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Phase II study of paclitaxel and carboplatin for advanced non-small-cell lung cancer

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Abstract

A prospective phase II study was conducted to determine the response, toxicity and survival rate of lung cancer patients treated with combination paclitaxel and carboplatin in stage IIIB and IV NSCLC. Eligible patients required measurable and/or evaluable diseases; performance status (ECOG) 0–2; no previous chemotherapy; adequate hepatic, renal and bone marrow function. Paclitaxel was administered at a dose of 200 mg/m^2, 3 h infusion, followed by carboplatin at an AUC of 6. Treatment was repeated every 3 weeks for six courses. G-CSF 5 microgram/kg was subcutaneously injected during subsequent courses if there was grade 3–4 leucopenia or granulocytopenia in the previous course. From April 1996 through July 1997, 53 patients were enrolled; all are assessable for toxicity and response. The median age was 56 years (range, 20–77 years). Sixty four percent were male, 64% had adenocarcinoma and 62% had stage IV disease. Two hundred and seventy two courses were administered; 36 patients (68%) completed all six cycles. Two patients achieved a complete response (4%) and 27 patients achieved a partial response (51%), for an overall response rate of 55%. Sixteen patients had stable disease (30%) and 8 patients had progressive disease (15%). The median progression free survival time for all patients, stage IIIB and stage IV patients was 28 weeks (range, 18–37 weeks), 31 weeks (range 21–41 weeks) and 22 weeks (range 16–29 weeks), respectively. The median survival time and 1 year survival rate for all patients was 55 weeks (range, 51–59 weeks) and 55%, respectively. Stage IIIB patients had better median survival time and 1-year survival rate than stage IV patients (75 vs. 46 weeks, $P = 0.007$; 80% vs. 42%, $P = 0.003$). Grade 3 and 4 granulocytopenia, anemia and thrombocytopenia were observed in 25, 3, and 1%, respectively, of the 272 courses administered. G-CSF was required in 28% of the 272 courses. There were four episodes of fibrile neutropenia (1.5%), three episodes of angina pectoris (1%) and one episode of anaphylaxis (0.4%). Other common toxicities, generally mild, included myalgia, arthralgia, peripheral neuropathy and asthenia. Most toxicities showed cumulative effect. Paclitaxel plus carboplatin is a moderately active regimen in advanced NSCLC. Toxicites of this regimen are well tolerated.

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1. Introduction

Lung cancer remains the leading cause of death from cancer in the United States [1], and in Thailand it ranked second of ten leading sites of cancers in men in 1994 according to Ramathibodi Cancer Registry [2]. Unfortunately, the majority of lung cancer patients present with inoperable stage III disease, or with metastatic disease (stage IV) [3]. Advanced non-small-cell lung cancer (NSCLC) has a median survival time of 6–8 months, and a 1 year survival rate of only 10–20% [4]. Although chemotherapy can effect a modest improvement in survival, the gain often comes with a substantial host toxicity, especially in patients who are less than fully ambulatory [5]. Cisplatin-containing chemotherapy regimens have led to only marginal improvement in survival [6]. Carboplatin is a cisplatin analogue that has less renal toxicity, neurotoxicity and ototoxicity of the parent compound. In a randomized trial comparing cisplatin/etoposide with carboplatin/etoposide in advanced NSCLC, carboplatin was shown to produce a survival rate equivalent to cisplatin but to produce less toxicity [7,8]. Another randomized trial conducted by the Eastern Co-operative Oncology Group [9] showed that single agent carboplatin significantly improved survival and produced significantly less toxicity than cisplatin-based combinations in stage IV NSCLC. Within the past 5 years, a number of new chemotherapeutic agents have been identified that have shown a high degree of activity both as single agents, and in combination regimens against NSCLC. One particularly promising new agent is paclitaxel. In separate phase II studies in advanced NSCLC, paclitaxel yielded an objective response rate of 21–24% and was associated with a 1 year survival rate of approximately 40% [10,11]. The combination of paclitaxel and carboplatin in the treatment of advanced NSCLC in a phase II study conducted by the Fox Chase Cancer Center has produced an objective response rate of 62% with a 1 year survival rate of 54% [12]. These observations prompted us to combine paclitaxel and carboplatin in a pilot trial for advanced non-small-cell lung cancer in Thailand. The results of our study are reported here.

