Paclitaxel and Carboplatin Plus Megestrol Acetate in the Treatment of Advanced Non-Small Cell Lung Cancer

SUMITRA THONGPRASERT, M.D.*, RATTIYA CHEEWAKRIANGKRAI, M.D.*,
JUNTIMA EUATHRONGCHIT, M.D.**, KANITTHA THAIKLA, M.B.A.***

Abstract

The present study evaluated the efficacy and toxicity of paclitaxel and carboplatin with megestrol acetate for patients with stage IIIb and IV non-small cell lung cancer (NSCLC). Forty patients with no prior chemotherapy and Karnofsky performance status of ≥60 were enrolled in the study. There were 18 males and 22 females with a median age of 57.5 years, and the median performance status was 70 per cent. Eleven cases were stage IIIb and 29 cases were stage IV. Twenty-five cases were adenoCA, 12 were squamous cell, 2 were large cell and one was undifferentiated NSCLC. These patients received paclitaxel 135 mg/m^2 by intravenous infusion over 24 hours before carboplatin was given at AUC=6 by 2 hours infusion. Megestrol acetate 160 mg/day was given to all patients from day 2 to 14. This treatment produced partial remission in 12 of 39 evaluable patients (30.76%). Toxicity caused mild nausea, vomiting, myalgia, neuropathy, 20.95 per cent grade 3 neutropenia and 4.15 per cent grade 4 neutropenia. Grade 3 thrombocytopenia was 5.4 per cent, without grade 4. There were no statistically significant changes in weight, serum albumin, and quality of life throughout the cycle 1-6.

Conclusion : The addition of megestrol acetate to chemotherapy benefitted these patients by minimizing constitute symptoms throughout the treatment period especially in the quality of life, weight loss and stabilized serum albumin.

Key word : Non-Small Cell Lung Cancer, Paclitaxel, Carboplatin, Megestrol Acetate, Chemotherapy of NSCLC

**THONGPRASERT S, CHEEWAKRIANGKRAI R,
EUATHRONGCHIT J, THAIKLA K
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* Divistion of Medical Oncology, Department of Medicine, Faculty of Medicine,
** Department of Radiology, Faculty of Medicine,
*** Research Institute for Health Science, Chiang Mai University, Chiang Mai 50200, Thailand.

Lung cancer remains the leading cause of death from cancer worldwide[1]. In Thailand, it ranked the first of ten leading sites of cancers in both sexes according to records in 1997 at Maharaj Nakorn Chiang Mai Hospital, Tumor Registry[2]. Unfortunately, the majority of lung cancer patients came in with inoperable stage III disease, or metastatic disease (stage IV). Although chemotherapy can effect a modest improvement in survival, this gain often comes with a substantial host toxicity, especially in patients who are less than fully ambulatory[3-5]. Two of the common toxicities of chemotherapy are poor appetite and weight loss. Megestrol acetate has been used to stimulate appetite and promote weight gain in a limited number of patients with cachexia associated with neoplastic diseases [6-8]. In advanced breast cancer, Kornblith et al[8] suggested that megestrol acetate at a dose of 160 mg/day is optimal with the fewest side effects and better quality of life. These observations prompted this study to administer megestrol acetate at 160 mg daily into a chemotherapeutic program consisting of paclitaxel and carboplatin in the treatment of advanced non-small cell lung cancer (NSCLC) in Thailand.

