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Phase II Trial of Celecoxib in Combination with Paclitaxel and Carboplatin in Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Background: *Prostaglandins (PGs) can enhance tumor growth and metastasis by stimulating angiogenesis and invasiveness, in addition to apoptosis and immune surveillance. Microtubule-interfering agents induce cyclooxygenase-2 (COX-2) and PG biosynthesis and this might reduce the efficacy of paclitaxel. Preclinical studies suggest that treatment with a selective COX-2 inhibitor may augment the antitumoral effects of chemotherapy. Thus, we designed a phase II trial to evaluate the efficacy of the combination of paclitaxel, carboplatin and celecoxib in advanced non-small cell lung cancer.*

Materials and Methods: *Thirty-seven patients were enrolled in this trial. The inclusion criteria were: chemotherapy-naïve advanced NSCLC (non-resectable locally advanced stage IIIA, stage IIIB and IV), age>18 yrs. and performance status (PS) of 0-2 (ECOG). All patients were given paclitaxel (200 mg/m^2) and carboplatin (AUC 6) on day 1, every 21 days and celecoxib (400 mg) daily.*

Results: *Most of the patients were male and the mean age was 58 yrs. Old. Performance status 0, 1, and 2 were 8.2%, 40.5% and 51.3%, respectively. Four patients were in stage IIIA (10.8%), 12 patients in stage IIIB (32.4%) and 21 (56.8%) in stage IV. The overall response rate was 54%. Time to progression and median overall survival were 5.7 and 9 months, respectively. Only one patient had grade 3 anemia. There was no grade 4 cytotoxicity. Three patients had cytotoxic drug allergy.*

Conclusion: *Based on this study, adding 400 mg celecoxib to the standard regimen (paclitaxel plus carboplatin) does not enhance time to progression and overall survival compared to historical data. Thus, we recommend combining higher dosage of celecoxib with other targeted agents in phase I/II trials. (**Tanaffos 2007; 6(1): 37-46**)*

Key words: *Non-small cell lung cancer, Celecoxib, Paclitaxel, Carboplatin*

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INTRODUCTION

Non small cell lung cancer (NSCLC) is the leading cause of cancer death in the world. The 5-year survival rate of 15% represents only a minimal improvement in survival in the last 25 years (1). Newly described mechanisms in the pathogenesis of lung cancer provide new opportunities for targeted therapies (2, 3). Research is under way using targeted therapeutic approaches in an effort to improve conventional therapeutic approaches such as surgery, radiotherapy, and chemotherapy. One of the targets currently being evaluated in the treatment of lung cancer and other cancers belongs to the cyclooxygenase class of enzymes. Cyclo-Oxygenase-2 (COX-2) is expressed in human colon, breast, lung and other cancers (4,5,6,7), whereas normal, quiescence vascular endothelial cells express only COX-1 (8). COX-2 is an inducible enzyme that catalyzes PGs synthesis. PGs promote stimulation of angiogenesis and invasiveness, in addition to inhibiting apoptosis and immune evasion which enhance tumor growth and metastasis (8-23). Increased tumor vascularity is associated with poor prognosis and the extent of angiogenesis has an inverse correlation with patient's survival (24, 25). Selective COX-2 inhibitors, which inhibit prostaglandins and other derivates involved in tumorgenesis, have been shown to induce apoptosis, antiangiogenic effects on lung cancer models, and decrease tumor invasiveness (15, 26, 27, 28). In addition, cytotoxic anticancer agents such as taxanes cause overexpression and up-regulation of COX-2 and foster this theory that it reduces the efficacy of these agents (29). Preclinical studies have demonstrated that selective COX-2 inhibitors enhance the cytotoxic activity of both chemotherapy and radiotherapy in experimental systems (30, 31, 32, 33, 34). Several clinical studies have been conducted to show the efficacy of selective COX-2 inhibitors in combination with microtubule-interfering agents and the outcome data was acceptable (35, 36, 37, 38, 39). Altorki et al. showed the safety and feasibility of the addition of a selective COX-2 inhibitor, celecoxib, in combination with preoperative paclitaxel and carboplatin in early-stage non-small cell lung cancer as first line therapy (40). Hence, this current study was designed to show if the addition of a selective COX-2 inhibitor to paclitaxel and carboplatin regimen would enhance the efficacy of these cytotoxic agents in advanced NSCLC.

