Carboplatin-Pemetrexed Adjuvant Chemotherapy in Resected Non-small Cell Lung Cancer (NSCLC): A Phase II Study

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Abstract. *Background: The aim of this study was to determine the progression-free survival (PFS) and toxicity associated with adjuvant administration of carboplatin and pemetrexed for completely resected patients with stage IB, II and IIIA non-small cell lung cancer (NSCLC). Patients and Methods: Forty-five eligible NSCLC patients received surgical resection for pathological stage IB, II or IIIA followed by postoperative adjuvant chemotherapy with carboplatin AUC5 and pemetrexed administered on days 1 and 14 on a 28-day cycle. Recombinant human granocyte colony-stimulating factor (rhG-CF) was given prophylactically. Results: The mean time to disease progression of patients was 26 months. Toxicities were generally mild to moderate and entirely manageable. Conclusion: The administration of carboplatin and pemetrexed is a safe, well-tolerated and convenient regimen in the adjuvant setting of completely resected NSCLC, with efficacy similar to that reported in other regimens but less toxicity.*

Although complete surgical resection is the optimal management of patients with operable non-small cell lung cancer (NSCLC), the five-year overall survival rate is poor, ranging from 23% to 67% , and dependent on the size of the primary tumor and the lymph node involvement (1). Postoperative radiotherapy reduces the rate of local recurrence in stage IIIA disease but it has a questionable, if not detrimental, effect in patients with stage I and II (2). Treatment failure following complete resection for early stage NSCLC is mainly due to the development of distant metastasis rather than local recurrence (1). The 1995 meta-analysis published by the Non-Small Cell Lung Cancer Collaborative Group suggested an absolute survival advantage at 5 years of 5% with cisplatin-based chemotherapy (3). Following this meta-analysis, three large adjuvant studies using cisplatin-based two-drug regimens for completely resected NSCLC showed absolute 5-year survival differences ranging from 4% to 15% (hazard ratio, HR: 0.69 to 0.86) (4-6). The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis using the data from 4,584 patients in five randomized adjuvant cisplatin-based chemotherapy trials with a median follow-up of 5.2 years showed an absolute 5-year survival benefit of 5.4% (7). Although the role of cisplatin-based adjuvant chemotherapy for stage II and IIIA NSCLC is well established, there is still some uncertainty regarding its utility in stage IB. Trying to answer this question, the Cancer and Leukemia Group B (CALGB) conducted a randomized trial (CALGB 9633) in 344 stage IB NSCLC patients using a paclitaxel/carboplatin regimen. The results of this study advocated the use of adjuvant paclitaxel/carboplatin only for stage IB patients with large tumors (8). There is strong evidence for administering cisplatin-based adjuvant chemotherapy in NSCLC patients after a complete surgical resection but the difficulty is that many patients are not able to receive such therapy because of co-morbidities. The aim of this study was to test an alternative adjuvant regimen using carboplatin and pemetrexed in patients with completed resected NSCLC in order to identify the possible best outcome with the least toxicity.

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Patients and Methods

Eligibility criteria. Forty-five patients with a mean age of 61.2 years (40-76) and completely resected stage IB, II and IIIA NSCLC by lobectomy, bilobectomy or pneumonectomy were included in the study. Additional eligibility criteria included: age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2,

adequate hematological (absolute neutrophil count (ANC) ≥1500/mL, platelet count ≥100,000/mL), renal (serum creatinine ≤1.5 mg/dL) and hepatic functions (bilirubin ≤1.5 x upper normal limit, serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) ≤2.5 x upper normal limit). Furthermore, surgery should have been completed within 4 to 8 weeks prior to enrollment. All patients required a complete history and physical examination including evaluation of performance status, recent 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), cardiac disease, peripheral neuropathy grade 3 or 4, psychiatric disorders or serious active infection. Females of childbearing potential required a negative serum or urine pregnancy test within 48 hours of enrollment and had to take adequate contraceptive measures during the study. Pregnant or lactating women were excluded. 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 IA, IIIB, or IV NSCLC were not eligible. 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 in order to be included in the study.