PATIENTS AND METHOD

Between January 1999 and April 2000, 40 patients with stage IIIB or IV NSCLC were enrolled. In order to be eligible for protocol enrollment, patients were required to have histologically confirmed, inoperable, stage IIIB or IV NSCLC. No prior cytotoxic chemotherapy was allowed. Bidimensionally measurable disease was required. All patients were aged over 18 years. They required a Karnofsky performance status of more than 60 and a life expectancy of more than 12 weeks. The required laboratory parameters included serum creatinine of less than 1.5 mg/dl, total bilirubin of less than 1.5 mg/dl, SGOT of less than 3 times the normal upper limit, granulocytes over 2000/mm^3, and hemoglobin over 9 g/dl. Pregnant or lactating females, patients with a history of other malignancies within the previous 5 years (excluding superficial non-melanoma skin cancer or carcinoma in situ of the cervix), and patients with other serious medical conditions that would interfere with chemotherapy treatment, were excluded. Pretreatment evaluation consisted of a complete history and physical examination, chest X-ray, complete blood count, serum chemistry analysis (which included a liver function test), blood urea nitrogen (BUN) and creatinine assessment. Weight, serum albumin, and the total protein of all patients were recorded at each visit prior to the start of chemotherapy. Quality of life questionnaires (modified FLIC)[9] were presented to all patients and data obtained by research nurses at each visit. Computed tomographic (CT) scans of the chest and upper abdomen, and bone scans were performed when indicated clinically. All pretreatment studies were performed within 2 weeks of treatment initiation. A chest X-ray was performed before each cycle of chemotherapy and if necessary, CT scan of the chest and abdomen were repeated after 4 and/or 6 cycles of treatment.

Patients received paclitaxel at a dose of 135 mg/m^2 by intravenous infusion over 24 h. Premedication, given to prevent potential hypersensitivity reactions, consisted of dexamethasone at 20 mg, given intravenously (IV) 24 h before paclitaxel initiation. Diphenhydramine at 50 mg orally, cimetidine 300 mg IV, and dexamethasone 10 mg IV, 30-60 minutes before paclitaxel administration. Carboplatin was given following paclitaxel by 60 minutes IV infusion, with the dose targeted to an area under the plasma concentration time curve (AUC) of 6 mg/dl per minutes as determined using the Calvert formula [10]. Creatinine clearance was estimated for each patient by using the pretreatment serum creatinine level and Cockroft-Gault formula. Megestrol acetate at 160 mg daily was administered orally on day 2-14.

Tumor response and toxicity criteria

Response evaluation was based on World Health Organization (WHO) criteria. 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 per cent reduction in the sum of the perpendicular diameter products 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 per cent increase in the sum of the perpendicular diameter products of all the measurable lesions or by the appearance of new lesions. Toxicities were assessed using the WHO common toxicity criteria and guidelines.

Statistical analysis

All patients enrolled were monitored for treatment related toxicity, response, and overall survival time, which were estimated using the Kaplan and Meier method. The SAS statistical package was used. The repeated measures analysis of variance was used to compare pre-and post-treatment weight, serum albumin, total protein and quality of life (QOL) scores.

RESILTS

From January 1999 through April 2000, 40 patients were enrolled. All 40 patients were assessed for toxicity and quality of life analysis and 39 patients were assessed for response and survival. The characteristics of the 40 patients are listed in Table 1. There were 18 men and 22 women, with a median age of 57.5 years (range, 40-73 years) and a median Karnofsky PS of 70 per cent (range, 60-90%). Eleven patients had stage IIIB and 29 had stage IV disease. The predominant histology was adenocarcinoma (25 cases). Four patients with stage IIIB (40%) were defined by malignant pleural effusion, one patient had pericardial effusion, and one had satellite nodules in the lung. Of 29 patients with stage IV disease, six cases had bone metastases, ten patients had contralateral lung metastases, three patients had liver metastases and two cases had soft tissue and lymph node metastases. There was one case with metastases to both the lung and liver, one with metastases to lung and adrenal gland, two cases with metastases to lung and liver, two with metastases to lung and bone and another two with lung, bone and retina metastases. A total of 174 cycles of paclitaxel and carboplatin were administered. The median number of cycles received was four (range

Table 1. Patient characteristics.

		%
Total Number	40 cases	
Sex		
Male	18	45.0
Female	22	55.0
Age		
Median (Range)	57.5 (40.0-73.0) years	
Karnofsky Performance Status		
60	8	20.0
70	21	52.5
80	10	25.0
90	1	2.5
Stage		
IIIb	11	27.5
IV	29	72.5
Histologic Diagnosis		
Adenocarcinoma	25 cases	
Squamous cell CA	12 cases	
Large cell carcinoma	2 cases	
Non-small cell carcinoma	1 cases	

Table 2. Responses.

