Paclitaxel and Carboplatin in Combination in the Treatment of Advanced Non-small-cell Lung Cancer (NSCLC) : A Preliminary Study

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Abstract

This study was aimed to determine the activity and toxicity of combination paclitaxel and carboplatin in stage III B and IV NSCLC. Eligibililty required performance status. Paclitaxel was administered at a dose of 200 mg/m^2, 3-hour infusion, followed by carboplatin at a tartgeted area under the concentration-time curve (AUC) of 6. Treatment was repeated at 3-week intervals for 6 courses. G-CSF 5 microgram/kg was subcutaneously injected during subsequent courses if there was grade 3-4 leukopenia or granulocytopenia in the previous course. From August 1996 through June 1997, 15 patients were enrolled. The median age was 47 years (range 20-68 years), 60 per cent were female. 73.3 per cent had adenocarcinoma, and 66.7 per cent had stage III B disease. Eighty three courses were administered; 13 patients (86.7%) completed all six cycles. The objective response rate was 53.3 per cent, with 1 (6.7%) complete response and 7 (46.7%) partial responses. Pleural effusion, lung lesion and lymph node were the three most common sites that responded to chemotherapy. The major toxicity was myelosuppression. Grade 3 or 4 granulocytopenia, anemia and thrombocytopenia were observed in 18 per cent, 7.2 per cent and 1.2 per cent, respectively, of 83 courses administered. Four episodes of febrile neutropenia (4.8%) occurred in 3 patients. There was one episode of anaphylaxis during Paclitaxel infusion. Other common toxicities were mild myalgia, paresthesias, alopecia and fatigue. Most of the toxicities showed cumulative effect. Paclitaxel plus carboplatin is a moderately active regimen in advanced NSCLC. Toxicities of this regimen are well tolerated.

Lung carcinoma remains the leading cause of death from cancer in Thailand, it ranked second as ten leading sites of cancers in men in 1994 according to Ramathibodi Cancer Registry(1). Fifty to sixty per cent of patients with non-small cell lung carcinoma (NSCLC) have distant meta-

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stases at the time of presentation. In addition, disease relapse occurs in many surgically resected patients and in unresectable patients who are treated with radiotherapy[2]. The devastating health impact of NSCLC is best illustrated by the poor prognosis of individuals with untreated metastatic disease, who typically survive less than 4 months[3]. Several studies have attempted to define those prognostic features that are important for survival in advanced NSCLC. Good performance status, female gender, and absence of extrathoracic disease consistently have been associated with a more favorable outcome[4]. Some studies have shown that poor prognostic features are weight loss, particular metastatic sites such as the brain, or the overall number of metastatic sites[5]. Histologic subtype, on the other hand, does not appear to significantly affect prognosis.

Although chemotherapy can effect a modest improvement in survival, the gain often comes at the expense of substantial host toxicity, especially in patients who are less than fully ambulatory[6]. There is a modest survival benefit in patients treated with a cisplatin-based containing combination (response rate 40% to 60%; median survival duration, 10 months)[7]. Carboplatin as a single agent produced the best 1-year survival rate with the least toxicity in a five-arm Eastern Cooperative Oncology Group study of cisplatin combinations and analog[8]. Within the past few years, several drugs with novel mechanisms of action and good activity against NSCLC have been identified. One particularly promising new agent is paclitaxel, a diterpene plant product that promotes microtubules assembly, which leads to disruption of mitosis and cell death[9]. In two separate phase II trials, paclitaxel yielded an objective response rate of greater than 20 per cent in patients with metastatic NSCLC and was associated with a 1-year survival rate of approximately 40 per cent[10,11]. The 1-year survival rate was 54 per cent for patients with advanced NSCLC treated with paclitaxel and carboplatin in the Fox Chase Cancer Center Study[12]. These results are intriguing and provocative and hopefully a first step toward reversing the nihilistic opinions regarding the role of chemotherapy in this disease. These observations prompted us to combine these two drugs in a pilot trial in the Thai population. The results of our study are reported here.