2. Patients and methods

2.1. Patient eligibility

Chemotherapy-naive non-small-cell lung cancer patients with stage IIIB or stage IV who were >18 years were eligible. Patients with stage IIIB were defined by malignant pleural effusion, great vessels involvement, contralateral mediastinal lymphadenopathy, or supraclavicular lymph node involvement. All patients had histologically or cytologically confirmed non-small-cell lung cancer, measurable or evaluable disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. All patients required adequate hematologic parameters, including a white blood count $\geq 4000/mm^3$, granulocyte count $\geq 2000/mm^3$ and platelet count $\geq 100\,000/mm^3$, adequate hepatic function with bilirubin level ≤ 2 mg/dl, adequate renal function with serum creatinine concentration ≤ 1.5 mg/dl, and adequate cardiac function, with no active arrhythmias or congestive heart failure. Exclusion criteria included mixed non-small-cell and small-cell histologies, brain metastasis, myocardial infarction within the previous year, previous extensive radiation to $>30\%$ of marrow bearing bone. Patients whose only measurable site of disease was contained within a site of previous irradiation were excluded. Patients with a history of malignancy within the preceding 5 years (except for non-melanomatous skin cancer) were excluded. Additional exclusions included pregnant women and completion of radiation or biologic therapy less than 4 weeks before initiation of treatment.

Pretreatment evaluation consisted of complete history and physical examination, chest X-ray, complete blood count, serum chemistry analysis, which included a liver function test, CEA level, blood urea nitrogen (BUN) and creatinine assessment. Computed tomographic (CT) scan of the chest and abdomen and bone scans were performed when clinically indicated. CT scans were obtained where an adequate lesion(s) was not clearly assessable by physical examination or chest X-ray. All pretreatment studies were performed within 2 weeks of treatment initiation. A chest X-ray was performed before each cycle, and if necessary CT scan of the chest and abdomen were repeated after 2 and 6 cycles of treatment.

2.2. Treatment

Patients received paclitaxel at a dose of 200 mg/m^2 by intravenous infusion over 3 h. Premedication, given to prevent potential hypersensitivity reactions, consisted of dexamethasone 10 mg, given orally 6 and 12 h before paclitaxel initiation; diphenhydramine 50 mg IV, ranitidine 50 mg IV, and dexamethasone 20 mg IV 30–60 min before paclitaxel administration. Carboplatin was given following paclitaxel by 30-minute infusion, with the dose targeted to an area under the plasma concentration time curve (AUC) of 6 mg/dl per min as determined using the Calvert formula [13]. Creatinine clearance was estimated for each patient using the pretreatment serum creatinine level and the Cockroft-Gault formula [14]. A 5-HT3 serotonin receptor antagonist, granisetron 3 mg was administered intravenously before chemotherapy. The regimen was repeated every 21 days to a planned maximum of 6 cycles. Patients who continued to respond were permitted to receive additional cycles of the same regimen. Granulocyte colony-stimulating factor 5 μg/kg by subcutaneous injection was administered to patients who developed grade 4 granulocytopenia or febrile neutropenia during the previous cycle, but was not routinely used during the subsequent courses. Treatment delay was allowed but not longer than 2 weeks. No dose adjustments were allowed. Treatment was discontinued in patients with progressive disease or in the presence of unacceptable toxicity or treatment delay of more than 2 weeks, caused by toxicity from chemotherapy. The post chemotherapy treatment i.e. radiation and/or surgery was determined by the investigator's judgment depending on the response, performance status, and remnant tumor after 6 cycles of chemotherapy. The treatment also took into account patients' desires.

2.3. Response and toxicity criteria

Response evaluation was based on World Health Organization (WHO) criteria [15]. A complete response was defined as complete disappearance of all disease on radiographic and physical examination for a minimum of 4 weeks. Partial response was defined as a greater than 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum of 4 weeks. Stable disease was defined as no detectable change in the tumor volume of all the lesions. Progressive disease was defined as a greater than 25% increase in the sum of the products of the perpendicular diameters of all the measurable lesions or by the appearance of new lesions. Toxicities were assessed using the WHO common toxicity criteria and guidelines.