Responses	Stage IIIb		Stage IV	
		%		%
Invaluable	1/11	9.1	-	-
PR	1/10	10.0	11/29	35.4
MR & SD	3/10	30.0	10/29	27.6
PD	6/10	60.0	8/29	37.9

2-6). Fourteen patients (35%) completed all six cycles of treatment. Of thirty-nine patients evaluated, twelve cases achieved partial response (30.76%), and thirteen had a minor response or stable disease (Table 2). The survival time is shown in Fig. 1. Median survival time was 47.29 weeks.

Changes in weight, serum albumin, total protein and quality of life

The changes in weight, serum albumin, total protein and quality of life commenced at each cycle of chemotherapy. There was no significant change in weight and serum albumin throughout the study. (Fig. 2, Fig. 3). However, there were significant changes in total protein (Fig. 3). Quality of life improved slightly throughout the study period, but this change was not significant (Fig. 4).

Toxicities

The toxicities of this regimen were generally well tolerated. One hundred and seventy four courses were administered. The major toxicity was myelosuppression. Grade 4 granulocytopenia occurred in 3.3 per cent of 174 assessable cycles and grade 3 or 4 granulocytopenia occurred in 11.5 per cent of assessable cycles (Table 3). Thrombocytopenia was uncommon. Grade 3 thrombocytopenia occurred in 5.3 per cent of assessable cycles. The toxicity was cumulative; grade 3 thrombocytopenia developed to a higher percentage in cycles 5 and 6 compared with cycles 1, 2 and 3. Anemia, although generally mild, was also cumulative, with an incidence of grade 1 or 2 anemia increasing from 53.9 per cent during the first cycle to 62.5 per cent by cycle 6 (Table 3).