PATIENTS AND METHOD

Patient Eligibility

Between August 1996 and June 1997, 15 patients with histologically or cytologically confirmed stage IIIb or stage IV NSCLC were enrolled in this study. All had either measurable or evaluable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. All patients were required to have a white blood cell count of $\geq 4000/mm^3$, a platelet count of $\geq 100,000/mm^3$, bilirubin ≤ 2 mg/dL, and creatinine concentration < 1.5 mg/dL. Patients with brain metastases, active infection, myocardial infarction during the preceding 6 months, or congestive heart failure were excluded. No patients had received prior chemotherapy. Patients whose measurable site of disease outside previous irradiation of more than 4 weeks were eligible. Patients with a history of malignancy within the preceding 5 years (except for nonmelanomatous skin cancer) were excluded. Women of childbearing age were required to have a negative pregnancy test before treatment if otherwise eligible.

Patients were evaluated with complete history and physical examination, standard chemistry panel, and appropriate radiologic imaging studies. Patients were followed with measurement of objective tumor parameters at baseline and after 2 and 6 cycles of treatment.

Treatment Regimen

Paclitaxel 200 mg/m^2 was prepared in glass bottles and administered intravenously using polyethylene lined PVC tubing over 3 hours. Premedication, given to prevent potential hypersensitivity reactions consisted of dexamethasone 20 mg, given orally (12 and 6 hours prior to paclitaxel administration); diphenhydramine 50 mg i.v. ; ranitidine 50 mg i.v., granisetron 3 mg i.v., and dexamethasone 20 mg i.v. 30-60 minutes prior to paclitaxel administration. Carboplatin was given following paclitaxel with carboplatin dosed to a target area under the concentration-time curve (AUC) of 6 mg/ml.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]. The regimen was repeated every 21 days to a planned maximum of 6 cycles. Patients who continued to respond were permitted to receive addi-

tional cycles of the same regimen. Granulocyte colony-stimulating factor 5 μg/kg by subcutaneous injection was administered for 10-14 days to patients who developed grade 4 neutropenia or neutropenic fever during the previous cycle, but was not routinely administered during the second and subsequent cycles. Maximum treatment delay allowed was two weeks. No dose adjustments were made for a nadir granulocyte count less than 500/mm^3 in the absence of neutropenic fever or documented infection, and provided the leukocyte and platelet counts were normal on the day of treatment.

Response and Toxicity Criteria

Response evaluation was based on World Health Organization (WHO) criteria[15] and on an intention-to-treat analysis. Evaluation of response was performed by CT scan after 2 and 6 cycles of chemotherapy, while toxicity was evaluated weekly. Follow-up included history, physical examination, complete blood cell counts, biochemistry panels, and chest X-ray.

Complete response was defined as complete disappearance of all disease on radiographic and physical examination. Partial response was defined as a greater than 50 per cent reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Minimal response was defined as a less than 50 per cent reduction in the sum of the products of the perpendicular diameters of all the measurable lesions. Stable disease was defined as no detectable change in the tumor volume of all the lesions, and progressive

Table 1. Patient characteristics.

	No. of patients (n = 15)	%
Age (year)		
Median	47	
Range	20-68	
Sex		
Women	9	60
Men	6	40
ECOG performance status		
0	4	26.7
1	10	66.7
2	1	6.7
Stage		
IIIB	10	66.7
IV	5	33.3
Histology		
Adenocarcinoma	11	73.3
Bronchioalveolar	1	6.7
Squamous cell carcinoma	3	20
Large cell carcinoma	1	6.7
Non-smoker	11	73.3
Pretreatment weight loss (%)		
Not change	8	53.3
< 5	3	20
≥ 5	4	26.7
Metastatic site		
Contralateral lung	1	6.7
Ipsilateral lung	1	6.7
Liver	1	6.7
Skeleton	3	20
Thyroid gland	2	13.3
Lymph nodes	2	13.3
Pretreatment CEA (ng/ml)		
Abnormal (≥ 5 ng/ml)	9	60
Median	107.97	
Range	17-952	

disease was defined as a greater than 25 per cent increase in the sum of the products of the perpendicular diameters of all the measurable lesions or by the appearance of new lesions.

Statistical Methods

The overall survival rates were studied by the Kaplan-Meier method[16]. A value of $p < 0.05$ was considered statistically significant[17].