MATERIALS AND METHODS

Patients

From August 2003 through August 2005, 37 patients with histologically confirmed NSCLC were enrolled in this prospective phase II trial. The eligibility criteria were as follows: Chemotherapy-naïve advanced NSCLC (unresectable locally advanced IIIA, IIIB or metastatic NSCLC), age>18 yrs, and performance status of 0-2 (based on ECOG scale). Patients were considered ineligible if they had received prior chemotherapy or radiotherapy, allergy to sulfonamides, uncontrolled congestive heart failure, active thromboembolic event within the past 4 weeks, history of peptic ulcer disease, GI bleeding within the past 6 months, age>70 yrs, brain metastasis or isolated bone metastasis in stage IV. Pretreatment evaluation included a complete history and physical examination, routine laboratory test (complete blood cell count, erythrocyte sedimentation rate, liver function test, renal function test and electrolytes), plain chest radiography, conventional chest, abdomen, and brain computed tomography. Clinical T stage was assessed by CT imaging as well as bronchoscopy for T_3 and T_4 lesions. Nodal stage was also determined by chest CT-scanning. Metastatic lesions were assessed by abdominal and brain CT-scan. In case of bone pain and/or elevated alkaline phosphatase; whole body

bone scan was also performed. Patients were divided into measurable (bidimensional) and non-measurable (unidimensional) groups. Informed consent was obtained from all patients. The consent form included the entire investigational nature of the treatment plan and the probable side effects, as well as the ability of the patient to withdraw consent at any time.

Treatment Plan

Paclitaxel at 200 mg/m^2 was given as a 3-hour infusion, followed by a 1-hour intravenous infusion of carboplatin dosed to an area under the curve of 6 by the Calvert formula. Paclitaxel and carboplatin were administered every 21 days. Four cycles were given to the patients, who achieved stable disease response and six cycles administered to patients who acquired partial response or complete response after two cycles. Dose-modification procedures in the case of hematologic toxicity consisted of a one-week delay when the white blood cell count was below 4000/mL on the first day of therapy or when the platelet count was less than 100000/mL. If values had not returned to normal within 1 week, dose reduction was recommended. All patients were premedicated by dexamethasone, promethazine and an H_2 receptor blocker. Celcoxib was administered orally at a dose of 200 mg twice daily, starting on the first day of chemotherapy and continued until patient's intolerance, refusal or any significant side effect. Toxicity and complete blood cell count were evaluated on the first day of each cycle of therapy and any adverse effect was graded according to World Health Organization (WHO) criteria. Sequential thoracic radiation therapy was considered for unresectable stage IIIA and non-effusion stage IIIB cases.

Evaluation of Efficacy

The primary efficacy variable was overall survival. The secondary efficacy variables were response rate and time to progression. Overall survival was defined as the time from the initiation of treatment to death from any cause. Patients who survived beyond the time of analysis were censored at the time of their last follow up visit. Time to progression defined as the time from the initiation of treatment to the recurrence of cancer in any site. The response was initially evaluated after the second cycle of chemotherapy. A major objective response consisted of a complete response or a partial response. The response was assessed based on Response Evaluation Criteria in Solid Tumors (RECIST) (41). We also used these criteria for the patients whose lesions were non-measurable.

Follow Up

After completion of the protocol, participants were seen every 2-month, 3-month and 4-month intervals for the first, second and third years, respectively. Standard follow-up surveillance consisted of clinical history, physical examination, routine laboratory tests and chest radiography. For patients who had abdomen and bone metastasis, abdominal CT-scan and bone scan were performed every 4 months. Second line chemotherapy and/or radiotherapy following disease recurrence or progression were permitted based on patient's performance status and site of disease.

Statistical Analysis

The results of this non-comparative study are presented with descriptive statistics. Descriptive statistics were used to summarize patients' baseline demographic and disease characteristics (age, sex, pathology, stages and performance status) and overall response rate. Time to progression and overall survival distribution were estimated using Kaplan-Meier method (42). Kaplan-Meier estimates were obtained for each of these end points and presented in life-table format with 2-month intervals. The Kaplan-Meier estimates also included the median time to progression and overall survival, 95% confidence interval and number of censored observations. A plot of Kaplan-Meier estimates was

made for each end point. Comparisons between groups employed the log rank test; variables found to be of interest in univariate analysis (p<0.05) were included.

