Effects of Paclitaxel and Carboplatin on Quality of Life and Survival in Patients with Advanced Non-Small-Cell Lung Cancer

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Abstract

The purpose of this phase II study was to determine the effects of paclitaxel plus carboplatin administered by short duration on response rate, toxicity, and quality of life (QOL) in patients with non-small cell lung cancer (NSCLC). Twenty-seven patients were enrolled in this study. The objective response rate was 48.2 per cent, grade 3 or 4 granulocytopenia and thrombocytopenia were observed in 22 per cent and 1.6 per cent, respectively. QOL was assessed in nineteen patients who completed six cycles of chemotherapy. Quality of Life Index (QLI) after six cycles of treatment showed no significant change from the baseline QOL. Compliance with the QOL protocol in this study diminished with the course of chemotherapy which is comparable to the literature figure. Thus, withholding current effective chemotherapy in patients with NSCLC with good performance status is no longer justified.

Key word : Non-Small-Cell Lung Cancer, Chemotherapy, Quality of Life, Paclitaxel, Carboplatin

RATANATHARATHORN V, et al
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Despite some evidence supporting a role for chemotherapy (CT) in patients with inoperable non-small-cell lung cancer (NSCLC), routine management practice varies worldwide. The role of chemotherapy is still controversial in advanced NSCLC due to the fact that prolonged survival is dismal in these groups. Given this fact, palliation of symptoms is a major goal of the management and radiation therapy plays an important role in this regard.

Cisplatin-based combination therapy is currently considered to be the most active treatment

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for advanced NSCLC[1,2]. A recent meta-analysis compared chemotherapy versus best supportive care in stage IV NSCLC, showing a 27 per cent relative reduction in mortality rate, which translated into an absolute improvement in median survival time of 2 months and a 10 per cent increase in 1-year survival[3]. The conclusion of this meta-analysis was that chemotherapy should be offered to selected patients with stage IV NSCLC and good performance status. However, meta-analysis has been criticized on a number of counts;[4] there is no clear guidance on the choice of regimens, toxicity, and quality of life (QOL) outcomes and there are no substitutes for large, randomized trials. Recently, several new agents have been shown to have a level of single-agent activity against NSCLC that is greater than the 15 per cent threshold[5]. Two phase II studies using paclitaxel alone showed response rates of 21 per cent and 24 per cent, respectively, which were among the highest ever recorded with single-agent therapy in NSCLC[6,7]. In combination with platinum compounds, paclitaxel has again shown promising results in terms of both response rate and overall survival including our own experience[8-10].

Because the prognosis is generally poor for metastatic NSCLC regardless of treatment, it is important to monitor the impact of treatment on QOL as well as on the disease process. The treatment, however, also has side effects that may negatively affect the patients' well-being and the overall benefit from palliative chemotherapy in advanced NSCLC has remained controversial. Patient's willingness to accept chemotherapy for the treatment of metastatic NSCLC varies widely. Many would not choose chemotherapy for its likely survival benefit of 3 months but would if it improved QOL[11]. In a Canadian randomized trial comparing supportive care with supportive care plus cisplatin-based chemotherapy in advanced NSCLC, the aim of the investigators was to evaluate response rate and survival as well as QOL information. Unfortunately, compliance with the QOL portion of the protocol was poor and the authors were unable to report the QOL aspect in their trial. However, the study demonstrated a significant survival benefit for patients who received cisplatin-based chemotherapy over the best supportive care only group ($p = 0.02$)[12].

In view of these considerations, we undertook this phase II study to determine the effect of PC (paclitaxel and carboplatin) chemotherapy on response rate, toxicity, and QOL in patients with advanced NSCLC.

MATERIAL AND METHOD

Patient Selection

Eligible patients had to fulfill the following criteria: histologic or cytologic diagnosis of NSCLC; stage IIIB or stage IV disease; no prior chemotherapy or radiation therapy; age between 18 and 75 years; performance status of ≤ 2 according to the ECOG scale; life expectancy of at least 12 weeks; no active infection; adequate bone marrow reserve; and normal liver and renal function. The presence of at least one unidimensional, measurable lesion was required, although bidimensionally measurable disease was preferred.

