Biweekly Administration of Docetaxel and Gemcitabine as Adjuvant Therapy for Stage II and IIIA Non-small Cell Lung Cancer: A Phase II Study

KONSTANTINOS N. SYRIGOS[1], MARIOS KONSTANTINOU[2], EVANGELLOS SEPSAS[3], GEORGE PAPAMICHALES[3], ACHILLEAS LOULLIAS[2], IONAS BELENIS[4], IONAS SKOTTIS[3], ANDRIANI CHARPIDOU[1] and CHARALAMBOS ROUSSOS[4]

[1]Oncology Unit, Third Department of Medicine, Athens School of Medicine,
[2]Second Department of Thoracic Surgery and
[3]First Department of Thoracic Surgery, Sotiria General Hospital, Athens;
[4]Department of Intensive Care and Respiratory Medicine, Athens School of Medicine, Evangelismos General Hospital, Athens, Greece

Abstract. *Background: The aim of this study was to determine the overall survival, progression-free survival, and toxicity associated with adjuvant administration of docetaxel and gemcitabine for completely resected patients with stage II and IIIA non-small cell lung cancer (NSCLC). Patients and Methods: Thirty-nine eligible patients had surgical resection for pathological stage II or IIIA disease and received postoperative gemcitabine 1000 mg/m^2 followed by docetaxel 80 mg/m^2 on days 1 and 14. Cycles were repeated every 28 days. Results: Treatment compliance was acceptable, at 83%. The median duration of follow-up, time to disease progression, and overall survival was 36.7 months, 17 months and 21 months, respectively. Toxicities were acceptable. Treatment failure revealed brain metastasis (15%), intrathoracic recurrence (24%) and systemic metastasis (36%). Conclusion: The biweekly administration of docetaxel and gemcitabine is a safe, well-tolerated and convenient chemotherapy regimen in the adjuvant setting of completely resected NSCLC stage II and III, with efficacy similar to that reported in other regimens. Hence, this non-platinum based regimen appears promising and warrants further evaluation.*

Correspondence to: Konstantinos N. Syrigos, MD, Ph.D., Asst. Prof. of Oncology in Medicine, Athens University School of Medicine, Head, Oncology Unit, Third Department of Medicine, Athens School of Medicine, Building Z, Sotiria General Hospital, Mesogion 152, 115 27 Athens, Greece. Tel: +30 210 7475034, Fax: +30 210 7781 035, e-mail: knsyrigos@usa.net / ksyrigos@med.uoa.gr

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Although complete surgical resection is the optimal management of patients with operable non-small cell lung cancer (NSCLC), yet the five-year overall survival rate is only 23-67%, depending on the size of the primary tumour and the lymph node involvement (1). Postoperative radiotherapy decreases the rate of local recurrence in stage IIIA disease but it has a questionable effect in patients with stage I and II (2). Moreover, post-surgical relapse occurs two to three times more frequently at distant sites, rather than locally. Adjuvant systemic chemotherapy has gained an established role in malignancies, such as breast and colorectal cancer, and recently there is a rapidly growing body of evidence that it might also have a role in NSCLC (3).

The randomized International Adjuvant Lung Cancer Trial (IALT) is the largest conducted trial of adjuvant chemotherapy: it included 1,867 patients with completely resected stage I, II or IIIA NSCLC treated with a cisplatin-based two-drug regimen. It demonstrated a clear, statistically significant clinical benefit with a 14% reduction in the risk of death and a 4% improvement in the five-year overall survival rate (4). The Cancer and Leukemia Group B (CALGB) conducted a randomised trial (GALGB 9633 trial) of adjuvant chemotherapy in 344 stage IB patients with a regimen including paclitaxel and carboplatin. The chemotherapy arm had an improved four-year survival by 12% (5).

It is well-established that platinum-based adjuvant chemotherapy should be recommended after complete resection in all patients with a good performance status (3, 6). Nevertheless, additional research is needed to lessen the toxicity and increase the compliance. Efforts aim at identifying the best possible non-platinum combinations and associated dosing schedules, while taking overall survival, symptom control and quality of life issues into consideration (7, 8).

We conducted a preliminary phase II trial to evaluate the feasibility, tolerability and activity associated with administering the gemcitabine and docetaxel combination on a biweekly basis, as adjuvant treatment for completely resected stage II and IIIA NSCLC patients.