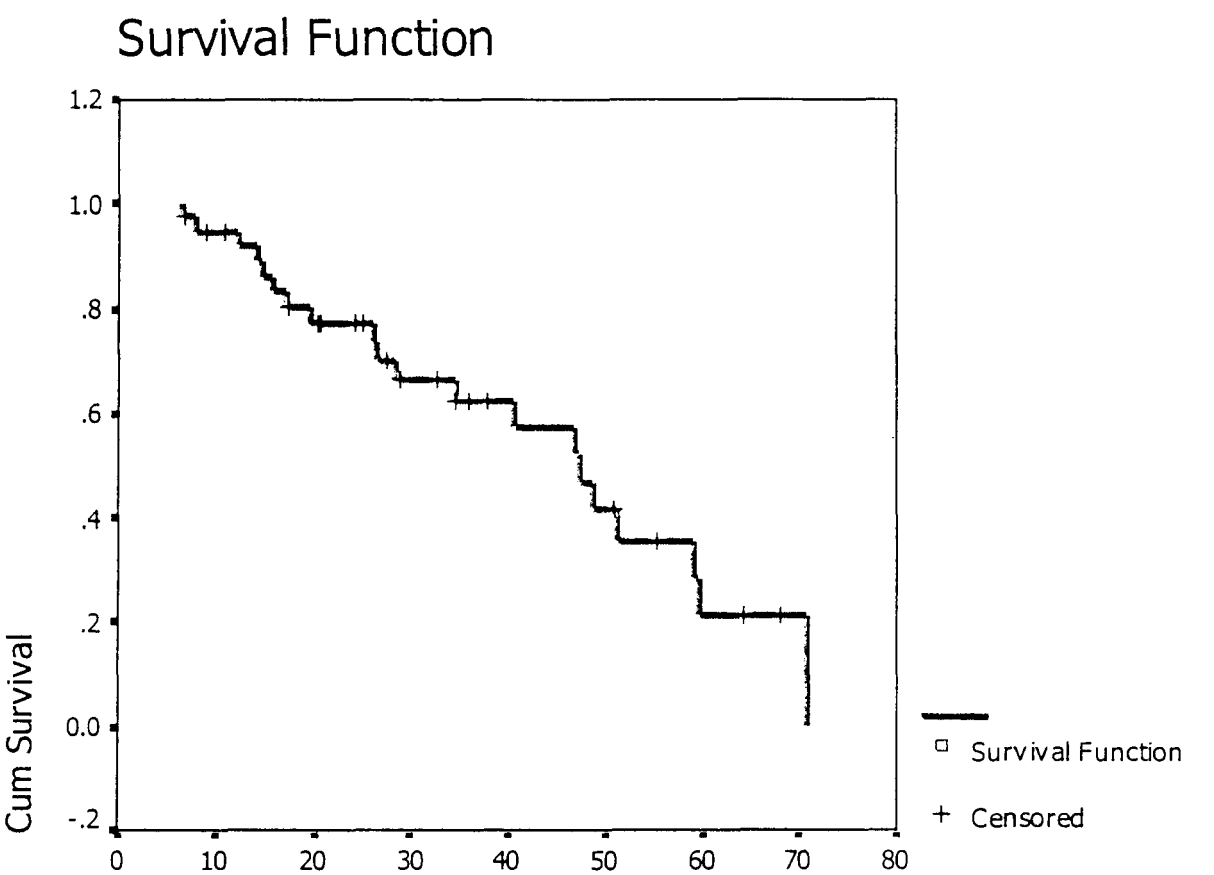
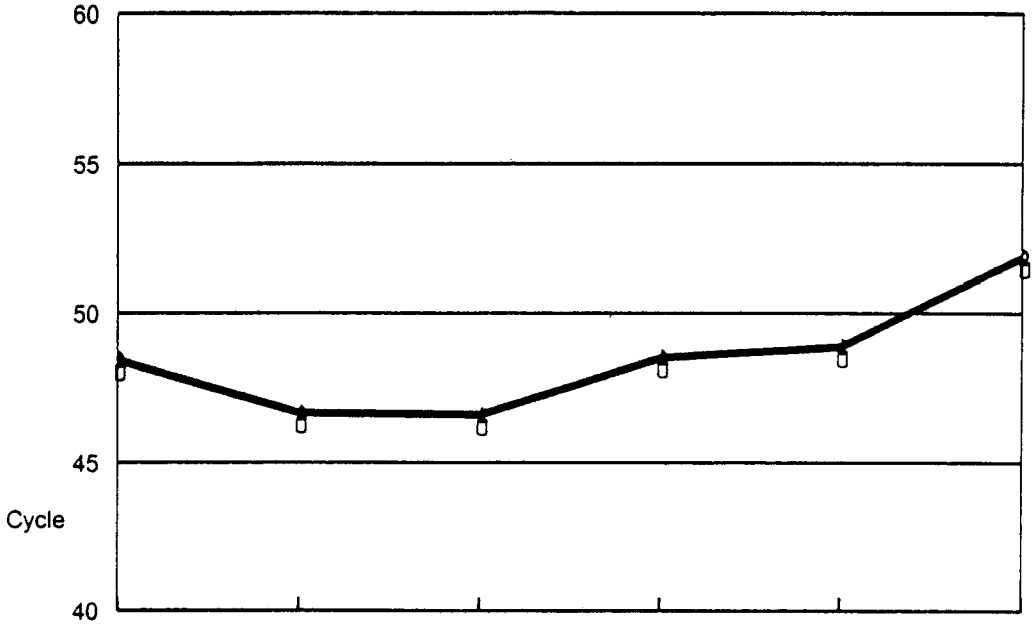
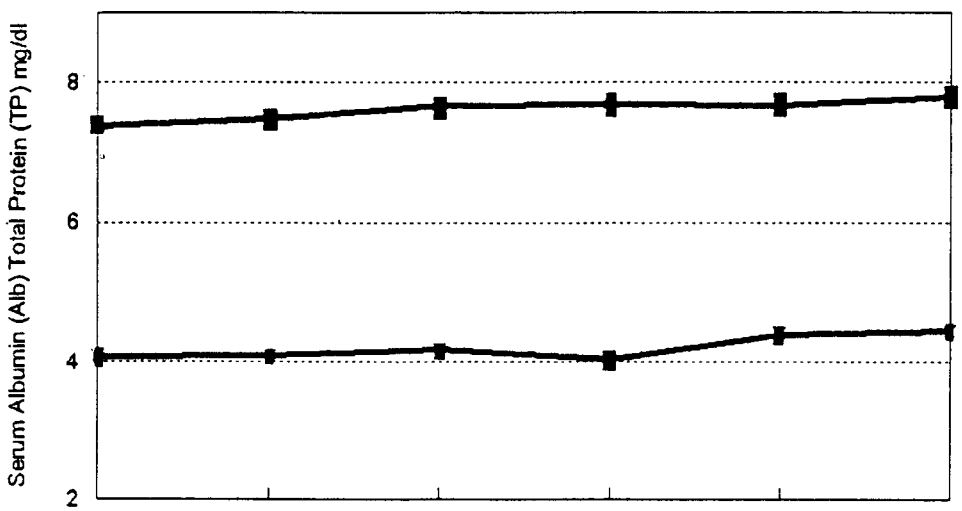


