after recovery with prophylactic G-CSF 5 mcg/kg/day for subsequent cycles. If the toxicity persisted despite the use of G-CSF, the docetaxel dose was decreased by 25% in all succeeding cycles. Grade 4 thrombocytopenia (platelet count  $\leq 25,000/\text{mm}^3$ ) required a 25% dose reduction of both docetaxel and carboplatin. A maximum of two 25% dose reductions of docetaxel was allowed (to 34 mg/m<sup>2</sup>).

Patients with stable or responding disease continued to receive treatment for 1 year or for 6 months beyond best response, whichever was greater. The ideal number of cycles was not known when this protocol was written. Patients with progressive disease were removed from the study. Protocol therapy was discontinued if any of the following toxicities occurred: grade 3 neurotoxicity, grade 4 hypersensitivity reactions (or 2 grade 3 hypersensitivity reactions), abnormal liver function tests persisting for more than 3 weeks, or

Table II. Objective response.

	Intent-to-treat population (n=25) n (%)	Evaluable population (n=19) n (%)
Partial response	4 (16)	4 (21)
Stable disease	10 (40)	10 (53)
Disease progression	5 (20)	5 (26)
Not assessable	6 (24)	NA

NA = not applicable

any persistent grade 3 nonhematologic toxicity or grade 4 hematologic toxicity at a docetaxel dose of 34 mg/m<sup>2</sup> with G-CSF.

**Study evaluations.** Prior to the administration of study medications, patients underwent a complete history, physical examination, computed tomography (CT) scans of the chest and upper abdomen, bone scan, chemical profile including electrolytes, blood urea nitrogen (BUN), creatinine, AST, ALT, alkaline phosphatase, calcium, uric acid and complete blood counts (CBC). History, physical examination and blood tests were repeated every 3 weeks, on the day of treatment and CBC was drawn weekly. Patients underwent radiographic disease assessment every 2 cycles (6 weeks).

**Criteria for response and toxicity.** Responses were defined as follows: complete response (CR)- disappearance of all measurable or evaluable disease for a minimum of 4 weeks; partial response (PR)- a 50% or greater decrease in the sum of the product of the diameters of the measurable indicator lesions for a minimum of 4 weeks and no simultaneous increase in the size of any lesion or the appearance of a new lesion; stable disease (SD)- no increase in size and no new lesions or disease that have not decreased in size sufficiently to qualify as a partial response; progressive disease (PD)- any new lesion or any increase in the size of an existing lesion as measured by CT, magnetic resonance imaging (MRI), or X-ray, or at least a 50% increase in the product of the diameters of any lesion measured by physical examination, as compared to either on study or to best response. New pleural effusions and cancer-related death were classified as progression.

Duration of response was determined by measuring the time of partial or complete response to the time of documented disease progression. Duration of survival was measured from the first day of chemotherapy to day of death.

Toxicities were graded on a scale of 1 to 5 using the NCI Common Toxicity Criteria. All registered patients were evaluable for toxicity and included in the intent-to-treat analysis (ITT) for response. Patients that received at least 2 cycles of therapy and were assessed at least once for response were considered part of the evaluable population.

The target enrolment for this study was 50 patients. If a response rate was  $\leq 16\%$  in the first 25 patients, there was a 95% probability that the maximum response rate was  $\leq 31\%$  and the study would be stopped.

Continuous data were summarized using descriptive statistics, including mean, median, minimum and maximum values. Survival time and other time-to-event estimates were calculated by Kaplan-Meier analyses.

Table III. Hematologic and nonhematologic toxicity by patient and cycle [n (%)].

Toxicity	Grade 3		Grade 4	
	By patient (N=25)	By cycle (N=150)	By patient (N=25)	By cycle (N=150)
Hematologic				
Neutropenia	16 (64.0)	41 (27.3)	11 (44.0)	42 (28.0)
Leukopenia	11 (44.0)	37 (24.7)	1 (4.0)	1 (0.7)
Thrombocytopenia	2 (8.0)	2 (0.7)	0	0
Nonhematologic				
Nausea	1 (4.0)	1 (0.7)	0	0
Fatigue	2 (8.0)	4 (2.7)	0	0
Anorexia	0	0	1 (4.0)	1 (0.7)
Allergic reactions	1 (4.0)	1 (0.7)	0	0
Infection*	0	0	2 (8.0)	2 (1.3)
Pulmonary	2 (8.0)	2 (1.3)	2 (8.0)	2 (1.3)
Cardiac arrhythmia	1 (4.0)	1 (0.7)	0	0

\* There was one septic death

## Results

Between July 1997 and July 1999, 25 patients were enrolled into this study. The median age was 67 years (range: 51-80). Most patients (80%) had Stage IV disease and five patients (20%) had received prior radiation. Patient characteristics at baseline are listed in Table I.