2.4. Statistical analysis

All patients enrolled were monitored for treatment related toxicity, response, time to response, site of response, time to progression and time to death. Time to progression and survival were calculated from the date of entry into the study. Time to progression was defined as time to disease progression or time to death in absence of disease progression. Time to death was defined as time to death or last follow up.

Event-free survival and overall survival time were estimated using the method of Kaplan and Meier [16] and groups were compared by log-rank test [17].

3. Results

From April 1996 through July 1997, 53 patients were enrolled: 20 at Pramongkutklao Hospital, 15 at Ramathibodi Hospital, 10 at Rajavithi Hospital and 8 at National Cancer Institute of Thailand. All 53 patients were assessable for toxicity, response and survival. The characteristics of the 53 patients are listed in Table 1. There were 34 men and 19 women, with a median age of 56 years (range, 20–77 years) and a median ECOG PS of 1 (range, 0–2). Twenty patients had stage IIIB and 33, stage IV disease. The predominant histology was adenocarcinoma (64%). Only one patient had received prior radiation therapy to bone metastasis. Seventeen patients (35%) had weight loss $\geq 10\%$. Twenty seven patients (54%) were smokers, of whom 21 patients (42%) smoked ≥ 20 packs per year. Twenty three patients (46%) had never smoked. Pretreatment CEA levels were available in 43 patients with a median level of 8 ng/ml (range, 1–952) and 21 patients (49%) had pretreatment CEA level higher than 10 ng/ml. Patients with stage IIIB were defined by malignant pleural effusion (8 patients), great vessels involvement (four patients) contralateral mediastinal lymphadenopathy (seven patients) and supraclavicular lymph node involvement (five patients). Of 33 patients with stage IV disease, sites of metastasis included bone ($n = 18$ (55%)), contralateral lung ($n = 8$ (24%)), lymph node ($n = 8$ (24%)), liver ($n = 7$ (21%)), pericardial effusion ($n = 4$ (12%)), adrenal glands ($n = 3$ (9%)), soft tissue ($n = 2$ (6%)), thyroid gland ($n = 2$ (6%)), and skin ($n = 1$ (3%)).

Table 1
Patient characteristics

	Number	%
Number of study	53	
Age (year)		
Median (range)	56 (20–77)	
Sex		
Male	34	64
Female	19	36
ECOG performance status		
0	15	28
1	27	51
2	11	21
Pretreatment weight loss ($n = 49$)		
$<10\%$	32	65
$\geq 10\%$	17	35
Smoking ($n = 50$)		
Never smoked	23	46
Smoker	27	54
≥ 20 pack per year	21	42
Histology		
Adenocarcinoma	34	64
Bronchoalveolar	3	6
Squamous cell carcinoma	15	28
Large cell carcinoma	2	4
Undifferentiated carcinoma	2	4
Stage		
IIIB	20	38
IV	33	62

4. Drug delivery

A total of 272 cycles of paclitaxel and carboplatin were administered. The median number of cycles received was six (range, 2–6). Fifty two cycles (24%) of the 219 subsequent cycles were delayed due to asthenia ($n = 33$ (63%)), prolonged neutropenia ($n = 5$ (10%)), myalgia, ($n = 5$ (10%)), paresthesia ($n = 5$ (10%)), infection ($n = 4$ (7%)), prolonged thrombocytopenia ($n = 2$ (4%)), anemia ($n = 1$ (2%)), deep vein thrombosis ($n = 1$ (2%)) and fractured femur ($n = 1$ (2%)). The median duration of delay was 7 days (range, 1–14). Thirty seven patients (70%) completed all six cycles of treatment. Fifteen patients received further courses of paclitaxel and carboplatin due to continued tumor shrinkage after the sixth cycle of treatment or continued in remission. The remaining 16 patients were taken off treatment before completing six cycles according to the following reasons: tumor progression ($n = 12$), toxicities (($n = 2$) prolonged thrombocytopenia (1 case), angina pectoris (1 case)), declining performance status ($n = 1$), cerebrovascular accident ($n = 1$).