RESULTS

Patients' Characteristics

Thirty seven patients were enrolled. Patients' characteristics are listed in Table 1. Median age was 58 years with a range of 28-70. Most of the patients were male (70%). Four patients were in stage IIIA (10.8%), 12 in IIIB (32.4%) and 21 (56.8%) in stage IV. The most common pathology was adenocarcinoma (56.8%), and the others were squamous cell carcinoma (24.3%), undifferentiated carcinoma (16.7%) and large cell carcinoma (2.7%), respectively. The majority of patients (29 cases) had non-measurable disease and almost half of them had performance status (PS) of 2.

Table 1. Characteristics of the study patients.

	No. of Patients
Patients	
Total	37
Male	26
Female	11
Age, years	
Median	58
Range	28-70
Clinical stage	
IIIA	4
IIIB	12
IV	21
Histology	
Adenocarcinoma	21
Squamous cell carcinoma	9
Large cell carcinoma	1
Undifferentiated carcinoma	6
ECOG score	
0	3
1	15
2	19
Measurability	
Measurable	8
Non-measurable	29

Table 2. Induction Therapy Adverse Events

	No. of Patients				
Toxicity	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic toxicity					
Anemia	32	2	2	1	0
Thrombocytopenia	33	4	0	0	0
Granulocytopenia	34	2	1	0	0
Gastrointestinal toxicity					
Nausea	30	6	1	0	0
Vomiting	30	6	1	0	0
Diarrhea	24	9	4	0	0
Neuropathy					
Parasthesia	11	13	12	1	0
Numbness	11	13	12	1	0
Stomatitis	27	5	2	3	0
Allergy	33	1	1	2	0

Patients received an average of 4.3 cycles. Twenty-five patients (67.5%) completed the protocol. In 3 patients the protocol discontinued due to severe cytotoxic drug reaction (2 patients received 1 cycle and 1 patient received 2 cycles). One patient after receiving 2 cycles, decided to withdraw consent. Celecoxib therapy was discontinued in three patients who had developed generalized allergic skin reaction after starting treatment with celecoxib. In one of the patients that celecoxib was discontinued, the protocol was discontinued as well due to the patient's consent withdrawal. Six patients had sequential thoracic radiotherapy in addition to chemotherapy in the setting of combined modality treatment. Another 8 patients received palliative radiation therapy to the lung, bone or brain. Four patients died from other causes (1 patient died due to myocardial infarction, two patients due to pulmonary emboli and one had unknown sudden death). Four patients were lost in the follow-up.

Efficacy

Response rate: Twenty patients had a major clinical response. The objective overall response rate was 54%. Four (10.8%) had a complete response, and 16 (43.2%) acquired partial response. Six patients (16.2%) had stable disease and in six, the response was not evaluable (3 due to drug hyper

insensitivity reaction, in 2 due to patient' s refusal and in 1 due to early death after one cycle). Among the three patients who discontinued celecoxib treatment, one had a partial response, one had progression and one was non-evaluable due to patient' s refusal.

Time to progression and overall survival: The estimated median time to progression for all thirty seven patients was 5.7 months (estimated 95% confidence interval, 3.8 to 7.5 months; nine patients censored; figure 1). At the time of analysis 11 patients (29.7%) were alive. The patients who were lost in the follow-up were censored. Median survival for all patients was 9 months (estimated 95% confidence interval, 2 to 15 months), calculated by using the Kaplan-Meier estimation procedure (Figure 2). The 1-year survival rate was 43% and survival correlated with pretreatment performance status. Patients with ECOG performance status of 0 and 1 had a median survival time of 14.4 months, compared with 8 months in patients with PS of 2 (log-rank, p=0.02). Disease stage was another variable associated with overall survival (log-rank, p between groups=0.006). Patients with stage IV (median 6.8 months) experienced poorer survival than those with disease stage of IIIA and IIIB (median 16.4 months). The performance status and disease stage had not any correlation with time to progression. There was no difference in survival time and in time to progression based on histology, gender and number of cycles.