Fig. 1. Overall survival curve (weeks).



Cycle	1(n=40)	2(n=39)	3(n=34)	4(n=27)	5(n=17)	6(n=12)	p
Mean weight±SD	48.44±10.59	46.67±10.41	46.61±10.48	48.51±10.61	48.88±10.69	51.87±11.00	0.5036

Fig. 2. Changes of weight during treatment.



Cycle	1 (n=40)	2 (n=39)	3 (n=34)	4 (n=30)	5 (n=19)	6 (n=12)	p
Mean Alb±SD	4.08± 0.51	4.06±0.55	4.17±0.44	4.03±0.64	4.39±0.35	4.44±0.33	0.88
Mean TP±SD	7.38±0.74	7.49±0.69	7.67±0.56	7.70±0.70	7.68±0.45	7.79±0.45	0.03

Fig. 3. Changes of serum albumin and total protein during treatment.

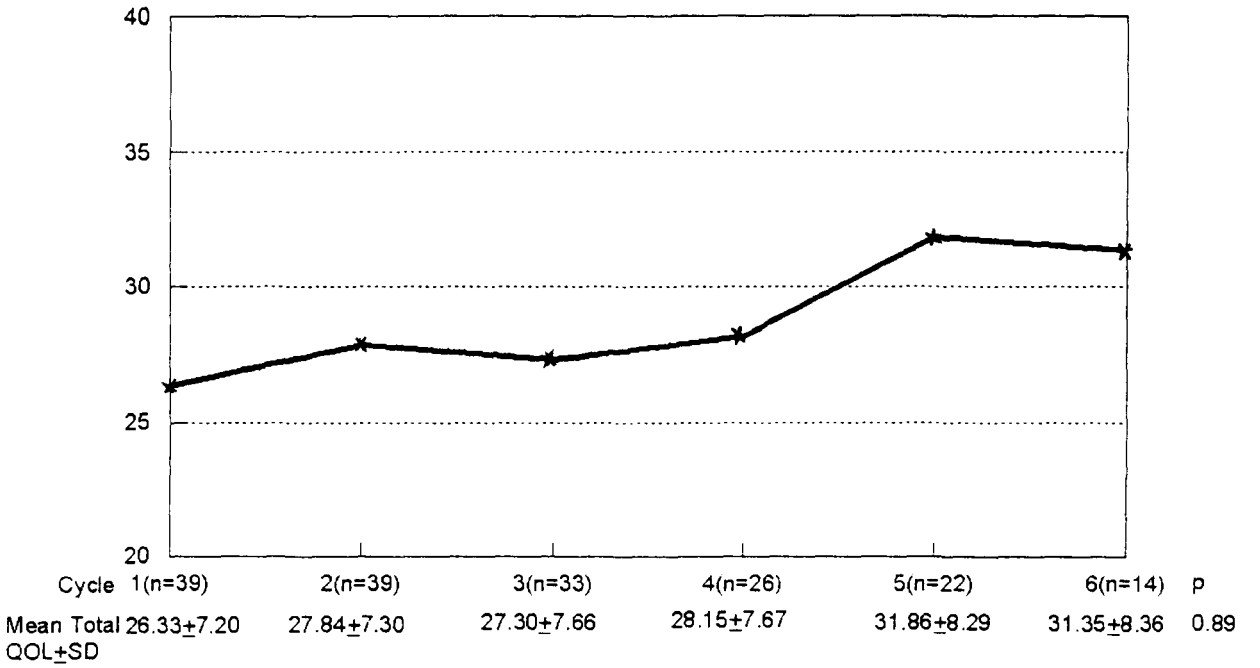


Fig. 4. Changes of total QOL.