Treatment

Paclitaxel was administered at a dose of 175 mg/m^2 intravenous infusion over 3 hours and the carboplatin dose was targeted to achieve an area under the time concentration curve (AUC) of 6 mg/mL.min. Premedication, given to prevent potential hypersensitivity reactions, consisted of dexamethasone, diphenhydramine, and cimetidine (30 minutes prior to paclitaxel administration). Treatments were repeated every 21 days and continued until progression of disease, fall in performance status to 3 or worse, intolerable toxicity, serious concomitant morbidity, or the patient requested termination of treatment.

Standard World Health Organization (WHO) criteria for response and toxicity assessment were used. The response to chemotherapy was evaluated after every 2 cycles of chemotherapy. Patients were monitored until death or until the time of analysis. The duration of response and survival were calculated from the date of entry into this trial.

Quality of Life Assessment

Quality of life was assessed by the Quality of Life Index (QLI) developed by Padilla et al[13] and translated into Thai by Hanucharurnkul[14]. The Thai version has been tested for reliability and validity and is frequently used in quality of life research in Thailand. The content validity index was explored and derived from a panel of experts. The internal consistency for the total scale of the QLI using Cronbach coefficient alpha was 0.85[15]. We

evaluated changes in QOL in the NSCLC patients by analyzing a 23-item questionnaire. The multidimensional aspect of QOL was reflected by the instrument's eight physical well-being subscales, eleven psychological well-being subscales, four social and interpersonal well-being subscales (Table 6).

Linear analog scales were used because they provide graphic representations of subjective states on continuous scales, responses may be normally distributed, and scales are usually reliable and valid[16]. For a given parameter a 100 mm-line was used, and the ends of the line were labeled with words descriptive of extremes for that symptom. The patients were asked to mark each line to indicate their feelings at that moment; the distance, in centimeters, along the line to the mark gave a score out of 100, the sum of all variables giving a score out of 2300. Each linear analog scale form was completed before treatment and then after every 2 chemotherapeutic cycles. A measurement 'window' of ± 1 weeks was allowed.

Statistical Analysis

The statistical software SPSS PC for windows was used for data analysis. The change overtime of overall QOL and of each subscale was tested by repeated measure of ANOVA. Changes in QOL scores were compared by Student's *t*-test. The mean score of each item of QOL was described by ranking order. Overall survival was estimated by the Kaplan-Meier product limit method.

RESULTS

Patient Characteristics

From August 1996 until December 1999, 27 patients were recruited for the trial. The patient characteristics are summarized in Table 1. Ninety-six per cent of patients had a performance status of 0 or 1. Fourteen patients had stage IIIB disease and 13 had stage IV disease, the median age was 59 years (range 20 to 72 years). The predominant histology was adenocarcinoma (70.4%).

Drug Delivery and Timing of QOL Assessment

A total of 158 treatment cycles were delivered with a median of six (range 2-10 cycles) to all 27 patients who were eligible for response evaluation. However, only patients who received 6 cycles or more of the treatment program were evaluated for QOL. The QOL assessment was performed before, during, and after 6 cycles of paclitaxel plus carboplatin. This rationale is based on literature reviewed which described that the effect of treatment appeared to decrease significantly after the first 6 months from therapy inception and the mean potential gain in survival, compared with supportive care, was approximately 6 weeks (95% CI, 1 to 10 weeks)[17] which was confirmed in a meta-analysis with more than 700 patients[18]. Besides, most studies on the role of chemotherapy in the palliation of patients with advanced stage NSCLC utilized only 6 cycles of chemotherapy regardless of regimens used[19,20].

Table 1. Patient characteristics.

