Quality of Life Achieved by Carboplatin Plus Etoposide as Third-Line Chemotherapy Compared with Best Supportive Care in Non-Small Cell Lung Cancer Stage IIIB/IV

Jedzada Maneechawakajorn MD*,
Sitthichok Hathaisanguan MD*

** Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Advanced stage (IIIB/IV) non-small cell lung cancers (NSCLC) are mostly treated with paclitaxel or gemcitabine combination chemotherapy as first-line treatment and docetaxel as second-line therapy under the national reimbursement program, but there is no treatment specified for use after disease progression. New third-line chemotherapy drugs including new targeted therapies are expensive and bring about only slightly prolonged progression-free survival and minimally better response in healthy patients.*

Objective: *Carboplatin plus etoposide chemotherapy, which was formerly used as a low-cost first-line treatment, was used as third-line therapy for advanced NSCLC in order to compare its results with those of best supportive care as a treatment for improved quality of life (QoL) and progression-free survival.*

Material and Method: *This prospective study of advanced NSCLC stage IIIB/IV enrolled 47 patients receiving either third-line chemotherapy with carboplatin plus etoposide or best supportive care in the Oncology Unit, Medicine Department, Rajavithi Hospital from 1 January 2005 to 31 December 2012. Results of treatment and quality of life of the two groups (QoL) were evaluated using the Functional Assessment of Cancer Therapy-Lung Cancer (FACT-L).*

Results: *The 47 advanced NSCLC patients were given either carboplatin plus etoposide chemotherapy (27 cases) or best supportive care (20 cases). No statistically significant differences were found in baseline characteristics and quality of life in the two groups. The median progression-free survival after two months was significantly higher (88.9% vs. 75.0%, p-value <0.001) in the chemotherapy group than in the best supportive care group, but no there were no statistically significant differences between QoL of patients in the two groups.*

Conclusion: *Carboplatin plus etoposide as third-line chemotherapy regimen demonstrated higher median progression-free survival in advanced NSCLC patients and did not adversely affect QoL.*

Keywords: *Advanced non-small cell lung cancer, Platinum combination chemotherapy, Functional assessment of cancer therapy-lung cancer (FACT-L), Quality of life, Best supportive care*

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Lung cancer is the second most commonly-found cancer in Thailand. It accounts for 15% of all cancers and is slightly more prevalent in males, with a high death rate of 25-30%. This cancer can be classified into two types: non-small cell lung cancer (NSCLC), which accounts for 84% of cases, and small cell lung cancer (SCLC), which makes up the other 16% of cases[1,2]. Squamous cell lung cancers, subtypes of NSCLC and SCLC, are associated with smoking. The overall survival rate is less than one year in untreated advanced stage NSCLC[3-5].

The American Joint Committee on Cancer (AJCC) has reported that chemotherapy is the most commonly-used treatment in advanced stage IIIb-IV NSCLC to improve progression-free survival and enhance quality of life (QoL). Patients with Eastern Cooperative Oncology Group (ECOG) performance status of less than 2 benefit more from combination chemotherapy than from best supportive care treatment[6-8]. Platinum-based combination chemotherapy of 4-6 cycles has demonstrated more benefit than single-agent treatment[9-11]. The first-line treatment is often platinum combination regimens with paclitaxel

Correspondence to:
Maneechavakajorn J, Division of Oncology, Rajavithi Hospital, 2, Phyathai Road, Rajathewi, Bangkok 10400, Thailand.
Phone: +66-2-3548059, Fax: +66-2-3548179
E-mail: jedzada@gmail.com

or gemcitabine and the second-line therapy is single-agent docetaxel. After second-line treatment progression, the majority of these NSCLC patients receive best supportive care because new third-line chemotherapies including new targeted therapies are expensive and achieve only slight improvement in progression-free survival and response. This study selected carboplatin plus etoposide, which was formerly used as first-line treatment, as third-line chemotherapy because of its low cost and ease of use in out-patient units[12-14]. Results of treatment and QoL assessments are gold standard evaluations in cancer therapy, and QoL is classified into four main domains: health and functioning; psychological and spiritual; social and economic; and family well-being[15-18]. The Functional Assessment of Cancer Therapy-Lung cancer (FACT-L) is a tool commonly used in the United States to assess QoL of lung cancer patients. It has been adapted from version 4 and translated into many Asian languages including Thai[19-24]. The objective of this study was to compare QoL and evaluate the results of carboplatin plus etoposide treatment as third-line chemotherapy in comparison with those of best supportive care in advanced NSCLC.