Patients and Methods

Eligibility criteria. Patients, aged <75 years, with previously documented NSCLC at stage II or stage IIIA which had been completely resected by either lobectomy or pneumonectomy were included in the study. Additional inclusion criteria included: age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, adequate haematological (absolute neutrophil count (ANC) ≥1500/μl, platelet count ≥ 100,000/μl), renal (serum creatinine ≤1.5 mg/dL) and hepatic (bilirubin ≤1.5x upper normal limit, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) ≤2.5x upper normal limit) functions. All patients required a complete history and physical examination including evaluation of performance status, recent weight loss, percent of weight loss, and concurrent non-malignant disease and its therapy.

Patients were excluded from the study if they had a history of other neoplasms (except *in situ* carcinoma of the cervix or basal-cell carcinoma of the skin), history of cardiac disease, peripheral neuropathy, psychiatric disorders or serious active infection. Patients were considered ineligible if they had received prior chemotherapy, prior thoracic radiation therapy, or prior immunotherapy within 5 years of study entry. Patients with stage I, IIIB, or IV NSCLC were not eligible. Females of childbearing age were required to have a negative serum or urine pregnancy test within 48 hours of enrolment and use adequate contraceptive measures during the study. Pregnant or breast-feeding women were not entered onto the study. The study was approved by the local hospital review board and ethics committee and was conducted in accordance with the Helsinki declaration. All patients were required to sign a study-specific informed consent form to be included in the study.

Treatment plan. Before registration, patients were required to complete a metastatic evaluation or staging with chest X-ray, computed tomography scans of the brain, chest, and upper abdomen, including the liver and adrenals, and bone scan. All X-rays were to be obtained within 6 weeks before definitive surgery. An ECG was also required. Pulmonary function tests (PFTs) were required postoperatively. A complete surgical resection of the tumour mass by lobectomy, or pneumonectomy was necessary for eligibility. A complete mediastinal lymph node dissection or nodal sampling was recommended, but not required. Complete mediastinal/nodal dissection or sampling included the following nodal levels: levels 2 and 4, level 8, levels 5 and 6 in left upper lobe primaries, level 7, level 9, and level 10. Ipsilateral lymph nodes at levels 11 to 13 were to be removed en bloc with the surgical resection. The presence or absence of evidence of invasion of the nodal capsule was required to be noted in the final pathological report for hilar and/or mediastinal lymph nodes.

Tumour status was assessed by Response Evaluation Criteria in Solid Tumours (RECIST) (9). Assesment of toxic effects were made according to the common toxicity criteria (version 2.0) of the National Cancer Institute. Upon study completion or discontinuation, disease status follow-up as well as survival and tolerance monitoring were performed every 3 months for the first year, every 6 months for the second year and yearly thereafter. Follow-up evaluations included medical history, physical examination, routine laboratory tests and chest and abdominal computed tomography. Bone scans and brain imaging were requested upon clinical symptoms.

Treatment regimen. Gemcitabine 1000 mg/m^2 was administered diluted in 500 ml 5% dextrose and was followed by docetaxel 80 mg/m^2 diluted in 500 ml 5% dextrose. Treatment was administered on an outpatient basis on days 1 and 14. Recombinant human granocyte colony-stimulating factor (rhG-CSF) was given prophylactically (150 μg/m^2/d subcutaneously on days 8-10 and days 21-23, or until the ANC was >1,200 μL on two consecutive measurements after the nadir). Cycles were repeated every 28 days. Standard anti-emetic treatment consisted of 8 mg ondansetron administered intravenously before treatment and 8 mg oral ondansetron ingested three 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 3 cycles (6 infusions). None of the patients included in the study received postoperative radiotherapy either before or after completion of adjuvant chemotherapy.

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. The primary end-points of the study were overall survival (OS) and progression-free survival. The secondary end-point was to evaluate acute and late toxicity in all enrolled patients on an intention-to-treat basis. All treated patients were included in the analysis. All patients that received at least one cycle were assessed for toxicity. The duration of response was calculated from the day of the first documented response until disease progression. Time to progression (TTP) was measured from the date of enrolment until the first evidence of disease progression. OS was measured from study entry until death. Event time distributions were estimated by the Kaplan-Meier method.