Treatment plan. Before registration, patients were required to complete a metastatic evaluation, or staging with computed tomography scans of the brain, chest, and upper abdomen, including the liver and adrenals, and bone scan. An ECG was also required. Pulmonary function tests (PFTs) were required postoperatively. Assessment of toxic effects were made according to the common toxicity criteria (version 3.0) of the National Cancer Institute (9). 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 and every 6 months afterwards. After progression, survival follow-up continued every 2 months. 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. Carboplatin (Megaplatin; Genepharm S.A. Athens, Greece) area under the curve (AUC5) diluted in 500 ml normal saline 0.9% in 60 minutes followed by Pemetrexed (Alimta®; Eli Lilly and Co, Indianapolis, IN, USA) 500 mg/m^2 diluted in 500 mL normal saline 0.9% over 30 minutes was given. Treatment was administered on an outpatient basis on days 1 and 14 in a 28-day cycle. Recombinant human granocyte colony-stimulating factor (rhG-CSF) was given prophylactically (150 mg/m^2/d subcutaneously on days 8-11 or until the neutrophil count was >1,200/mm^3 on two consecutive measurements after the nadir). 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. Folic acid and vitamin B12 were also administered. Treatment was continued in the absence of disease progression and unacceptable toxicity for a maximum of 3 cycles (6 infusions).

Statistical analysis. The primary end-point of the study was the recurrence-free survival (RFS). The secondary endpoint 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 were assessed for toxicity. RFS was measured from the date of enrolment until the first evidence of disease recurrence. For time events, the actuarial survival function was estimated by the Kaplan-Meier method. All statistical analyses were carried out in SPSS V 15.0 Chicago, IL, USA.

Table I. *Baseline patient characteristics*.

Characteristic	Number	%
Total	45	100
Gender		
Male	36	80
Female	9	20
Age (years)	61.2±8.83 (40-76)	
Smoking status		
Yes	7	15.6
No	38	84.4
ECOG PS		
0	35	77.8
1	8	17.8
2	2	4.4
Tumour site (lung)		
Right	26	57.8
Left	19	42.2
Tumour site (lobe)		
Upper	22	48.9
Lower	16	35.6
Median	7	15.6
Operation type		
Lobectomy	32	71.1
Bilobectomy	5	11.1
Pneumonectomy	8	17.8
Histology		
Adenocarcinoma	26	57.8
Squamous cell	17	37.8
Other/ n/a	2	4.4
pStage		
IB	14	31.1
IIA	4	8.9
IIB	9	20.0
IIIA	18	40.0

ECOG PS: Eastern Cooperative Oncology Group Performance Status; pStage: pathological stage; n/a: not available.

Results

Demographics. Between May 2006 and January 2008, a total of 45 patients (36 men and 9 women) with completely resected 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 61.2 years (range 40-76 years). With regard to performance status (PS), 35 patients had a PS of 0 (78%), 8 patients had a PS of 1 (17.8%) and 2 patients had a PS of 2 (4.4%). The majority of patients had stage IIIA disease (40.0%), received lobectomy (71.1%) and the predominant histological type was

Table II. *Toxicity of adjuvant chemotherapy.*

Toxicity	Grade NCI-CTC[a]							
	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
Anemia	8	17.8	3	6.7	0	0	0	0
Neutropenia	2	4.4	1	2.2	0	0	0	0
Thrombocytopenia	1	2.2	0	0	0	0	0	0
Neurotoxicity	1	2.2	0	0	0	0	0	0
Elevated SGPT	3	8.9	6	13.3	0	0	0	0
Alopecia	1	2.2	0	0	0	0	0	0
Nausea/vomiting	8	17.8	0	0	0	0	0	0
Elevated creatinine	3	6.7	0	0	0	0	0	0

[a]The National Cancer Institute Common Toxicity Criteria (version 3.0) (g); SGPT, serum glutanate pyruvate transaminase.

