

Bi-weekly Administration of Docetaxel and Gemcitabine as First-line Therapy for Non-small Cell Lung Cancer: A Phase II Study

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Abstract. *Background:* The standard treatment for advanced non-small cell lung cancer (NSCLC) currently consists of platinum-based, combination chemotherapy of limited efficacy and possible toxicity. The bi-weekly administration of docetaxel and gemcitabine for advanced NSCLC was evaluated in a phase II study (objective response rate, median survival, median duration of response and safety). *Patients and Methods:* A total of 170 cycles were administered to 31 patients with advanced NSCLC and a median age of 66 years (range 47-75 years). Patients received docetaxel 80 mg/m² and gemcitabine 1000 mg/m² on days 1 and 14 of a 28-day cycle. *Results:* Sixteen patients achieved a PR (16/31, 55.2%), 3 patients had SD (3/31, 10.3%) and 10 (10/31, 34.5%) had PD. The median time to disease progression was 3 months (range 0-12 months) with a mean survival of 10 months (range 3-31 months). Haematological and non-haematological toxic effects were generally mild to moderate and manageable: Grade 3 neurotoxicity and allergy occurred in 2 patients (6.4%) and 1 patient (3.2%), respectively. Peripheral neuropathy, mostly grades 1 and 2, was reported in 24 patients (77.4%). *Conclusion:* The bi-weekly administration of a docetaxel/gemcitabine combination with G-CSF support constitutes a tolerable and convenient regimen for the treatment of advanced NSCLC, with efficacy similar to that reported in other regimens.

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Hence, this non-platinum-based regimen appears promising and warrants further evaluation.

Lung cancer remains the leading cause of malignancy-related death in the Western world, with non-small cell lung cancer (NSCLC) accounting for approximately 75% of those cases. Treatment options for patients with NSCLC remain obscure since most patients are diagnosed with metastatic disease (stage IV) and, without systemic chemotherapy, have a median survival of 6 months, with less than 10% alive at 1 year (1). Platinum-based chemotherapy confers a small but statistically significant survival benefit and control of symptoms in this group of patients when compared to the best supportive care (2-6). Furthermore, platinum-based chemotherapy regimens improve overall survival and achieve symptom management in stage IIIA and IIIB, when combined with surgery or radiotherapy (7-9). Nevertheless, the positive impact of cisplatin in NSCLC patients is accomplished at the cost of significant toxicity, due to its low therapeutic index, and includes nephrotoxicity, peripheral neuropathy, hearing loss, nausea and vomiting (10).

Recently, meta-analysis has demonstrated that combination chemotherapy is superior to single-agent chemotherapy, producing an almost 2-fold increase in the response rate and a modest improvement in 1-year survival (11). Several newer agents, such as taxanes (paclitaxel and docetaxel), vinorelbine and gemcitabine have been used in combination with cisplatin (12-17). However, again, according to the same meta-analysis, platinum-based combination chemotherapy had a 3.6-fold increase in the risk of treatment-related death compared with single-agent regimens in patients with NSCLC (11). Based on the above data, several research groups have questioned the standard inclusion of platinum in combination chemotherapy for NSCLC (18). In fact, the combinations of gemcitabine and

vinorelbine (19), gemcitabine and paclitaxel (20) and gemcitabine and docetaxel (21) have shown that non-platinum-containing combinations offer similar median and 1-year survival rates as those containing platinum. Hence, efforts are being aimed at identifying the best possible alternative combinations and associated dosing schedules, while taking symptom control and quality of life issues into consideration.

A preliminary phase II trial was conducted in order to evaluate the feasibility, tolerability and activity associated with administering the gemcitabine/docetaxel combination on a bi-weekly basis, as first-line treatment for inoperable NSCLC.

Patients and Methods

Eligibility criteria. Chemotherapy-naïve patients, aged ≤ 75 years, with histologically or cytologically confirmed unresectable stage IIIB with pleural effusion (IIIBw), IV or relapsed post-operative metastatic NSCLC, were included in the study. Other eligibility criteria included an age > 18 years; Eastern Cooperative Oncology Group (ECOG) (23) performance status ≤ 2 ; life expectancy ≥ 12 weeks; at least one bi-dimensional, measurable lesion (2 cm x 2 cm minimum) situated outside previously irradiated locations; adequate haematological (absolute neutrophil count [ANC] $\geq 1,500/\mu\text{L}$, platelet count $\geq 120,000/\mu\text{L}$, renal (serum creatinine ≤ 1.5 x upper limit) and hepatic (bilirubin ≤ 1.5 x upper normal limit, serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) ≤ 2.5 x upper normal limit) functions.