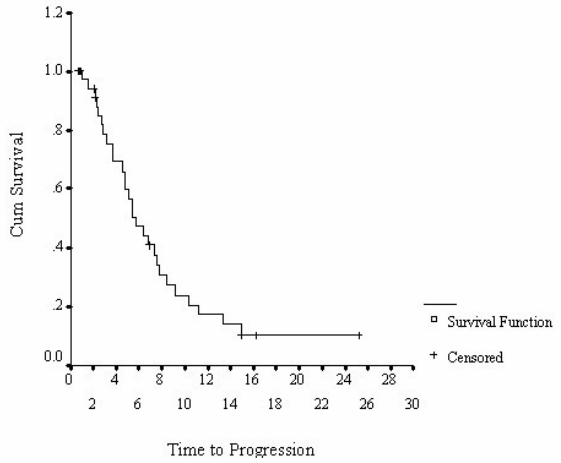

Figure 1. Kaplan-Meier estimation of time to progression (months)

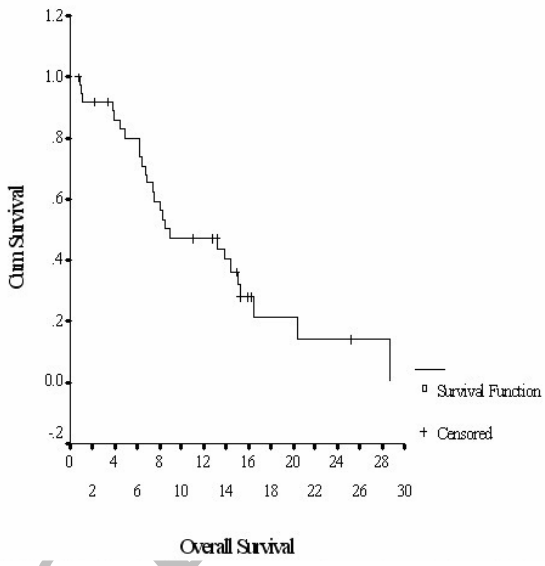

Figure 2. Kaplan-Meier estimation of overall survival (months)

Treatment-Related Toxicity

There was no treatment-related death. Chemotherapy- related toxicity is listed in table-2. There were no grade 4 of granulocytopenia, thrombocytopenia or anemia, and only one patient had grade 3 anemia. Three patients suffered from grade 3 stomatitis but it recovered after 3-4 days. Three patients had cytotoxic drug allergy (one patient had grade 3 and 2 patients had grade 4 drug allergy). There was only one case of severe paresthesia (grade 4) in which the protocol was discontinued after 5 cycles.

DISCUSSION

A fundamental change in clinical oncology is under way. After decades of basic research, steps in carcinogenesis are now being targeted through specific pharmacological agents. Consequences of this changing clinical paradigm are therapeutic regimens that combine a targeted therapy with cytotoxic chemotherapy and are under study. One of these major targets is the COX-2 receptor. Altorki evaluated the potential for favorable clinical interactions in the preoperative treatment of lung

cancer by combining cytotoxic chemotherapy with COX-2 inhibition (40). The hypothesis underlying his study was that inhibiting COX-2 activity might enhance the efficacy of cytotoxic agents through inhibition of angiogenesis, promotion of apoptosis, or other possible mechanisms (12, 13, 14, 15, 16, 17, 18, 19, 43). A paclitaxel-containing regimen was selected for the study because the prior work of this team showed that paclitaxel could induce COX-2 and prostaglandin biosynthesis (28). A selective COX-2 inhibitor would be expected to prevent the possible negative action of this chemotherapeutic agent. Altorki and his colleagues conducted this study for early-stage NSCLC and there is no report of this combination efficacy on advanced NSCLC as the first line therapy. Several studies have been done to show the efficacy of COX-2 inhibitor in combination with a taxane (especially docetaxel) in recurrent NSCLC. Hence, we designed this study to determine if there is considerable benefit in administrating paclitaxel and carboplatin with a COX-2 inhibitor in advanced NSCLC. In contrast to other studies that 800 mg/d celecoxib was selected, we decided to select 400 mg/d, because patients were more compliant taking two capsules of 200 mg twice daily instead of four for a long period of time. Otherwise the lower doses of celecoxib that would be sufficient to maximally inhibit COX-2 activity are unknown and we concluded that doses less that 800 mg/d could be efficient. The addition of celecoxib to paclitaxel and carboplatin regimen appears to be feasible and safe. Treatment-related toxicity was acceptable. As we mentioned, there was no death due to drug toxicity. The lack of grade 3 and 4 neutropenia and thrombocytopenia could reduce the possibility of the hypothesis that COX-2 might play a role in the recovery phase of chemotherapy-induced bone marrow injury (44). Solomon showed dose-related cardiovascular toxicity in a clinical trial for colorectal adenoma prevention (the group given 200 mg of celecoxib twice daily had a hazard ratio for death from cardiovascular causes of 2.3, and the group receiving 400 mg of celecoxib twice daily had a hazard ratio of 3.4) (45). Moreover the cardiovascular safety committee completed a preliminary review of cardiovascular safety in another study, the prevention of spontaneous adenomatous polyps (PreSAP) trial, which randomly assigned patients with a history of colorectal adenomas to receive either 400 mg of celecoxib once a day or placebo. The preliminary analysis did not show an increase in risk at this dose. In our study we had one death due to a cardiovascular event (myocardial infarction) that was a postradiotherapy event, although we could not rule out its relation to celecoxib consumption.