RESULTS

Patient Population

Between August 1996 and June 1997, 15 patients were enrolled at Ramathibodi Hospital. All patients were assessable for survival, toxicity and response. The characteristics of the 15 eligible patients are listed in Table 1. There were 6 men and 9 women, with a median age of 47 years (range, 20 to 68) and a median ECOG performance status of 1 (range, 0 to 2). Ten patients had stage IIIb and five patients had stage IV disease. The predominant histology was adenocarcinoma (73.3%). No patient had received prior radiation therapy. Eleven patients (73.3%) were non-smokers. Patients with stage IIIb disease were defined by malignant pleural effusions (8 patients), contralateral mediastinal lymphadenopathy (2 patients), supraclavicular lymph node involvement (5 patients), and malignant pericardial effusion (3 patients). Patients with stage IV disease, sites of metastases included skeleton (3 patients), contralateral lung (1 patient), ipsilateral lung (1 patient), liver (1 patient), thyroid gland (2 patients), and lymph node (2 patients). The median pretreatment CEA level was 108 ng/ml (range, 17 to 952).

Drug Delivery

A total of 83 cycles of paclitaxel and carboplatin were administered. The median number of cycles received was six (range, 3 to 6), with a median cycle interval of 22 days. Five cycles of treatment were delayed due to infection, prolonged neutropenia, prolonged anemia, and prolonged thrombocytopenia. The mean duration of treatment delayed was 6 days (range, 4 to 7). There were thirteen patients (86.7%) who received all planned courses of chemotherapy. The remaining patients were taken off treatment before completing six cycles for the following reasons : cerebral vascular accident (n = 1), tumor progression and death (n = 1).

Toxicities

Treatment was generally well tolerated. The major toxicity associated with this regimen was myelosuppression. All 15 patients were eva-

Table 2. Hematologic toxicity (WHO).

Toxicity	Grade	Course							
		1	2	3	4	5	6	Total	%
Neutropenia (n=83)	1	2	-	2	-	-	1	5	6
	2	2	-	1	2	-	1	6	7.2
	3	-	3	1	1	-	-	5	6.0
	4	4	3	1	1	1	-	10	12.0
G-CSF prophylaxis		-	5	6	8	8	9	36	43.4
Neutropenia without G-CSF	1	2	-	1	-	-	-	3	6.4
prophylaxis (n=47)	2	2	-	1	2	-	-	5	10.6
	3	-	3	1	-	-	-	4	8.5
	4	4	3	1	1	1	-	10	21.3
Anemia	1	6	7	4	7	6	1	31	37.3
(n=83)	2	2	4	4	4	4	4	22	26.5
	3	-	-	2	-	2	2	6	7.2
	4	-	-	-	-	-	-	-	-
Thrombocytopenia	1	-	-	1	-	-	1	2	2.4
(n=83)	2	1	1	-	1	1	-	4	4.8
	3	-	-	-	-	-	1	1	1.2
	4	-	-	-	-	-	-	-	-

Table 3. Non hematologic toxicity (WHO).

Toxicity (n=83)	Grade	Course						Total	%
		1	2	3	4	5	6		
Febrile	1,2	1	1	1	1	-	-	4	4.8
	3,4	-	-	-	-	-	-	-	-
Myalgia	1,2	10	12	11	9	9	10	61	73.5
	3,4	-	-	1	2	3	2	8	9.6
Arthralgia	1,2	9	11	11	10	10	11	62	74.7
	3,4	1	1	1	1	2	1	7	8.4
Paresthesia	1,2	7	11	14	13	13	12	70	84.3
	3,4	-	-	-	-	-	1	1	1.2
Fitigue	1,2	11	12	12	12	11	10	68	81.9
	3,4	-	-	-	-	1	1	2	2.4
Mucositis	1,2	2	-	1	2	-	-	5	6.0
	3,4	-	-	-	-	-	-	-	-
Diarrhea	1,2	1	-	1	-	1	1	3	3.6
	3,4	-	-	-	-	-	-	1	1.2
Alopecia	1,2	15	14	14	12	12	11	78	93.9
	3,4	-	-	-	1	1	2	4	4.8
Constipation	1,2	1	2	2	2	1	-	7	8.4
	3,4	-	1	1	-	-	-	2	2.4
Allergy	1,2	-	1	-	-	-	-	1	1.2
	3,4	-	1	-	1	1	-	4	4.8

Table 4. Tumor response.