Patients were excluded if they had a history of neoplasm (except for carcinoma-*in-situ* of the cervix or basal-cell carcinoma of the skin), cardiac disease (uncontrolled hypertension, unstable angina, congestive heart failure, second or third degree heart block, myocardial infarction within the previous year, cardiac ventricular arrhythmias requiring medication), peripheral neuropathy, a psychiatric disorder, serious active infection or allergic reaction. Females of childbearing potential required a negative serum or urine pregnancy test within 48 hours of enrolment and had to take adequate contraceptive measures during the study. Pregnant or lactating women were excluded. Patients with previous radiotherapy, either in the adjuvant setting, or for the treatment of bone metastases, were included provided the measurable disease was outside the radiation fields, therapy was completed 4 weeks prior to starting treatment, they had recovered from all adverse effects and had less than 30% of the marrow-bearing bones irradiated. Additionally, major surgery must have been completed at least 2 weeks prior to enrolment. Patients with brain metastases were also included if the previously irradiated brain lesions presented clinical and radiological improvement. The study was approved by the local hospital review board and ethics committee and was conducted in accordance with the Helsinki declaration. All patients gave their written, informed consent to participate in the study.

Treatment plan. Pre-treatment evaluation included a complete medical history and physical examination, laboratory tests (haematology and standard biochemistry), chest radiographs, electrocardiogram (ECG) and an isotopic whole-body bone scan.

Table I. Patient characteristics.

	Patients	
	Number	%
Total	31	100
Sex		
Male	28	90.3
Female	3	9.7
Age (years)		
Median	66	
Range	47-75	
ECOG performance status		
0	5	16.1
1	21	67.8
2	5	16.1
Histology		
Adenocarcinoma	13	
Large cell carcinoma	4	
Squamous cell carcinoma	12	
Other	2	
Smoking exposure		
Packs per year: 0	4	12.9
: 1-40	5	16.1
: 41-60	9	30.1
: 61-80	8	25.8
: 81+	5	16.1

The tumour site was assessed by physical evaluation and computed tomography (CT) scans of the thorax, abdomen and brain. During the course of treatment, a physical examination, an ECG, a blood-cell count with differential and platelet count and standard biochemical assessment preceded each cycle. Tumour lesions were measured after every cycle, if assessable by physical examination, and evaluated by CT scans after the 3rd and 6th cycle.

Standard WHO toxicity and response criteria were used. All objective response rates had to be validated by two independent observers and maintained for at least 4 weeks. Upon study completion or discontinuation, disease status follow-up as well as survival and tolerance monitoring were performed every 2 months until disease progression. After progression, survival follow-up continued every 3 months.

Patient treatment. Gemcitabine 1,000 mg/m² was administered diluted in 500 ml 5% dextrose and was followed by docetaxel 80 mg/m² diluted in 500 ml 5% dextrose. Treatment was administered on an out-patient basis on days 1 and 14. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) was given prophylactically (150 µg/m²/d subcutaneously on days 8-10 and days 21-23 or until the ANC was $> 1,200 \mu\text{L}$ on 2 consecutive measurements after the nadir). Cycles were repeated every 28 days. Standard antiemetic treatment consisted of 8 mg ondansetron

Table II. *Toxicities.*

Toxicity	Number of Patients (%)			
	Grade NCI-CTC ^a			
	1	2	3	4
Dermopathy	6 (19.4)	6 (19.4)	-	-
Alopecia	9 (29.0)	21 (67.8)	-	-
Neurotoxicity	15 (48.4)	7 (22.6)	2 (6.4)	-
Anaemia	18 (58.1)	5 (16.1)	-	-
Neutropenia	10 (32.3)	9 (29.0)	-	-
Diarrhea	10 (32.3)	3 (9.6)	-	-
Nausea	10 (32.3)	9 (29.0)	-	-
Allergy	14 (45.2)	4 (12.9)	1 (3.2)	-

^aThe National Cancer Institute Common Toxicity Criteria

administered intravenously before treatment and 8 mg oral ondansertion ingested 3 times daily for 2 to 3 days. All patients received standard pre- and post-medication with oral dexamethasone. Treatment was continued in the absence of disease progression and unacceptable toxicity for a maximum of 6 cycles.