Results

Between June 2000 and July 2002 a total of 39 patients (35 men and 4 women) with NSCLC, treated in the Oncology Unit, Third Department of Medicine, Sotiria General Hospital, Athens, Greece, were enrolled in the study. They had a median age of 65 years (range 47-74 years). With regard to performance status, 27 patients had a PS of 0 (27/39, 70%) and 12 patients had a PS of 1 (12/39, 30%). The majority of patients were stage IIIA (31/39, 79%) and the remaining 8 patients (8/39, 21%) were stage II.

A total of 97 cycles were administered to 39 patients, with a treatment compliance of 82.9% (Table I). All patients

Table I. *Patient characteristics.*

	Patients	
	Number	%
Total	39	100
Gender		
Male	35	89.7
Female	4	10.2
Age (years)		
Median	65	
Range	47-74	
ECOG performance status		
0 27	70	
1 12	30	
Histology		
Adenocarcinoma	19	
Large cell carcinoma	5	
Squamous cell carcinoma	12	
Other	3	
Smoking exposure		
Packs per year		
0	2	5.1
1-40	6	15.3
41-60	4	10.2
61-80	10	25.7
81+	17	43.7

Table II. *Toxicities reported during therapy.*

Toxicity	Number of patients (%)			
	Grade NCI-CTC[a]			
	1	2	3	4
Dermopathy	6 (15.3)	3 (7.6)	-	-
Alopecia	11 (28.2)	23 (58.9)	-	-
Neurotoxicity	19 (48.7)	10 (25.6)	2 (5.1)	-
Anaemia	18 (46.1)	9 (23.0)	-	-
Neutropenia	10 (25.6)	9 (23.0)	-	-
Diarrhea	10 (25.6)	3 (7.6)	-	-
Nausea	10 (25.6)	9 (23.0)	-	-
Allergy	11 (28.2)	4 (10.2)	1 (2.5)	-

[a]The National Cancer Institute Common Toxicity Criteria (version 2.0).

were included in the follow-up and analysis. Docetaxel dose modifications were needed only for two patients due to peripheral neuropathy. No patients discontinued therapy or were excluded from the study once the study began.

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 (5.1%) and 1 patient (2.5%), respectively. Peripheral neuropathy, mostly grades 1 and 2, was reported in 29 patients (74.3%) 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.

Effectiveness and survival. All patients were included in the analysis. No patient discontinued therapy or dropped out of the study. The median duration of follow-up was 36.7 months (range 3 to 48 months). The median time to disease progression was 17 months (range 3 to 34 months), with a median overall survival of 21 months (range 3 to 45 months). Progression-free survival and overall survival curves are shown in Figures 1 and 2, respectively. None of the factors studied (histological subtype, degree of differentiation, ECOG PS and smoking exposure (number of packs per year) correlated to the response rate. Patterns of treatment failure analysis revealed brain metastasis in 15% of patients, intrathoracic recurrence in 24% and systemic metastasis in 36%.

Discussion

Surgery alone has been the standard treatment for patients with operable NSCLC for decades. Postoperative radiation therapy has failed to demonstrate a survival benefit (10-13). Since death was due mainly to distant metastasis, efforts at improving overall survival were mainly focused on adding chemotherapy in the preoperative or postoperative setting.

The positive impact of cisplatin in NSCLC patients is compromised by its significant toxicity even though a meta-analysis published in 1995 favoured platinum based chemotherapy, with a 13% reduction in the risk of death and an absolute benefit of 5% at five-year survival (14). The significant toxicity of platinum-based regimens has resulted in poor compliance to treatment schedules when patients with poor performance status (ECOG PS>1) and/or elderly patients were deprived from treatment or delayed for more than six weeks post-surgically until chemotherapy was initiated. This compromised the outcome of the adjuvant treatment.

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 NSCLC. Several randomized studies evaluating combinations of these newer agents have produced equal, if not superior results, in inoperable disease regarding response rate, disease-free survival, 1-year survival, overall survival and quality of life when compared to platinum-based regimens.