5. Toxicities

The toxicities of this regimen were generally well tolerated. Two hundred and seventy two courses were administered. The major toxicity was myelosuppression.

Table 2
Hematologic toxicity[a]

Toxicity	Cycle number						Total %
	1	2	3	4	5	6	
Anemia							
Grade 1–2 (%)	32	42	47	61	64	59	49
Grade 3 (%)	0	0	4	2	5	6	3
Leucopenia							
Grade 1–2 (%)	42	43	35	41	39	38	40
Grade 3 (%)	6	4	2	7	3	0	4
Granulocytopenia							
Grade 1–2 (%)	20	19	29	27	31	29	25
Grade 3–4 (%)	32	32	18	30	18	18	25
Thrombocytopenia							
Grade 1–2 (%)	2	4	6	5	3	9	4
Grade 3 (%)	0	0	2	2	0	3	1
G-CSF usage (%)	23	28	33	32	26	29	28
Number of cycles	53	53	49	44	39	34	N = 272

[a] ($n = 272$).

Grade 4 granulocytopenia occurred in 13% of 272 assessable cycles and grade 3 or 4 granulocytopenia occurred in 25% of assessable cycles (Table 2). Granulocytopenia was most pronounced during the first cycle, during which 32% of patients had grade 3 or 4 toxicity without G-CSF prophylaxis. Febrile neutropenia documented in three patients occurred in 4 treatment cycles (1.5%). After intravenous antibiotics and G-CSF, all of them recovered. G-CSF was administered in 28% of assessable cycles due to febrile neutropenia 4 cycles (5%), grade 3–4 granulocytopenia 27 cycles (35%) and prophylaxis 46 cycles (60%). Grade 3 infection occurred in 4 treatment cycles which developed in patients with febrile neutropenia. One treatment cycle associated with grade 2 infection. Of the 272 treatment cycles, the median ANC was 1.9×10^6/l (range, 0–57).

Thrombocytopenia was uncommon. Grade 3 thrombocytopenia occurred in 3 treatment cycles (1%). The median platelet nadir was 200×10^6/l (range, 41–781). The toxicity was cumulative; grade 3 thrombocytopenia developed in cycles 3, 4 and 6 compared with none during cycles 1 and 2. Only one patient required platelet transfusions during cycle 5 of treatment.

Anemia, although generally mild, was also cumulative, with the incidence of grade 1 or 2 anemia increasing from 32% during the first cycle to 64% by cycle 5 (Table 2). Grade 1 or 2 anemia occurred in 49% of assessable cycles, grade 3 anemia developed in only 3% of assessable cycles, and grade 4 anemia was not observed. Seven patients with grade 2 or 3 anemia required a transfusion of a total of 15 units of packed red blood cells during cycles 3 to 6 of treatment.

Myelosuppression associated with this regimen tended to be cumulative (Table 2) except granulocytopenia which can be salvaged by G-CSF.

Non hematologic toxicities were generally modest. Neuropathy, asthenia and myalgia/arthralgia were generally mild but cumulative. Grade 3 myalgia and arthralgia occurred in 10 and 3% of treatment cycles, respectively. Hypersensitivity occurred in three patients. Grade 1 allergy occurred in one patient who developed flushing on her face during paclitaxel infusion but no other symptoms and signs. One patient developed grade 3 allergy with fainting and hypotension (blood pressure 90/60 mmHg) during paclitaxel infusion in her first, fourth and fifth cycles of treatment. Her blood pressure and symptoms fully recovered after normal saline intravenous infusion and pacli-

taxel infusion was completed uneventfully. One patient developed anaphylactic shock during paclitaxel infusion in the second cycle. She fully recovered after intravenous dexamethasone, antihistamine and normal saline infusion. After further premedication was given, rechallenge of paclitaxel infusion was completed uneventfully. All three patients had received premedication as outlined in the protocol. Grade 3 alopecia occurred in 52% of treatment cycles. Mucositis and diarrhoea were rare. There were no other cardiac events noted except one patient who developed angina pectoris with 3 different treatment cycles.