Treatment modifications. A 25% dose reduction of both drugs was performed in subsequent cycles if chemotherapy-induced febrile neutropenia, grade 4 neutropenia, thrombocytopenia or hepatotoxicity (bilirubin or persistent elevated transaminases grade 3) occurred. In addition, the doses of docetaxel alone were reduced by 25% in the event of severe myalgia/arthralgia or peripheral neurotoxicity grade 3. Dose re-escalations were not permitted.

Statistical analysis. Overall survival (OS), overall response rate (ORR), time to progression (TTP) and toxicity were assessed in all enrolled patients on an intention-to-treat basis. All patients that received at least 1 cycle were assessed for toxicity. The duration of response was calculated from the day of the first documented response until disease progression; TTP was measured from the date of enrolment until the first evidence of disease progression; OS was measured from study entry until death. For time events, the actuarial survival function was estimated by the Kaplan-Meier method.

Results

Between June 2000 and July 2001, a total of 31 patients (28 men and 3 women) with NSCLC, treated in the Oncology Unit, Third Department of Medicine, Sotiria General Hospital, Athens, Greece, were enrolled in the study. Patients had a median age of 66 years (range 47-75 years). With regard to performance status (PS), 5 patients had a PS of 0 (5/31, 16%), 21 patients had a PS of 1 (21/31, 68%) and 5 patients had a PS of 2 (5/31, 16%). All patients were evaluated for toxicity and 29 patients for response. The majority of patients were stage IV (27/31, 87%) and 2 had

previously received adjuvant chemotherapy. A total of 170 cycles were administered to 31 patients, with a median of 5 cycles per patient (range 1-6) and a mean interval between courses of 28 days (Table I).

Toxicity. The major haematological and non-haematological toxicities associated with this regimen are shown in Table II. Grade 3 neurotoxicity and allergy occurred in 2 patients (6.4%) and 1 patient (3.2%), respectively. Peripheral neuropathy, mostly grades 1 and 2, was reported in 24 patients (77.4%) and was no more severe or prolonged than expected for single-agent docetaxel. No grade 4 toxicity was observed. Non-haematological and haematological toxic effects were generally mild to moderate and entirely manageable.

Response and survival. The response rate was evaluated in 29 patients. Of these, 16 patients achieved a PR (16/31, 55.2%), 3 patients had SD (3/31, 10.3%) and 10 (10/31, 34.5%) had PD. The median time to disease progression was 3 months (range 0-12 months), with a mean survival of 10 months (range 3-31 months) (Figure 1). None of the factors studied (histological subtype, degree of differentiation, EORTC PS, smoking exposure (number of packs per year) and number of chemotherapy cycles administered) correlated with the response rate.

Discussion

The recent development of newer active antineoplastic agents, such as taxanes, gemcitabine and vinorelbine, has provided us with the opportunity to challenge the predominant role of platinum-based regimens in the treatment of inoperable NSCLC. In fact, several randomised studies, evaluating combinations of these newer agents, have produced equal, if not superior results, regarding response rate, disease-free survival, 1-year survival, overall survival and quality of life, when compared to platinum-based regimens. Hence, research is now focused on the development of optimal combination and dose scheduling in order to establish the best possible outcome with the minimum toxicity.

Gemcitabine, a deoxycytidine analogue, has demonstrated a satisfactory role as a first-line treatment of NSCLC, either alone or in combination. Docetaxel is a semi-synthetic taxoid that promotes the assembly of stable microtubules *in vitro* and blocks mitosis in proliferating cells. When administered as a single agent, objective response rates ranging from 26% to 54% and from 7% to 10% have been achieved in chemotherapy-naïve and refractory/resistant NSCLC patients, respectively (22). Its combination with cisplatin has resulted in objective response rates of 33% to 46% and a median survival time of 8.4 to 13 months. The definite role