Response rates are summarized in Table II. In the ITT population (N=25), there were 4 partial responses (16%), 10 patients (40%) with stable disease and 5 patients (20%) with disease progression. Six patients (24%) were not eligible for response evaluation. The 6 inevaluable patients received 0-1 cycles (1 registered but was not treated, 2 were removed from study by investigator due to early progression, 2 died within or after the first cycle and 1 was lost to follow-up). The response rate in the evaluable population (N=19) was 21%. The duration of response for the 4 patients with partial responses ranged from 6 to 115 weeks. Additionally, a total of 159 cycles were administered. The median number of cycles per patient was 6, with a range from 1 to 34.

Median survival in the ITT population was 54 weeks (range 1-214 weeks) or 12.5 months. Two patients remained alive 37 and 49 months from enrollment.

Table III summarizes the toxicity data by patient and cycle for the ITT population. Serious side-effects were generally limited to hematologic toxicity with grade 3 and 4 neutropenia. No grade 3 or 4 anemia or grade 4 thrombocytopenia occurred and there were 2 cycles in which grade 3 thrombocytopenia occurred in 2 patients. There was 1 septic death, which was potentially related to treatment.

Grade 4 nonhematologic toxicity was confined to infection in 2 patients, pulmonary toxicity (dyspnea, pleural effusion and respiratory distress) in 2 patients and anorexia in 1 patient. One patient each experienced grade 3 nausea, anorexia and weakness. Two patients experienced grade 3 fatigue during a total of 4 cycles.

## Discussion

The combination of docetaxel and carboplatin was well tolerated in this population of advanced NSCLC patients. Additionally, it demonstrated a positive efficacy profile with a median survival of 12.5 months in the ITT population. Single agent docetaxel is active in the dose range of 60 to 100 mg/m<sup>2</sup> in advanced NSCLC (13). We deliberately chose a dose at the lower end of its therapeutic range, hypothesizing that, in combination with carboplatin at full therapeutic doses, it would be just as efficacious with a more favorable toxicity profile. Although our response rate was not as high as other docetaxel/carboplatin combinations, which range from 27-43% (14-19), our median survival results (12.5 months) were similar to the 13.9-month median survival reported by Belani *et al.*, with a docetaxel dose of 80 mg/m<sup>2</sup> and carboplatin AUC of 6 mg/mL/min (14). Our results were also comparable to the 13.3-month survival seen by Schütte *et al.* with docetaxel 90 mg/m<sup>2</sup> and carboplatin AUC of 5 mg/mL/min (15).

Since advanced NSCLC is considered incurable, quality of life becomes a prime consideration when initiating treatment. Both hematologic and nonhematologic toxicities in our study compared favorably to other studies using docetaxel/carboplatin combinations in advanced NSCLC, with an advantage seen in our study with a reduction in hematologic toxicity (14). Three studies using higher doses of docetaxel (75 mg/m<sup>2</sup>-100 mg/m<sup>2</sup>) (14,17,19) with carboplatin AUC 6 reported higher rates of grade 4 neutropenia and febrile neutropenia compared to our study. Specifically, grade 4 neutropenia was seen in 73-79% (14,17) of patients and febrile neutropenia was seen in 10-26% of patients (14,17,19). Our study demonstrated dramatically lower rates with only 44% of patients demonstrating grade 4 neutropenia, 64% with grade 3 neutropenia and one septic death.

Our study also reported low rates of non-hematologic toxicity, which are consistent with other docetaxel/carboplatin combinations (14,17,19). Neurotoxicity, a concern with paclitaxel/carboplatin combinations, was absent.

## Conclusion

Randomized trials of cytotoxic chemotherapy in NSCLC in recent years have yielded similar efficacy results across the board, mainly employing platinum-based doublets, with no regimen clearly showing superiority over any other (20). We hope that the addition of novel biologics will break the

current efficacy plateau, although the recent phase III results of gefinitib (Iressa, Astra-Zeneca), given concurrently with either cisplatin and gemcitabine or paclitaxel and carboplatin, have not shown superior survival outcomes (21,22). While we await further improvements in the efficacy of NSCLC treatment, factors such as toxicity, cost and convenience will drive our decision making process in choosing an appropriate regimen. As shown, docetaxel at a conservative dose in combination with carboplatin, demonstrates favorable efficacy in the treatment of advanced NSCLC. The low dose of docetaxel used in our study minimized the neutropenia commonly seen with higher docetaxel doses or with paclitaxel. Additionally, the substitution of docetaxel for paclitaxel avoided the additive neurotoxic effects commonly seen with paclitaxel and carboplatin. Docetaxel 60 mg/m<sup>2</sup> and carboplatin AUC 6 may be a viable option for patients with advanced NSCLC to minimize treatment-related toxicities while maintaining therapeutic efficacy.

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