6. Response and survival

The objective response rate for 53 patients was 55% (95% confidence interval (CI) 41–68%) with 27 (51%) partial responses and 2 (4%) complete responses. Stable disease was observed in 16 patients (30%) and progressive disease after two cycles in eight patients (15%) (Table 3). Among the 20 stage IIIB patients, 1 (5%) had a complete response, 10 (50%) had a partial response, for an overall response rate of 55%, and 9 (45%) had stable disease. The patient with complete response had primary pulmonary lesion and malignant pleural effusion. He received 8 cycles of paclitaxel and carboplatin and remained progression free with good performance status for 50 weeks. Of the 33 patients with stage IV disease, 1 (3%) had a complete response, 17 (52%) had a partial response, for an overall response rate of 55%, and 7 (21%) had stable disease. (Table 3). The stage IV patient with a complete response had complete resolution of primary pulmonary lesion, mediastinal lymph node and pleural effusion that lasted 55 weeks. The abnormal bone scan of this patient was unchanged after completing 6 cycles of treatment.

Table 3
Tumour responses

Response	Number of patients (%)		
	Stage III B+ IV	Stage III B	Stage IV
Overall response	29(55)	11(55)	18(55)
Complete response	2(4)	1(5)	1(3)
Partial response	27(51)	10(50)	17(52)
Stable disease	16(30)	9(45)	7(21)
Progressive disease	8(15)	0(0)	8(24)

Table 4
Time to response

	Time to response (weeks)						Total	
	<6		$>6 \leq 12$		>12			
Response	No	(%)	No	(%)	No	(%)	No	(%)
CR			2		–		2	4
PR	9		12		6		27	51
SD							16	30
PD							8	15
CR/PR	9	17	14	27	6	11	29	55

The median time to response was 8 weeks; 2 complete responses were observed after 3 and 4 cycles. Nine of 27 partial responses were observed after two cycles and 12 of 27 partial responses occurred after 3 or 4 cycles (Table 4). The predominant sites of responses were lung mass (28/53, 53%), pleural effusion (11/22, 50%), and lymph nodes (15/47, 32%) but responses have also been observed in two of three (67%) adrenal metastases, two of seven (29%) liver metastasis, and one of two (50%) soft tissue metastases.

The median progression free survival time for all patients, defined as time to disease progression or time to death in the absence of disease progression, was 28 weeks with a 95% CI of 18 to 37 weeks. The median progression free survival time in patients with stage IIIB was 31 weeks (95% CI, 21–41 weeks) compared with 22 weeks (95% CI, 16–29 weeks) for stage IV patients with no significant difference between the two groups ($P = 0.19$) (Fig. 1). At a median follow-up of 55 weeks, the median survival time for all 53 patients is 55 weeks (95% CI, 51–59 weeks) and the1-year survival rate is 55% (95% CI, 41–68%). Patients with stage IIIB had a significantly longer median survival time (75 weeks (95% CI, 51–92 weeks))

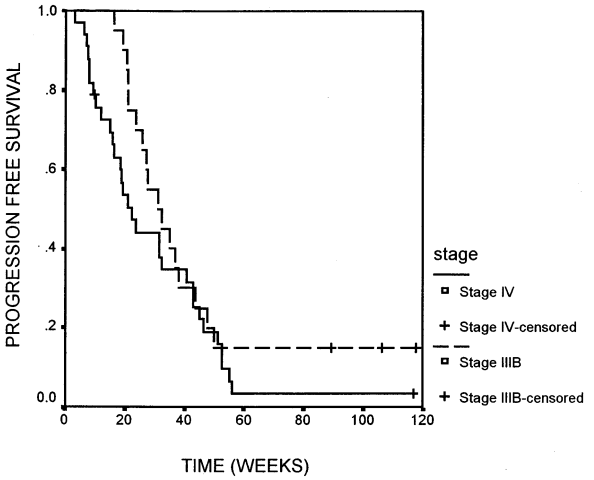

Fig. 1. Median progression free survival time, defined as freedom from disease progression or death from other causes for stage III B and stage IV patients was 31 weeks (95% CI, 21–41 weeks) and 22 weeks (95% CI, 16–29 weeks), respectively ($P = 0.19$).

when compared with those who had stage IV disease (median survival 46 weeks (95% CI, 34–58 weeks), P $= 0.007$; Fig. 2). The 1-year survival rate for stage IIIB group was also significantly higher than stage IV group (80% (95% CI, 62–97%) vs. 42%(95% CI, 26%–59%); $P = 0.003$)).