Characteristics		N	%
Sex	Male	14	51.9
	Female	13	48.1
Age	Range (yrs)	20-72	
	Median (yrs)	59.00	
Stage of disease			
	IIIB	14	51.9
	IV	13	48.1
Histology			
	Adenocarcinoma	19	70.4
	Squamous cell carcinoma	6	22.2
	Bronchioloalveolar	1	3.7
	Large cell carcinoma	1	3.7
Performance status (ECOG)			
	0	10	37.0
	1	16	59.3
	2	1	3.7
Weight Change			
	No change	12	44.5
	≥ 5%	9	33.3
	< 5%	6	22.2

Toxicities

The complete hematologic and non-hematologic toxicities available in 127 cycles are listed in Table 2. No death due to toxicity occurred. Toxicities were assessed up to 6 cycles of chemotherapy only which was the duration of QOL analysis.

Response and Survival

Twenty-seven eligible patients were accrued into this trial. Although only 19 patients were assessed for QOL, all 27 patients were assessed for response and survival. Among 27 assessable patients, there was 1 complete response (3.7%) and 12 partial responses (44.5%), for an

Table 2. Toxicity profile.

Toxicity	Grade	Cycle						Total	%
		1	2	3	4	5	6		
Neutropenia	1,2	6	2	3	2	2	2	17	13.4
	3,4	9	7	5	4	1	2	28	22.0
Anemia	1,2	15	21	15	18	10	16	95	74.8
	3,4	2	1	3	1	4	2	13	10.2
Thrombocytopenia	1,2	1	2	1	1	2	4	11	8.7
	3,4	0	0	1	0	1	0	2	1.6
Myalgia	1,2	17	19	13	13	12	13	87	68.5
	3,4	0	0	2	2	3	3	10	7.9
Arthralgia	1,2	12	19	16	14	14	13	88	69.3
	3,4	3	2	1	1	1	2	10	7.9
Paresthesia	1,2	16	21	19	18	15	18	107	84.3
	3,4	0	0	0	0	1	0	1	0.8
Fatigue	1,2	16	20	17	17	13	16	99	77.9
	3,4	2	2	1	0	1	1	7	5.5
Mucositis	1,2	5	2	4	2	1	1	15	11.8
	3,4	0	0	0	0	0	0	0	0.0
Diarrhea	1,2	1	1	3	0	0	1	6	4.7
	3,4	0	0	0	0	1	0	1	0.8
Constipation	1,2	3	4	5	3	0	1	16	12.5
	3,4	0	0	0	0	0	0	0	0

overall response rate of 48.2 per cent (Table 3). The median survival time of the 27 patients was 68.1 weeks. The median follow-up time was 57.7 weeks The median survival of patients with response, stable disease, and progressive disease was 96.3 weeks (range 36-117), 68.1 weeks (range 32-150), and 26.3 weeks (range 7-108) respectively. Survival of the responsive and stable disease patients was significantly better than the nonresponsive patients ($p < 0.004$) (Fig. 1).

Table 3. Tumor response (N = 27).

Response	No. of patients	%
Overall response	13	
Complete	1	3.7
Partial	12	44.5
Stable disease	8	29.6
Progressive disease	6	22.2

Quality of Life and Treatment Response

Baseline questionnaires were filled in by all subjects (100%). Compliance with the protocol diminished with the course of chemotherapy. Responding to the fourth questionnaire at the comple-

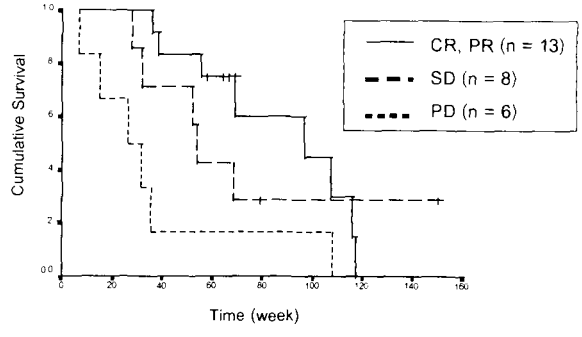

Fig. 1. Overall survival (N = 27).