Response	No.of patients	%
Overall response	8	53.3
Complete	1	6.7
Partial	7	46.6
Stable disease	4	26.7
Progressive disease	3	20

luable for toxicity. Grade 4 neutropenia occurred in 6 treatment cycles (7.4%) and grade 3 or 4 neutropenia occurred in 15 treatment cycles (18%) without G-CSF prophylaxis. Febrile neutropenia documented in 3 patients occurred in 4 treatment cycles. After intravenous antibiotics and G-CSF, all of them recovered and there were no treatment related deaths due to neutropenia and infection. The median ANC nadir was 2580/mm^3 for all treatment cycles without G-CSF prophylaxis. While grade 3 or 4 neutropenia was quite common, severe platelet toxicity was unusual. Grade 1 or 2 thrombocytopenia occurred in 23 treatment cycles (27.7%) with only 1 episode of grade 3 or 4 thrombocytopenia. The median platelet nadir was 215,000/mm^3 (range, 45,000 to 781,000). Grade 3 anemia occurred in 6 cycles (7.2%), grade 4 anemia was not observed. The median hemoglobin nadir was 10.3 g/dL (range, 7 to 18.1). Myelosuppression tended to have cumulative effect (Table 2) except neutropenia which can be salvaged by G-CSF.

Nonhematologic toxicities were generally modest (Table 3). Almost every patient developed reversible alopecia but only 4.8 per cent developed grade 3 or 4 alopecia. Seventy episodes (84.3%) of mild (grade 1 or 2) paresthesia were reported. Myalgia and arthralgia were other common toxicities but were mild in nature, however, it tended to have a cumulative effect with increased severity after subsequent cycles of therapy. One patient developed anaphylactic shock during paclitaxel infusion in the second cycle. She fully recovered after intravenous fluid infusion, dexamethasone, and antihistamine. After another premedication was given, rechallenge was completed uneventfully.

Response and Survival

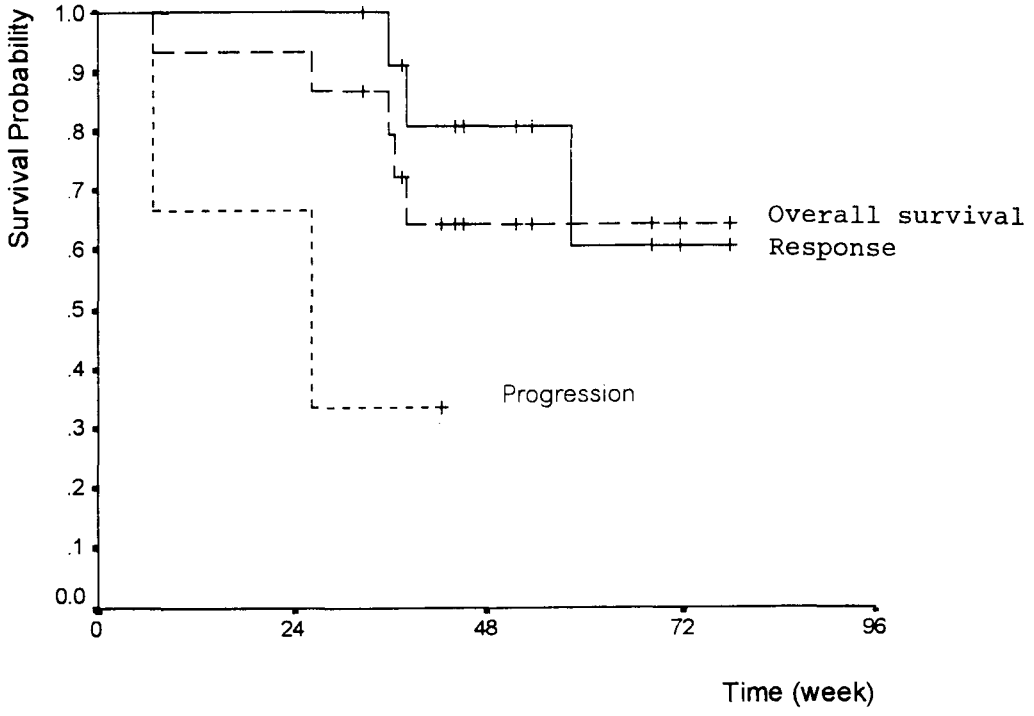
Among 15 eligible and assessable patients, there were 1 complete response (6.7%) and 7 partial