Table 3. Hematologic toxicity[a].

Toxicity	Cycle number					
	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)
Anemia						
Grade 1-2	53.9	58.9	68.3	54.5	69.3	62.5
Grade 3	5.1	8.8	3.4	27.3	7.7	-
Grade 4	5.1	8.8	6.9	4.5	-	-
Leucopenia						
Grade 1-2	17.9	38.2	41.4	50.0	38.5	57.2
Grade 3	20.5	17.6	27.6	22.7	38.5	14.3
Grade 4	7.7	2.9	-	-	23.0	14.3
Thrombocytopenia						
Grade 1-2	2.6	5.6	10.3	9.0	7.7	42.9
Grade 3	2.6	-	3.4	4.5	7.7	14.3
Grade 4	-	-	-	-	-	-
Number of Cycles	40	39	34	30	19	12

[a] (n=174)

Non hematologic toxicities were generally modest. Neuropathy, asthenia and myalgia/arthralgia were generally mild but cumulative. Grade 3 myalgia and arthralgia occurred in 5 per cent and 2 per cent of treatment cycles, respectively. No hypersensitivity was observed. Regarding megestrol acetate, there was no evidence of hypertension, edema or any other side effects.

DISCUSSION

This phase II trial was designed to investigate the feasibility of administering megestrol acetate to minimize the toxicity of chemotherapy. Besides the evaluation of toxicity, response to treatment, and overall survival; the change in weight, serum albumin, total protein and quality of life were the key endpoints of the study. The choice of chemo-

therapeutic agents wàs based on a review of the most active regimens that had been reported as of late 1999[11]. Accordingly, paclitaxel and carboplatin were the treatment drugs. The innovative feature of this study was the concomitant use of megestrol acetate throughout the peak period of anorexia post chemotherapy (two weeks). In most trials, this hormonal agent was administered as a single agent to patients who were no longer receiving chemotherapy [6-8]. These studies demonstrated an improvement in the appetite and quality of life of patients receiving megestrol acetate with doses ranging from 160 to 1,800 mg per day. The protocol described herein represents a departure from standard practice in that megestrol acetate was administered concurrently with chemotherapy. Three prior studies have used the concomitant administration of chemotherapy and megestrol acetate in lung cancer. In a phase II trial[12], megestrol acetate was given daily to NSCLC patients receiving the CODE regimen. Compared to patients receiving prednisone as supportive care, those receiving megestrol acetate had less pronounced weight loss. Rowland et al[13] conducted a trial in which 243 patients with extensive stage SCLC were randomized to receive cisplatin and etoposide chemotherapy, plus either megestrol acetate at 800 mg per day or a placebo. Patients who received megestrol acetate experienced improvements in non-fluid weight gain and gastro-intestinal toxicity. Levitan et al[14] conducted a phase II trial using brief intensive cisplatin-based chemotherapy, plus filgastrim and megestrol acetate at 250 mg taken orally throughout the treatment period (ten weeks). They reported the effect of megesterol acetate in the stabilization of weight in patients having completed more than two cycles of chemotherapy. In the present study, there was no statistically significant difference between pre-and post-treatment weights. It is likely that the use of megestrol acetate contributed to this outcome. Serum albumin, and quality of life scores did not change throughout the treatment.

In summary, the trial described herein, demonstrates the feasibility of administering megestrol acetate concomitantly with a chemotherapy regimen to patients with advanced NSCLC. The dosage of megestrol acetate in this trial was relatively low compared to the other studies. Therefore, further studies using a higher dosage of megestrol acetate concurrently with chemotherapy or longer duration of megestrol acetate is warranted. A prospective randomized trial is needed to assess the survival outcome, cost benefit and quality of life impact when megestrol acetate is added to chemotherapy treatment in patients with advanced NSCLC.