Table 4. Compliance, number and percentage of patients who completed the questionnaires.

Time of assessment	No. of patients (N = 27)		
	Questionnaire completion	%	Reasons for non-compliance
Baseline	27	100	
After 2nd cycle	26	96	patient too ill (1)
After 4th cycle	25	9	disease progression (1)
After 6th cycle	19	70	patient too ill, patient refusal, disease progression and death (6)

Table 5. Overall QOL score and subscale scores during the treatment (N = 19).

Study parameter	Total score	Total QOL score, mean (SD)				
		Baseline	After 2nd cycle	After 4th cycle	After 6th cycle	P value
Overall QOL	100	76.57 (11.6)	75.61 (11.70)	74.75 (10.9)	76.00 (13.42)	NS
Physical well-being	100	78.35 (12.85)	77.99 (14.2)	75.37 (12.68)	76.49 (15.71)	NS
Psychological well-being	100	72.72 (13.40)	72.31 (12.45)	72.00 (11.55)	74.55 (15.02)	NS
Social and interpersonal well-being	100	85.56 (11.79)	83.66 (13.69	80.02 (15.38)	79.90 (5.90)	NS

tion of the sixth treatment cycle was reduced to 70 per cent from baseline of 100 per cent (Table 4).

No clinically significant differences in change from baseline QOL after each successive course of chemotherapy was observed regardless of type of responses (Fig. 2).

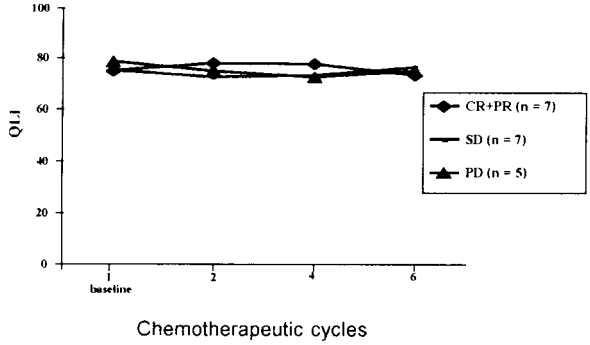

Fig. 2. QOL and treatment response (N = 19).

The mean score for overall QOL was measured at the beginning, after second, fourth, and sixth cycle of chemotherapy were 76.57, 75.61, 74.75, and 76.0 respectively. There were no statistically significant changes during the treatment and also no significant changes for its three-dimensional model (Table 5). However, for each QOL item, the ranking did change after 6 cycles of chemotherapy compared with the baseline (Table 6).

DISCUSSION

Advanced lung cancer patients have reported the poorest QOL and are frequently selected as the initial target population for QOL study in clinical trials due to the high incidence and the relatively rapid progression of the disease, facilitating both patient accrual and evaluation of responsiveness of the questionnaire to change in health status over time[21,22]. Raby et al reported that although a majority of Canadian clinicians involved in lung cancer therapy believed chemotherapy prolonged median survival in stage IV NSCLC, only 20 per

Table 6. Comparison of ranks and means of total Items and each was scored for quality of life before and after treatment with 6 cycles of chemotherapy. (N = 19)