This current phase II study has yielded overall survival and time to progression data. Compared with two similar studies of paclitaxel and carboplatin without concurrent COX-2 inhibitor therapy published by Langer et al. (46, 47) (in 1995 and 1997), the median overall survival achieved was less than the median overall survival in these two studies (9 months versus 13.2 months in 1995 and 9 months versus 11.7 months in 1997). Additionally, time to progression (5.7 months versus 7 months in 1995 and 5.7 months versus 6 months in 1997) did not have significant difference. In another study conducted by Johnson et al (paclitaxel plus carboplatin in advanced non small cell lung cancer) in 1996 the median overall survival was 9.5 months (48). We achieved a major objective response of 54% which was not significantly different compared to the studies performed by Langer and Johnson (47, 48). We expected improved overall survival and time to progression, so why did not we fulfill our expectations? While the patients' characteristics were

generally similar between Langer's studies and the current study, there were higher proportions of patients with ECOG performance status of 0 or 1(100% in 1995 and in 1997 81% of patients had performance status 1) in both of his studies compared to this trial. As we demonstrated, there was a significant difference between median survival time of patients with performance status 0 or 1 and patients with performance status 2 (log-rank *p* between groups=0.02). Consequently, the reduction of our survival time and time to progression exhibited by our patients could be attributed, in part, to the worse overall performance status. Furthermore, in the current study it was shown that there is significant difference between overall survival in patients with stage IV and patients with stage IIIA and IIIB. As mentioned in our results, most of our patients (56.8%) had stage IV disease which correlated with a poorer overall survival. In Johnson's study 88% of patients had stage IV and time to progression and overall survival were 32 and 38 weeks, respectively. So, we can also attribute the time to progression and overall survival in our study to higher rate of stage IV disease.

Altorki showed remarkable reduction in levels of PGE_2 that were similar to non-neoplastic lung (40). In a preliminary report of trial by Johnson et al., it was revealed that combined docetaxel and celecoxib reduced intratumoral COX-2 resulting in decreased tumor PGE_2 levels (37). The authors failed to measure intratumoral PGE_2 levels, so we do not know what the response of PGE_2 level to this celecoxib dose (400 mg/d) is. One of the underlying hypotheses is that the higher disease stage leads to a greater overexpression of COX-2 receptors on tumor. This overexpression of COX-2 does not seem to be inhibited by 400 mg/d of celecoxib.

Most targeted agents have been developed to modulate a specific pathway in the malignant cells. These agents have been combined with different cytotoxic agents and there were hopeful results. Gefitinib (a tyrosine kinase inhibitor) has been combined with second-line docetaxel (49). Disease control (partial response plus stable disease) was seen in 63% of those receiving gefitinib combined with docetaxel compared with 32% for docetaxel alone. Cetuximab (a humanized monoclonal antibody to the extracellular domain of epidermal growth factor receptor) is well tolerated in combination with both first-line platinum-based chemotherapy and with second-line docetaxel (50, 51, 52). There is a study similar to our study that conducted by Johnson et al. He combined bevacizumab (a recombinant human monoclonal antibody to vascular endothelial growth factor) with paclitaxel and carboplatin and higher response rate, longer time to progression and longer median survival were achieved in comparison to bevacizumab alone (53). Opportunities exist for combining multiple targeted agents with the hope of additive or synergistic activity. It is expected that least toxicity would result if we combine these agents. Clinical benefits might have been derived from the regimen that combined higher dosage of celecoxib (with consideration of cardiovascular toxicity) and new targeted agents such as gefitinib, cetuximab and bevacizumab.

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