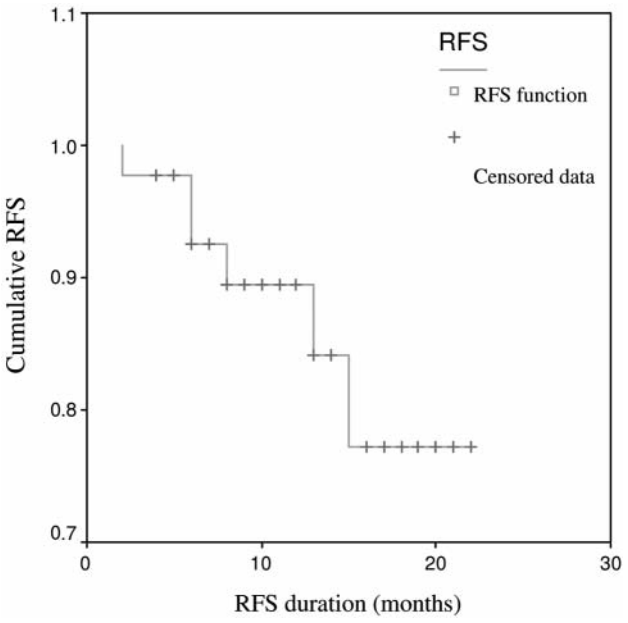

Figure 1. *Kaplan-Meier recurrence free survival (RFS) curve of the patients treated with the carboplatin-pemetrexed adjuvant regimen.*

adenocarcinoma (57.8%) (Table I). All patients were included in the follow-up and analysis. No patient discontinued therapy or was excluded from the study once the study began. All patients were evaluated for RFS and toxicity.

Toxicity. The major hematological and non-hematological toxicities associated with this regimen are shown in Table II. The reported side-effects were only grade I and II and entirely manageable. Anemia was present in 24.5% of patients (grade I and II) and did not lead to cycle delay or omission. Grade II neutropenia occurred in 1 patient (2.2%).

Effectiveness and survival. All patients were evaluated for relapse and toxicity. No patient discontinued therapy or dropped out of the study. The median time to disease recurrence was 26 months (95% confidence interval (CI): 23 to 29 months). The RFS curve is shown in Figure 1. None of the factors studied (histological subtype, degree of differentiation, ECOG PS and smoking exposure) correlated to the time to progression of disease.

Discussion

The most effective treatment for early stage NSCLC is surgical resection. However, up to 60% of patients with IB to IIIA NSCLC relapse after surgery and die (1). The presence of micrometastatic disease at the time of resection is the most likely cause of recurrence, even after complete surgical removal of all macroscopically recognizable disease (10). If micrometastases are indeed responsible for disease recurrence, adjuvant chemotherapy would be a rational treatment, and this hypothesis has led to attempts to reduce the risk of relapse and death from lung cancer by giving adjuvant chemotherapy to patients with complete surgical resection. The LACE study was based on a pooled meta-analysis of individual patient data from the five largest randomized trials (ALPI, ANITA, BLT, IALT and JBR10), conducted after the NSCLC meta-analysis. This study may help to put some critical findings into perspective. With a median follow-up of 5.2 years, the overall HR of death was 0.89 (95% CI: 0.82-0.96; p=0.004), which corresponds to a 5-year absolute benefit of 5.4% with chemotherapy. The benefit varied with stage as the HR for stage IA was 1.40 (95% CI: 0.95-2.06), stage IB; 0.93 (95% CI: 0.78-1.10), stage II 0.83 (95% CI: 0.73-0.95) and stage III; 0.83 (95% CI: 0.72-0.94). These analyses indicated that adjuvant cisplatin-based chemotherapy improved survival in patients with completely resected NSCLC, especially in stages II and III. This meta-analysis also showed that the effect of chemotherapy did not vary significantly with the associated drugs. Nevertheless, the positive impact of cisplatin in NSCLC patients is accomplished at the cost of significant toxicity. Late side-effects of cisplatin-containing chemotherapy regimens, particularly vascular disease, have been well characterized after treatment of testicular cancer (11). The Interantional Adjuvant Lung Cancer Trial (IALT) study reported a higher rate of non-cancer-related deaths after 5 years of follow-up (12). Moreover, the average age of NSCLC patients was 70 years and it is highly likely for these patients to present with renal, peripheral neuropathy or hearing impairments. Although the cisplatin *versus* carboplatin meta-analysis in first-line treatment of advanced