Quality of life questionnaire items	Sub Scale*	Baseline		After 6 th cycle	
		Rank	$\bar{x}$	Rank	$\bar{x}$
I feel useful and loved by my family.	Soc	1	94.44	2	90.26
I feel rejection from my neighbors or others.	Soc	2	95.59	3	89.47
I am satisfied with my sex life.	Phy	3	88.33	12.5	74.73
I feel lonely.	Phy	4	87.96	4	88.94
I get help from others.	Soc	5	85.00	10	76.57
I have difficulty sleeping.	Phy	6	84.81	6	82.63
I have enough activity daily living (ADL).	Phy	7	82.22	1	91.31
I am able to control my bowels.	Phy	8	81.85	9	78.68
I am able to achieve my goals.	Phy	9	80.39	7	81.05
I have adequate strength.	Phy	10	79.81	5	82.89
I feel calm and peaceful.	Phy	11	79.63	8	80.00
I am hopeful things will improve.	Phy	12	77.59	11	76.05
I have a satisfying life.	Phy	13	77.41	12.5	74.73
I am able to get around.	Phy	14	75.74	19	68.68
I have trouble getting along with friends or relatives.	Soc	15	74.44	22	65.26
I have fear of the future.	Phy	16	72.59	14.5	74.47
I am able to accept the changes in my life.	Phy	17	69.44	20	67.89
I get enough sleep.	Phy	18	68.70	18	70.78
I eat a sufficient amount of food.	Phy	19	65.55	14.5	74.47
I am able to accept my physical appearance.	Phy	20	65.18	17	73.15
I have a good appetite.	Phy	21	64.25	16	74.21
I worry about my health.	Phy	22	59.62	23	60.26
I am satisfied with my health in general.	Phy	23	53.51	21	66.84

* Phy = Physical well-being, Psy = Psychological well-being, Soc = Social and interpersonal well-being

cent would recommend it for an asymptomatic patient[23]. The authors believed that, although randomized trials may demonstrate that a treatment works, they often fail to show that it is worthwhile.

In the early and advanced disease settings older trials using long term alkylating agents tended to show a detrimental effect of chemotherapy, but the mechanism for this is unknown[3]. A number of novel agents have been developed with significant activity against NSCLC in the past 6 to 8 years and are being incorporated into the therapy of this disease. Clearly there has been improvement in response rates, and in some cases the responses have been durable with an increase in the number of 1 and 2-year survivors. 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[8]. Phase III trial comparing etoposide plus cisplatin *versus* paclitaxel plus cisplatin ± G-CSF demonstrated clearly that the former regimen was inferior to the latter regimen in terms of response rates (12% *vs* 26.5%, $p < 0.001$) with a trend toward better survival for the latter regimen ($p = 0.091$)[24]. Our treatment response and survival results are comparable with the cited literature. However, less than 5 per cent of all randomized controlled trials reported on the quality of life issue, and this proportion was below 10 per cent even for cancer trials[25].

In a limited phase II study of patients with metastatic NSCLC treated with single-agent paclitaxel 200 mg/m^2 by 3-hour infusion, Tester et al did note a relation between response status and baseline FACT-G scores[26]. Patients with higher baseline FACT-G scores were more likely to show partial response, and those with lower baseline FACT-G scores were more likely to have disease progression. There was no consistent trend between FACT scores and patients with responsive or stable disease. Cullen et al reported a randomized trial in patients with extensive-stage NSCLC between chemotherapy (mitomycin, ifosfamide, and cisplatin) plus palliative care or palliative care alone[27]. Short-term change in QOL was assessed in a subgroup of patients. The corresponding QOL figures were -0.09 for chemotherapy (95% CI, - 0.21 to

0.03) and 0.20 for palliative care alone (95% CI, 0.01 to 0.4). Negative values in this study implied that the level of symptom scores reduced, on average, over the 0- to 6-week time period, thus indicating an improvement in QOL (EORTC QOL - LC 13). In a smaller, non-randomized trial, Han et al using the same MIP regimen reported an overall improvement of QOL (58.3%) despite a modest and short-lived response (38.9%, median 3.5 months), and change of QOL emerged as a clinical significant predictor of survival ($p = 0.0007$)[28].