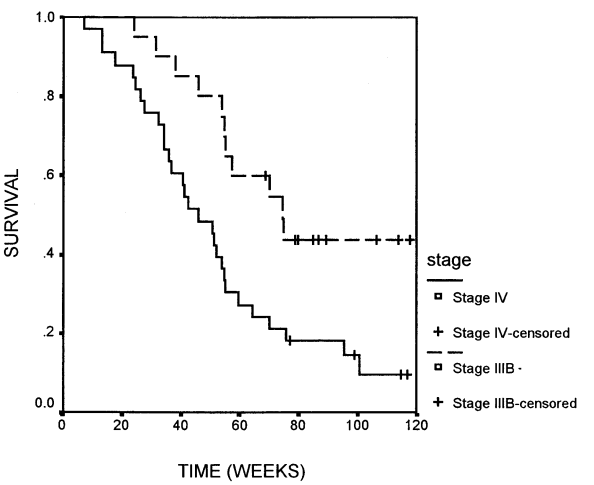

Fig. 2. Overall survival curve, median survival time for stage III B and stage IV patients was 75 weeks (95% CI, 51–92 weeks) and 46 weeks (95% CI, 34–58 weeks), respectively ($P = 0.007$). 1 year survival rates for stage III B and stage IV were 80% (95% CI, 62–97%) and 42% (95% CI, 26–59%), respectively, ($P = 0.003$).

Among 20 stage IIIB patients, additional radiation was given to 11 patients for remnant tumour in the chest. Two patients with stage IIIB disease had a lobectomy after completing 7 and 8 cycles of chemotherapy and radiation to the chest and remain progression free at 117 + and 87 + weeks. One stage IIIB patient developed brain metastasis after 6 cycles of chemotherapy and received brain mass resection with cranial radiation afterwards. The median progression free survival of stage IIIB patients who received chemotherapy plus radiation plus surgery was significantly longer than patients who received chemotherapy alone (90 + weeks vs. 35 weeks, $P = 0.036$). The stage IIIB patients who received chemotherapy plus radiation had shorter median progression free survival time when compared with either patients who received chemotherapy alone (26 vs. 35 weeks, $P = 0.42$) or patients who received chemotherapy plus radiation plus surgery (26 vs. 90 + weeks, $P = 0.051$). The differences in median overall survival time in stage IIIB patients, depending on the treatment: chemotherapy alone versus chemotherapy plus radiation versus chemotherapy plus radiation plus surgery, were not statistically significant. (70 vs. 57 vs. 89 + weeks). However, it is noteworthy that the survival estimates cannot be computed since all three patients in the chemotherapy plus radiation plus surgery group are still alive, as are a small number of patients in each treatment group. In 33 patients with stage IV disease, 19 patients received chemotherapy alone, 13 patients received additional radiation for remnant tumor in chest; 12 cases, for brain metastasis; 1 case. One patient received additional radiation for remnant tumor in the chest and a resection for metastatic adrenal gland after finishing chemotherapy. The median progression free survival and median survival time of stage IV patients who received either chemotherapy alone or chemotherapy plus radiation or chemotherapy plus radiation plus surgery were 22, 19, and 117 + weeks, respectively; and 41, 54 and 117 + weeks, respectively. Similar to the stage IIIB group, it was noted that in a small number of patients in each group of treatment, the differences in progression free survival and overall sur-

vival time in stage IV patients who received either chemotherapy or chemotherapy plus radiation or chemotherapy plus radiation plus surgery, were not statistically significant. Thus, survival estimates cannot be calculated.

At the time of analysis, four patients (7%) remain progression free at 87+ to 117+ weeks, and 13 patients (24%) remain alive. Five patients survived more than 2 years (106+ −117+ weeks). Three of these were stage IIIB. One patient achieved complete remission after 6 cycles of chemotherapy, 1 patient had a stable disease response after chemotherapy and received additional radiation, 1 patient had a partial response after chemotherapy and received additional radiation and lobectomy. The latter two patients still had not progressed. Two of the five patients who survived longer than 2 years were stage IV. One of these achieved stable disease after 6 cycles of chemotherapy alone. Another stage IV patient achieved a partial response after chemotherapy, received additional radiation and adrenalectomy and still had not progressed.