NSCLC showed a better response rate for patients receiving chemotherapy involving cisplatin (30%) over these receiving chemotherapy involving carboplatin (24%), with an odds ratio of 1.37 (95% CI: 1.16- 1.61; $p<0.001$) (13), NSCLC patients may be offered the alternative of carboplatin adjuvant therapy based on its milder toxicity profile.

Pemetrexed is a folate antimetabolite whose primary mechanism of action is the inhibition of the enzyme thymidylate synthase (TS). Firstly, pemetrexed was compared to docetaxel in a randomized phase III study in patients with locally advanced or metastatic NSCLC who had received prior chemotherapy. Both arms showed similar tumor response rates (9.1% for Alimta® *vs*. 8.8% for docetaxel), progression-free survival (2.9 months in both arms), median survival time (8.3 months for Alimta® *vs*. 7.9 months for docetaxel) and 1-year overall survival (29.7% in both arms). Pemetrexed gained approval in the second-line treatment of NSCLC due to its favourable toxicity profile, which resulted in satisfactory compliance with treatment schedules even for patients with poor performance status (14). Later, the cisplatin-pemetrexed combination was tested over cisplatin-gemcitabine combination as first-line treatment in patients with stage IIIB or IV NSCLC in a non-inferiority randomized trial. Overall survival was statistically superior for cisplatin/pemetrexed *vs*. cisplatin/gemcitabinin patients with adenocarcinoma (12.6 *vs*. 10.9 months, respectively) and large-cell carcinoma histology (10.4 *vs*. 6.79 months, respectively). The toxicity profile was significantly better for the cisplatin/pemetrexed arm. With respect to this study, the combination of cisplatin/pemetrexed was approved for the first-line treatment of NSCLC patients with tumors of non-squamous histology (15).

In our study, we administered carboplatin AUC5 and pemetrexed 500 mg/m^2 on days 1 and 14 in a 28-day cycle along with prophylactic administration of rhG-CSF on days 8-11, in an attempt to improve efficacy with the lowest possible toxicity (16). Since the chemotherapy schedule was administered on an outpatient basis, it proved convenient for both the patients and the hospital oncology unit. In fact, with regard to toxicity, the chemotherapy regimen was well tolerated, with completely manageable mild to moderate hematological and non-hematological toxic effects that did not require dose reductions or cycle delays. Neither grade III nor grade IV toxicity was observed.

The cumulative experience of adjuvant chemotherapy for stage II and III NSCLC has shown that although it has a statistically significant benefit, this is marginal, with the majority of patients still dying of lung cancer, while treatment-associated comorbidity is the second most common cause of death (17). In our study, we were able to demonstrate a median time to disease progression of 26 months, which is comparable with previous studies that have applied cisplatin-based regimens. The majority of patients included in our study were stage III (40.0%) and none of the participants received postoperative radiotherapy in addition to adjuvant chemotherapy.

Toxicity is of major concern in the adjuvant setting; being mainly asymptomatic, patients are less willing to conform to the schedule of a toxic treatment and physicians are more reluctant to recommend a highly toxic therapy of only marginal benefit. It would be important to offer a less toxic and more convenient chemotherapy regimen, if proven equally effective (18). Data from metastatic NSCLC disease provide evidence that there is no survival advantage from any of the commonly used regimens (19).

Conclusion

Our study suggests that the administration of carboplatin-pemetrexed is a safe, well-tolerated and convenient chemotherapy regimen in the adjuvant setting of completely resected NSCLC, with efficacy which seems to be similar to that reported in other regimens but with less toxicity. Hence, this combined treatment appears promising and warrants further evaluation

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