responses (46.6%), for an overall response rate of 53.3 per cent (Table 4). The only one patient who achieved complete response had stage IIIb disease (malignant pleural effusion). He remained progression-free with good performance status for 50 weeks. Three patients had partial responses after the second treatment cycle but one patient developed progressive disease after the sixth treatment cycle. The other four patients had partial responses after the sixth treatment cycle. The predominant sites that responded to chemotherapy were pleural effusion (87.5%), lung lesions (81.8%), and lymph nodes (72.7%). Three patients (20%) had progressive disease at the end of the study, one had partial response and the other two had stable disease after the second treatment cycle. Two patients did not have disease progression up to January 1998. Three patients were lost to follow-up at the 26th, 37th, and 45th week of the study.

The median survival time of all 15 patients has not been reached since more than 50 per cent of the patients still survive. Survival for the responsive and stable patients was significantly better than survival for unresponsive patients (long-rank test, $p < 0.05$). The median survival of patients with progressive disease was 26.3 weeks. (Fig. 1)

DISCUSSION

Although real progress has been made in the management of advanced non-small cell lung cancer (NSCLC) in recent years, this malignancy continues to be viewed as an illness for which little can be done other than surgery. Consequently, NSCLC is frequently treated suboptimally[18-20]. Studies indicate that non-oncologists (and many oncologists) often believe that treatment of lung cancer provides little or no survival benefits to



Survival for the response patients was significantly better than for progressive patients (log-rank test, P<.05)

Fig. 1. Overall survival.

their patients[21,22]. In addition, treatment of lung cancer is commonly perceived as costly and even harmful to the patient. Although prevalent, these attitudes are not supported by the available published data[23]. A recently published meta-analysis of chemotherapy improves survival data in patients with advanced NSCLC compared to best supportive care[24]. Besides, tumor-related symptoms frequently improve with the use of chemotherapy, in many instances to a degree unanticipated relative to the level of objective tumor response[25]. Patients receiving chemotherapy required fewer hospitalizations and less radiotherapy as reported by the National Cancer Institute of Canada[26,27]. Thus, the available data indicate that a strong argument can be made for administering chemotherapy to good performance status NSCLC patients as it is both cost effective and useful for the palliation of symptoms.

While existing chemotherapeutic agents provide some measure of benefit in the management of NSCLC, more effective therapies are needed. A number of new drugs have been shown to possess good activity againt NSCLC, including paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan[28]. Paclitaxel is particularly noteworthy with apparent improvement in 1-year survival in two separate phase II trials[10,11]. These findings, coupled with the excellent toxicity profile of paclitaxel and carboplatin in combination,[29] prompted our group to investigate this regimen in a pilot study in advanced NSCLC.

We observed a relatively satisfying objective response rate of 53.3 per cent, the median survival time has not been reached and is encouraging. The optimal duration of treatment with any of these regimens is not clear. The usual practice is to treat for two to three cycles to determine tolerance and to evaluate response. If there is evidence of response, treatment is continued to six or eight cycles. Abandoning treatment due to lack of response after a few cycles may deprive some patients of a useful treatment. There is randomized evidence that NSCLC patients with stable disease on chemotherapy have similar survival to those with objective response[30]. Furthermore, patients who responded very slowly fared as well or better than those who responded quickly[31]. The taxanes in particular have been noted to cause late responses in patients with lung cancer or breast cancer[32]. As a result, minimally responding patients may benefit from persisting with treatment unless toxicity outweighs any potential benefit. These observations suggest that a treatment resulting in stability in a disease that is usually rapidly progressive may have significant antitumor activity. Experience with neoadjuvant chemotherapy in early-stage disease has taught us that at the time of surgery, an unshrinking tumor mass consists of mostly fibrosis or necrotic debris that would not be evident with noninvasive imaging[33]. Thus, the survival curve of the responding and stable disease patients was superior to the nonresponsive patients.