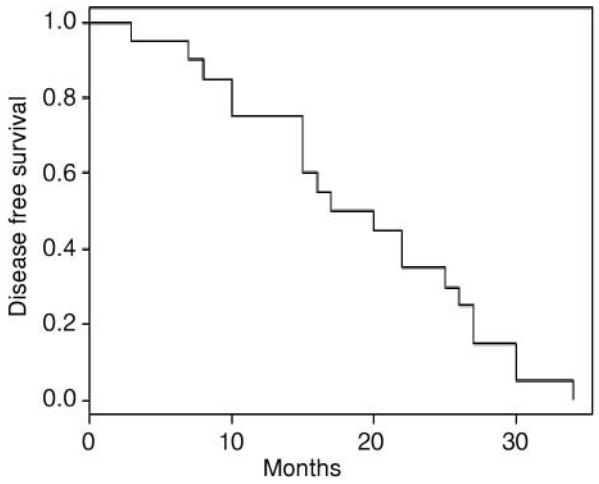

Figure 1. *Kaplan-Meier disease-free survival curve of the patients treated with the docetaxel/gemcitabine adjuvant regimen.*

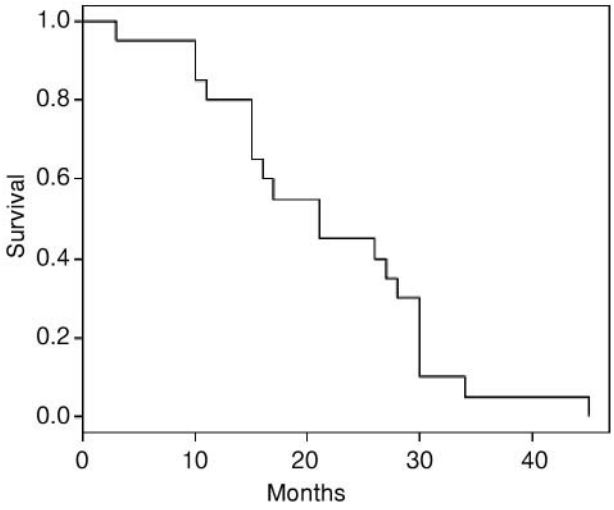

Figure 2. *Kaplan-Meier overall survival curve of the patients treated with the docetaxel/gemcitabine adjuvant regimen.*

Gemcitabine, a deoxycytidine analogue, has demonstrated a satisfactory role as a first-line treatment of NSCLC, either alone or in combination (15). 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 (16, 17). 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 (18). The definite role 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 scheduling, with efficacy and toxicity comparable to those observed in platinum combinations (19). 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 (20, 21). 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 which was manifested with dyspnea, hypoxia and fever (22).

In our study, we administered increased doses of both agents on a biweekly schedule, along with G-CSF support, in an attempt to improve efficacy at the lowest possible toxicity cost. 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 two patients experienced grade III neurotoxicity, while there was no incidence of haematologic toxicity grade III or diffuse interstitial pneumonitis. This regimen has been used in the past by our group, in metastatic NSCLC disease with satisfactory compliance, proven effectiveness and acceptable toxicity (23).

Data from metastatic NSCLC disease provide evidence that there is no survival advantage of any of the commonly used regimens (24-26). The cumulative experience of adjuvant chemotherapy for stage II and III NSCLC has shown that although it has a statistically significant benefit, it is still marginal, with the majority of patients still dying of lung cancer, while treatment-associated comorbidity is the second most common cause of death (27). In our study, we were able to demonstrate a median time-to-disease progression of 17 months and a median overall survival of 21 months, which are comparable with previous studies with cisplatin based regimens (28, 29).

It is of particular interest that the majority of patients included in our study were stage III (79%) and none of the participants received postoperative radiotherapy in addition to adjuvant chemotherapy. Although our patients did not receive postoperative radiotherapy, distant metastasis, including brain metastasis, rather than intrathoracic, remained the main pattern of disease recurrence. This may reflect the shift observed over the last two decades from squamous cell carcinomas to adenocarcinomas as the primary histological type.

In addition, our study kindless several questions to be addressed regarding adjuvant chemotherapy of NSCLC such as the optimal number of cycles administered (3 *vs.* 4 cycles), the potential role of prophylactic brain irradiation

(especially in heavily treated patients) and finally, the molecular identification of patients most likely to benefit from the multimodality treatment. Other issues indeed remain to be solved the role of preoperative chemotherapy, the addition of biological or targeted therapies, and the potential benefits for the elderly and for those patients with poor performance statuses regarding adjuvant treatment and the goal to achieve a patient-tailored treatment.

Conclusion

Our study suggests that the biweekly administration of docetaxel and gemcitabine is a safe, well-tolerated and convenient chemotherapy regimen in the adjuvant setting of completely resected NSCLC stage II and III, 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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