Material and Method

A prospective cohort study was conducted by examining the medical profiles of patients diagnosed with advanced NSCLC stage IIIb-IV in the Oncology Unit, Department of Medicine, Rajavithi Hospital, from 1 January 2005 to 31 December 2012. These advanced-stage patients received two regimens of chemotherapy and their disease progression was evaluated using response evaluation criteria in solid tumors (RECIST). They were given advice about the available choices of treatment, and they made their own decision about whether to accept chemotherapy with carboplatin 5-6 Area under the curve (AUC) mg on day1 plus etoposide 100 mg/m^2 on day 1 to day 3 (CE regimen) or receive only symptomatic or supportive treatment called best supportive care (BSC). Ondansetron and dexamethasone were used in premedication treatment for the patients who chose chemotherapy because other more potent antiemetic drugs were not available except by special request in the case of failure to control emetic symptoms. These patients had ECOG performance status 0-2, with normal complete blood count, and normal liver and renal function. They evaluated their own QoL using the FACT-L questionnaire at two stages: first, before starting chemotherapy treatment; and second, before commencing chemotherapy treatment cycles 3-5. Their negative questionnaire scores were calculated as part of the data collection process with a high score meaning good QoL. The results of treatment were evaluated using RECIST criteria[25].

Statistical analysis

The results of a previous study by Maneechawakajorn[26] reported QoL after receiving chemotherapy of $Z_{\alpha/2} = 1.09$ and the difference between the results of chemotherapy and best supportive care was estimated to be less than 10%. In the present study, a sample size of at least 29 patients per group was required to detect significant differences in QoL with 80% power and alpha-level 0.05.

Baseline characteristics of categorical data in the two groups were calculated using Pearson Chi-square or Fisher's exact test while Independent sample t-test was used for continuous data. The comparison of QoL before and after treatment within groups was calculated by Paired t-test, and Independent Sample t-test was used for between-group comparisons. Progression-free survival was estimated using the Kaplan-Meier method, and comparison was made between the two groups using the Log-rank test.

Progression-free survival (PFS) was calculated from the date of start of disease progression after second-line therapy until date of progression or death as a result of any cause. Statistical analysis was performed with SPSS version 17.0.

This study was approved by the Research and Ethics Committee of Rajavithi Hospital.

Results

The 47 patients in this study were divided into two groups: the carboplatin plus etoposide regimen group, which comprised 27 patients, and the best supportive care group, which consisted of 20 cases as shown in Table 1. The clinical characteristics of the two groups were not significantly different. Most participants were male, over 50 years old, with adenocarcinoma cell subtype and ECOG performance status of 0-1.

Table 2 shows QoL scores before and after treatment. Before intervention, the chemotherapy group demonstrated slightly higher scores in physical well-being, emotional well-being, and functional well-being, but the differences were not statistically significant. After follow-up at the second QoL assessment, no significant difference was observed between overall well-being of the two groups, but there was a significant

Table 1. Baseline characteristics of 47 patients

	CE group*, n = 27	BSC group**, n = 20	*p*-value
Age (year) mean ± SD	56.59±5.13	55.45±4.78	0.442
Sex			0.528
Male, n (%)	16 (59.3)	10 (50.0)	
Female, n (%)	11 (40.7)	10 (50.0)	
Status			0.137
Married, n (%)	19 (66.7)	9 (45.0)	
Single/divorced, n (%)	8 (33.3)	11 (55.0)	
Comorbid illness			0.251
No, n (%)	13 (48.1)	13 (65.0)	
Yes, n (%)	14 (51.9)	7 (35.0)	
Education			0.391
Below bachelor degree, n (%)	23 (85.2)	15 (75.0)	
Bachelor degree, n (%)	4 (14.8)	5 (25.0)	
Right to treatment			0.848
Government reimbursement, n (%)	6 (22.2)	4 (20.0)	
Health insurance, n (%)	15 (55.6)	13 (65.0)	
Social security, n (%)	6 (22.2)	3 (15.0)	
Cell type			0.913
Adeno-carcinoma, n (%)	18 (66.7)	15 (75.0)	
Squamous, n (%)	3 (11.1)	1 (5.0)	
Other/cytology, n (%)	6 (22.2)	4 (20.0)	
ECOG performance status			0.682
PS = 0-1, n (%)	22 (81.5)	18 (90.0)	
PS = 2, n (%)	5 (18.5)	2 (10.0)	

* CE = carboplatin plus etoposide; ** BSC = best supportive care; ECOG = the eastern co-operative oncology group

Table 2. QoL assessment before and after treatment in the two groups

QoL*	CE group** mean ± SD	BSC group*** mean ± SD	*p*-value
Before treatment (n)	27	20	
Physical well-being (GP)	3.95±0.67	3.84±0.90	0.620
Social/family well-being (GS)	3.59±0.74	3.88±0.47	0.134
Emotional well-being (GE)	4.03±0.73	3.81±0.91	0.363
Functional well-being (GF)	3.34±0.67	3.22±0.66	0.520
Additional concerns(C)	3.54±0.52	3.53±0.45	0.963
Overall first assessment	3.72±0.56	3.76±0.49	0.583
After treatment 2-4 cycles (n)	27	20	
Physical well-being (GP)	3.70±0.73	3.40±0.69	0.398
Social/family well-being (GS)	3.80±0.55	3.74±0.58	0.828
Emotional well-being (GE)	3.40±0.69	2.91±0.62	0.159
Functional well-being (GF)	3.06±0.48	3.23±0.64	0.499
Additional concerns (C)	3.49±0.37	3.30±0.25	0.261
Overall second assessment	3.49±0.34	3.32±0.48	0.355

* QoL = quality of life; ** CE = carboplatin plus etoposide; *** BSC = best supportive care

deterioration within both groups compared with the first assessment (chemotherapy arm *p*-value = 0.027, best supportive care arm *p*-value = 0.013).