Our present study demonstrated no significant change in QOL regardless of response status throughout the 6 cycles of chemotherapy. We did note a change in ranking of QOL items. Activity daily living (ADL) which ranked seventh at baseline became number one in the ranking system after six cycles of chemotherapy which clearly indicated improvement in this subscale although the over all QOL showed no significant change from baseline. This information is crucial since toxicity is frequently cited as a reason to withhold systemic chemotherapy. Furthermore, 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[20]. However, the instrument for measuring QOL in our study differed from the afore cited literature. Among the QOL instruments for cancer patients, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy General (FACT-G) are probably the most commonly used. The latter instrument may be viewed as the United States counterpart of the EORTC instruments[29]. However, the EORTC QLQ-C30 and the FACT-G were found to measure markedly different aspects of QOL, despite considerable overlap. Neither of the two QOL instruments can be replaced by the other and a direct comparison of results obtained with the two instruments is not possible[30]. Sloan et al reported a four- arm randomized trial comparing four instruments that provided overall QOL scores in patients with advanced colorectal cancer[31]. The results demonstrated that a simple single-item tool (UNISCALE) did correlate well with the Functional Living Index Cancer (FLIC) and appeared to be appropriate to obtain a measure of overall QOL. Thus, it seems that several instruments can be used in measuring QOL with comparable results. While there have been numbers and substantial attempts in recent trials at incorporating and validating health-related QOL (HRQOL) instruments for cancer, at present no tool can reasonably lay claim to the title of 'gold standard'[32,33].

In conclusion, our instrument (Quality of Life Index or QLI) is a multidimensional tool and reasonably easy to complete with 70 per cent compliance after the sixth cycle of chemotherapy which is comparable to the 73.3 per cent overall compliance during treatment reported by Hahn et al[34]. Our results convey a very important message which is consistent with literature review in the treatment of advanced NSCLC, namely, chemotherapy brings a definite survival advantage without worsening the patients' QOL throughout the treatment program in advanced stage NSCLC patients with good performace status.

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คุณภาพชีวิต,อัตราการอยู่รอดของผู้ป่วยมะเร็งปอดชนิดนอน-สมอลล์เซลล์ระยะท้ายที่ได้รับการรักษาด้วยยาแพ็คลิแทคเซลและคาร์โบพลาทิน

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การศึกษาประสิทธิภาพ ผลข้างเคียงของการรักษา และคุณภาพชีวิตของผู้ป่วยมะเร็งปอดชนิด Non-small-cell lung ระยะ IIIB และ IV ด้วยยา Paclitaxel ร่วมกับ Carboplatin ขนาดยาที่ให้ Paclitaxel 175 มิลลิกรัมต่อพื้นที่ผิวหนึ่งตารางเมตร และ Carboplatin คำนวณโดยใช้พื้นที่ใต้ concentration-time curve (AUC) เท่ากับ 6 ประเมินการตอบสนองต่อการรักษาร่วมกับคุณภาพชีวิตของผู้ป่วยภายหลังได้รับยาครบ 2, 4 และ 6 ชุด ผลการศึกษาพบว่า ผู้ป่วยจำนวน 27 ราย มีการตอบสนองโดยรวม 13 ราย (48.2%) แบ่งเป็น complete response 1 ราย (3.7%), partial response 12 ราย (44.5%) และมีอัตราการอยู่รอดเฉลี่ย 68.1 สัปดาห์ ผลข้างเคียงที่พบได้บ่อยคือ การกดไขกระดูกเกิดภาวะเม็ดเลือดขาวต่ำ ซีด และเกร็ดเลือดต่ำ ในระดับเกรด 3 และ 4 เท่ากับร้อยละ 22, 10.2 และ 1.6 ตามลำดับ ประเมินคุณภาพชีวิตในผู้ป่วยที่ได้รับการรักษาครบ 6 ชุด จำนวน 19 ราย พบว่าคุณภาพชีวิตโดยรวมไม่แตกต่างจากก่อนรับการรักษา สรุปได้ว่าการรักษาผู้ป่วยมะเร็งปอดในระยะท้าย ด้วยยาเคมีบำบัด ได้ผลที่ดีทั้งในด้านการตอบสนองต่อการรักษา การมีชีวิตรอด และคุณภาพชีวิตของผู้ป่วย และควรพิจารณาให้การรักษาดังกล่าวในผู้ป่วยที่มี performance status ที่ดี

คำสำคัญ : คุณภาพชีวิต, มะเร็งปอด, เคมีบำบัด

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