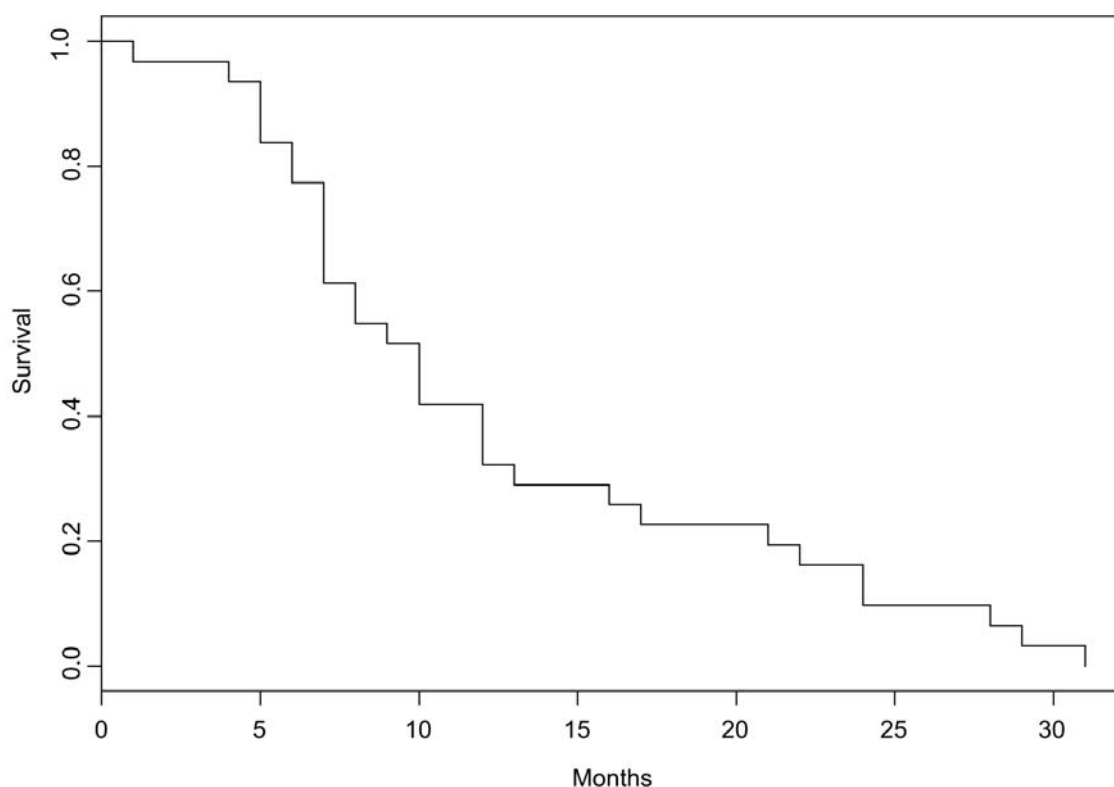


Figure 1. *Kaplan-Meier survival curve of the patients treated with the docetaxel/gemcitabine regimen.*

of docetaxel in NSCLC, along with its favourable toxicity profile, has prompted several investigators to combine it with other active agents. Several studies have evaluated the combination of docetaxel with gemcitabine in a 21-day administration schedule, with efficacy and toxicity comparable to those observed in platinum combinations: docetaxel was administered at doses of 75-100 mg/m² every 21 days and gemcitabine at doses of 800-1,000 mg/m² on days 1 and 8 of a 21-day cycle. In an attempt to increase efficacy and improve the toxicity profile, several schedules have been proposed that administer docetaxel either on days 1 or 8 of a 21-day cycle (23, 24). Others have attempted to administer both agents on a weekly basis, but a high incidence of severe pulmonary adverse events was observed in terms of diffuse interstitial pneumonitis manifested with dyspnoea, hypoxia and fever.

In our study, increased doses of both agents were administered on a bi-weekly schedule, along with G-CSF support, in an attempt to improve efficacy at the lowest possible toxicity cost. We were, in fact, able to administer docetaxel at 80 mg/m² and gemcitabine at 1,000 mg/m² every 2 weeks, along with prophylactic administration of G-CSF on days 8-10. Since the chemotherapy schedule was

administered on an outpatient basis, it proved convenient for both the patients and the hospital oncology unit. With regard to toxicity, the chemotherapy regimen was well tolerated, with completely manageable mild to moderate haematological and non-haematological toxic effects that did not require dose reductions or cycle delays. Only 2 patients experienced grade III neurotoxicity, while there was no incidence of haematological toxicity grade III or diffuse interstitial pneumonitis. With regard to efficacy, our study achieved an overall response rate of 65.5% (19 patients), an overall median survival time of 10 months (range 3-31 months) and a median time to disease progression of 3 months (range 0-12 months). Our data are comparable with previous studies, substantiating the assertion that non-platinum-based regimens combining newer agents are as equally effective as platinum-based combinations (25-27).

In conclusion, our study suggests that the bi-weekly administration of docetaxel and gemcitabine is a safe, well tolerated and convenient chemotherapy regimen for the treatment of advanced NSCLC, with efficacy similar to that reported in other regimens. Hence, this non-platinum-based regimen appears promising and warrants further evaluation.

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