7. Discussion

In the past 5–6 years a number of new drugs have been shown to have good activity against NSCLC, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan [18]. One promising novel agent is paclitaxel, since it has yielded objective response rates of greater than 20% in patients with advanced NSCLC and has been associated with promising improvement in 1 year survival in two phase II studies [10,11]. Single agent carboplatin has been shown to significantly improve survival and produce less toxicity than cisplatin-based combination chemotherapy in advanced NSCLC in a randomized study conducted by the Eastern Co-operative Oncology Group [9]. It was these observations, coupled with the good response rate and manageable toxicity profile of paclitaxel (24 h infusion) and carboplatin in combination [12], that prompted our group to investigate a more convenient regimen of paclitaxel (3 h infusion) and carboplatin in combination in a pilot study in advanced NSCLC in the Thai population.

In this study, we observed a favorable objective response rate of 55%, a median survival time of 55 weeks, and a 1 year survival rate of 55%. Our results are encouraging and compare favorably with response rate and survival results following cisplatin based chemotherapy [5,6,9]. Responses were observed in most of the measurable disease sites; some responses lasted more than 1 year. The median progression-free survival time of 28 weeks exceeded the duration of therapy. In subgroup analysis, stage IIIB NSCLC patients had a significantly longer median survival time and better 1 year survival rate than stage IV (75 vs. 46 weeks; 80 vs. 42%). Stage IIIB NSCLC patients who received chemotherapy followed by radiation and surgery had a significantly longer progression free survival time than those who received chemotherapy alone. The median survival time of neither stage IIIB nor stage IV NSCLC patients was statistically influenced by the additional treatment after finishing 6 cycles of chemotherapy.

The majority of patients enrolled onto our study tolerated treatment well and received all six cycles planned. Although 24% of subsequent cycles of treatment were delayed mostly due to asthenia, the median duration of the delay was only 1 week. Three patients were taken off the study because of thrombocytopenia or angina pectoris or progressive fatigue respectively. The most common complication was grade 3 or 4 granulocytopenia, which developed in only 25% of treatment cycles. In contrast, the low incidence of severe thrombocytopenia (1%) was actually less than anticipated based on reports with carboplatin alone [9] or in combination with etoposide [7]. This platelet-sparing phenomenon was also observed in trials in patients with NSCLC and ovarian cancer [19–21]. Although the exact mechanism of the platelet effect observed with paclitaxel/carboplatin has not yet been identified, several hypotheses have been proposed. One such hypothesis is that since paclitaxel is heavily sequested in tubulin-rich platelets, these paclitaxel-containing platelets may have a prolonged circulation time, or they may impair platelet clearance [22]. Other hypotheses are the possibilities that paclitaxel may stimulate cytokine production, leading to increased production of thrombopoietin [23].

Alternatively, a component of the drug formulation vehicle, such as cremophor or ethanol may directly affect platelet production or affect cytokines to elicit a secondary bone marrow response [24].

In addition to our study, several other investigators have used the combination of paclitaxel and carboplatin in advanced NSCLC with promising results i.e. response rates of 27–62%, median survival time of 9.5-13 months, and estimated 1-year survival rates of 32–54% [12,19,25,26]. Their results are comparable to our results.