Several other investigators have used the combination of paclitaxel and carboplatin with excellent results[12,34]. Whether patients who are doing well on chemotherapy after six cycles benefit from continuing until there is a reason to stop has not been tested. Presently, we use our own judgement and the values of the patients to decide each specific situation. There was no treatment-related death in this study. The toxicities of this regimen were modest and, for the most part, easily managed.

In summary, the combination of paclitaxel and carboplatin is active against advanced NSCLC and is relatively well tolerated. It is still premature to conclude that this regimen is superior to existing cisplatin-based regimens. Patients with advanced stage NSCLC and good performance status may benefit a modest improvement in survival with this regimen. The decision to use chemotherapy must incorporate physician judgement and patient values on a case-by-case basis. Chemotherapy should at least be offered as an option to all eligible patients and cost should not be considered a barrier.

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การรักษามะเร็งปอดชนิดนอน-สมอลล์เซลล์ระยะท้าย ด้วยยาแพ็คลิแทคเซลและคาร์โบพลาทิน

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เป็นการศึกษาถึงประสิทธิภาพ และผลข้างเคียงของการรักษาผู้ป่วยมะเร็งปอดชนิด Non-small cell ระยะ III B และ IV จำนวน 15 ราย ด้วยยา Paclitaxel ร่วมกับ Carboplatin โดยให้ Paclitaxel 200 มิลลิกรัมต่อพื้นที่ผิวหนึ่งตารางเมตรทางเส้นเลือดดำ นาน 3 ชั่วโมง ต่อด้วย Carboplatin คำนวณขนาดโดยใช้พื้นที่ใต้ concentration-time curve (AUC) เท่ากับ 6 โดยให้ทั้งหมด 6 course แต่ละ course ห่างกัน 3 สัปดาห์ ผู้ป่วยที่มี neutropenia เกรด 3 และ 4 จะได้รับ G-CSF 5 ไมโครกรัมต่อน้ำหนักตัวหนึ่งกิโลกรัมทางใต้ผิวหนังหลังจากได้รับเคมีบำบัดครั้งต่อไปเพื่อป้องกัน neutropenia อายุเฉลี่ยของผู้ป่วย 47 ปี (ค่าพิสัย 20-68 ปี) เป็นเพศหญิง 60% มะเร็งชนิด Adenocarcinoma มากที่สุด (73.3%) และโรคอยู่ในระยะ III B 10 ราย มีการให้ยาเคมีบำบัดทั้งหมด 83 course ตลอดการศึกษา ผู้ป่วยจำนวน 13 ราย ได้รับยาเคมีบำบัดครบ มีการตอบสนองทั้งหมด 53.3% โดยแบ่งเป็นชนิด complete response 1 ราย (6.7%) และ partial response 7 ราย (46.7%) ตำแหน่งของรอยโรคที่ตอบสนองต่อยาได้ดีที่สุดคือ น้ำในช่องปอด รอยโรคในปอด และต่อมน้ำเหลือง ตามลำดับ ผลข้างเคียงที่พบได้บ่อยคือ การกดไขกระดูก พบว่า มีภาวะ granulocytopenia, anemia และ thrombocytopenia เกรด 3 และ 4 18%, 7.2% และ 1.2% ตามลำดับ และพบภาวะ febrile neutopenia 4 ครั้งในผู้ป่วย 3 ราย ผู้ป่วยรายหนึ่งเกิดภูมิแพ้ชนิด anaphylaxis ในระหว่างรับยา Paclitaxel ผลข้างเคียงอื่นที่พบบ่อยได้แก่ ปวดกล้ามเนื้อ ชาปลายมือปลายเท้า ผมร่วง และอ่อนเพลีย ผลข้างเคียงส่วนใหญ่จะมีผลสะสมใน course ถัดมา สรุปว่า การรักษามะเร็งปอดชนิด Non-small cell ด้วยยา Paclitaxel และ Carboplatin ได้ผลดีปานกลาง และไม่มีผลข้างเคียงมากเกินไป

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