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ยาเคมีบำบัด Paclitaxel ร่วมกับ Carboplatin และ Megestrol Acetate ในการรักษามะเร็งปอดชนิดเซลล์ไม่เล็ก ระยะแพร่กระจาย

สุมิตรา ทองประเสริฐ, พ.บ., รัตติยา ชีวเกรียงไกร, พ.บ.*, จันทิมา เอื้อตรงจิตต์, พ.บ.**, กนิษฐา ไทยกล้า, บธ.ม.****

การศึกษาเพื่อประเมินประสิทธิภาพและผลข้างเคียงของยาเคมีบำบัด paclitaxel และ carboplatin ร่วมกับ megestrol acetate ในการรักษาผู้ป่วยมะเร็งปอดชนิด non-small cell lung cancer (NSCLC) ระยะ IIIb และ IV ผู้ป่วยใหม่ซึ่งไม่เคยได้รับยาเคมีบำบัดจำนวน 40 ราย เข้ารับการรักษาแบ่งเป็นชาย 18 ราย หญิง 22 ราย อายุเฉลี่ย 57.5 ปี และค่าเฉลี่ยของ performance status เท่ากับร้อยละ 70 ผู้ป่วย 11 ราย เป็นระยะ IIIb และ 29 ราย เป็นระยะ IV ผู้ป่วย 25 ราย เป็น adenocarcinoma 12 รายเป็น squamous cell 2 รายเป็น large cell และ 1 ราย เป็น undifferentiated cell ยาเคมีบำบัดประกอบด้วย paclitaxel 135 มก/ม^2 โดยหยดเข้าหลอดเลือดดำในเวลา 24 ชั่วโมง และ carboplatin คำนวณปริมาณยาจากค่า AUC=6 หยดเข้าหลอดเลือดดำในเวลา 2 ชั่วโมง ผู้ป่วยได้รับ Megestrol acetate ขนาด 160 มก รับประทานวันละ 1 ครั้ง ในวันที่ 2-14 ของการรักษา ช่วงเวลาระหว่างการให้ยาแต่ละชุด = 21 วัน ผลการรักษาพบว่าผู้ป่วย 12 ราย จากจำนวน 39 ราย ตอบสนองต่อการรักษาเป็นแบบ partial remission (30.76%) ผลข้างเคียงที่สำคัญคืออาการคลื่นไส้ อาเจียน อาการปวดกล้ามเนื้อ อาการชาบริเวณปลายมือ-ปลายเท้า ผู้ป่วยร้อยละ 4.15 มีอุบัติการณ์ของเม็ดเลือดขาวต่ำเกรด 4 ผู้ป่วยร้อยละ 20.95 มีเม็ดเลือดขาวต่ำเกรด 3 เกร็ดเลือดต่ำพบได้ ร้อยละ 5.4 ผลต่อการรักษาในแง่น้ำหนักตัว ระดับ albumin ในเลือด และคุณภาพชีวิตไม่มีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติตลอดการรักษา

สรุป : การให้ megestrol acetate ร่วมกับยาเคมีบำบัดอาจช่วยผู้ป่วยในแง่ลดผลข้างเคียง ทำให้ผู้ป่วยสามารถรักษาน้ำหนักตัว ระดับ albmin ในเลือดและทำให้คุณภาพชีวิตไม่เลวลงระหว่างการรักษา

คำสำคัญ : มะเร็งปอด, ยาเคมีบำบัด (paclitaxel) และยา Megestrol Acetate

สุมิตรา ทองประเสริฐ, รัตติยา ชีวเกรียงไกร, จันทิมา เอื้อตรงจิตต์, กนิษฐา ไทยกล้า
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 424-432

* หน่วยมะเร็งวิทยา, ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์,
** ภาควิชารังสีวิทยา, คณะแพทยศาสตร์,
*** สถาบันวิจัยวิทยาศาสตร์สุขภาพมหาวิทยาลัยเชียงใหม่, มหาวิทยาลัยเชียงใหม่, เชียงใหม่ 50200