Regarding the post chemotherapy treatment, among 20 stage IIIB patients, 11 (55%) received additional radiation and three patients (15%) received additional radiation and surgery. The median survival time of the stage IIIB patients who received chemotherapy plus radiation plus surgery of 22 + months was longer than that of the chemotherapy alone group (17months) and chemotherapy plus radiation group (14 months). However, the difference in median survival times of the post chemotherapy treatment subgroups in stage IIIB disease was not statistically significant. This could be due to the small number of patients in each subgroup. The median survival time of other studies in stage IIIB NSCLC that used sequential radiation after the combination mitomycin, vindesine and cisplatin or concurrent chemoradiation after induction paclitaxel and carboplatin were 13 months and 14 months, respectively. [27,28]. Their results were comparable to our results in stage IIIB patients who received chemotherapy and subsequent radiation. In our study, although only 3 stage IIIB patients received chemotherapy followed by radiation and surgery, one of them is still alive and has not progressed. The median survival time of this subgroup of 22 + months was comparable to the results of the study using intensive preoperative chemotherapy and concurrent chemoradiation followed by surgery in stage IIIB NSCLC (18 months) [29]. Choy et al [30] have recently demonstrated that combined modality therapy with paclitaxel, carboplatin, and radiation in the treatment of stages IIIA and IIIB, has a high response rate of 76%, a median survival time of 20.5 months, and a I-year survival rate of 56%. Although our study was not originally designed to evaluate the effect of chemoradiation in the treatment of stage IIIB NSCLC, survival data from stage IIIB patients in our study and others [28,30] have shown that the combined modality therapy with paclitaxel, carboplatin and radiation is a promising treatment for locally advanced NSCLC. In the stage IV patient group, 13 patients (39%) received additional radiation and only 1 patient (3%) received radiation and surgery after finishing chemotherapy. Similar to the stage IIIB group, possibly due to the small number of patients in post chemotherapy treatment subgroups, the difference in median survival time between post chemotherapy treatment subgroups in stage IV patients was not statistically significant. However, it should be pointed out that one patient in the stage IV group who received chemotherapy plus radiation plus surgery, had a median progression free survival time, and median survival time of more than 29 months. Therefore, it appears that additional radiation and surgery of the resectable tumor, after chemotherapy might be beneficial to some good performance status, stage IV patients.

The median survival time of 46 weeks for stage IV patients in our study was better than the 24 weeks reported by the other study using the combination of cisplatin and etoposide in stage IV NSCLC [5]. In other studies with a high percentage of stage IV patients (88–93%), which used paclitaxel and carboplatin in the treatment of advanced NSCLC, the median survival times were 32 weeks [31], 38 weeks [19], and 53 weeks [12]. These are all comparable to the median survival time of 46 weeks for our stage IV patients. Similarly, the 1 year survival rates of those studies were 32, 36, and 54% [12,19,31] which also compare with our results of 42%, reported here, in stage IV patients.

Two randomized phase III trials have recently been carried out, comparing paclitaxel plus carboplatin with other standard regimens used in NSCLC, including cisplatin/etoposide and vinorelbine/cisplatin [31,32]. Results of a reported randomized phase III study showed that paclitaxel/carboplatin arm produced a superior response rate when compared with a standard

cisplatin/etoposide regimen (22 vs. 14%, $P = 0.059$) [32]. Results of another recently reported phase III randomized South West Oncology Group (SWOG) trial showed that paclitaxel/carboplatin produced similar response rates and survival when compared with the SWOG standard vinorelbine/cisplatin regimen (PR 27 vs. 27%; median survival time 8 vs. 8 months) [31]. The results of the SWOG study were comparable to the results reported here. The SWOG study also showed that the paclitaxel/carboplatin arm had a favorable toxicity profile and better tolerability and compliance when compared with the vinorelbine/cisplatin arm. It has additionally been shown that quality of life (QOL) was maintained (improved or stable) in 60% of patients in both arms.

From the promising results of our study and other paclitaxel (1–3 h infusion) plus carboplatin studies [25,26,31–33], we surmise that a shorter infusion of paclitaxel in combination with carboplatin both provides effective palliation and is convenient in the management of advanced NSCLC.

Paclitaxel (3 h infusion) in combination with carboplatin, has the advantage of being moderately active and well tolerated in patients with advanced NSCLC and also much easier to administer on an outpatient basis. At the moment, it is premature to conclude that this regimen is superior to existing cisplatin-based regimens. Shortly, however, the mature data from the two randomized phase III trials [31,32] comparison of paclitaxel plus carboplatin to cisplatin plus etoposide regimen or vinorelbine plus cisplatin regimen will give us more information. Additional randomized control trials comparing carboplatin plus paclitaxel to existing cisplatin-based regimens are warranted.\

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