Table 3 demonstrates that the median PFS was

higher after 3 months in the chemotherapy group than in the best supportive care group, and there was a significant difference in PFS after 2 months (88.9% vs. 75.0%, *p*-value <0.001); however, none of these patients demonstrated partial or completed response according to RECIST criteria. Fig. 1 shows Kaplan-Meier estimates of PFS, which were higher in the carboplatin plus etoposide group.

Discussion

The reasons for using carboplatin plus etoposide as third-line chemotherapy rather than best supportive care in treating advanced NSCLC are that it maintains QoL and prolongs progression-free survival. The number of patients included in this study was lower than the calculated required sample size because only one-fourth of advanced NSCLC patients were able to continue cancer chemotherapy through the third-line treatment, and including data of new patients in this single-institute study to arrive at a QoL assessment of less than 10% would have been very time-consuming. The overall QoL score before starting treatment was not significantly different in the two groups, but scores were slightly higher in terms of physical well-being, emotional well-being, and functional well-being in the chemotherapy group. This may be associated with the better health of the patients that were willing to undergo chemotherapy, as they benefitted from two pre-chemotherapy regimens. In addition, this group requested treatment whereas the other group chose best supportive care, and this may be because the latter group may have been tired from previous long-term treatment, which may have limited their activities. The non-randomized method in which patients selected treatment by themselves may have influenced results. Although the Right to Treatments were universal coverage in about 60-70% of cases, the three categories of health care groups in this study were not statistically different in the chemotherapy and best supportive care arms. All of our patients were able to avail of this chemotherapy regimen in accordance with their right to treatments, so this should not have affected their basic QoL difference.

After treatment at the second QoL assessment, no significant difference was found in the two groups, and this may indicate that side effects in the treatment group were minimal and that the patients were able to adapt and cope with the disease and treatment. Compared with before treatment, the second overall QoL assessment showed a statistically significant deterioration in both groups; the main reasons for this could be related to their tumor progression in a short period with more symptoms and only marginal response in the treatment arm. The chemotherapy group demonstrated significantly higher PFS at 2 months (88.9% vs. 75.0%, *p*-value <0.001) and also higher PFS after 3 months, and these findings are compatible with those of other studies, which found higher PFS at 2-4 months using erlotinib as third-line treatment[27-29]. None of the chemotherapy treatment patients demonstrated complete or partial response. This may be related to the limitations in detection of

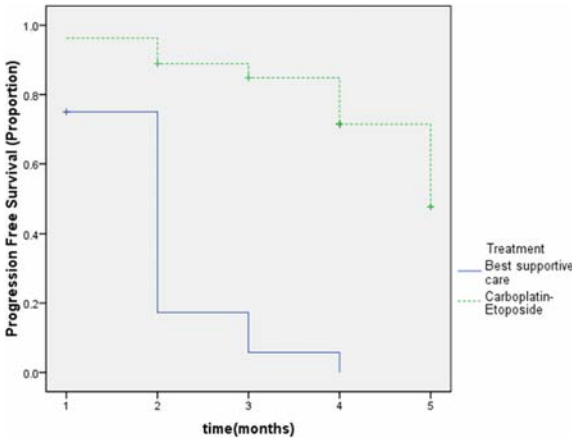

Fig. 1 Kaplan-Meier estimates of progression free survival.

Table 3. Results of treatment and progression-free survival (PFS)

Result	CE group* (n = 27)	BSC group** (n = 20)	*p*-value
PFS at 2 months, n (%)	24 (88.9)	15 (75.0)	<0.001
PFS at 4 months, n (%)	19 (70.0)	0 (0.0)	
Median PFS (months)	5 (-)***	2 (1.69-2.3)	
Response (PR/CR)****	0	0	

* CE = carboplatin plus etoposide; ** BSC = best supportive care; *** Not reach 50% PFS; **** PR/CR-partial/completed response

tumor size by film chest x-ray which was mostly used in this study instead of computer scan detection which is more accurate but more expensive, and there was not enough time to arrange for it to be available for our investigations.

The limitations of this study were the small number of patients in a single institute; non-randomized selection; and less accurate investigation using plain film that made the findings less reliable. Carboplatin and etoposide nowadays are generic drugs with which most oncologists are familiar, and they are often used as third- or fourth-line treatment in clinical practice, but few studies have been performed to confirm their efficacy and effects on Qol.

Conclusion

Carboplatin plus etoposide as a third-line chemotherapy regimen demonstrated higher 3-month median progression-free survival rates in advanced NSCLC patients and did not adversely affect QoL.

What is already known on this topic ?

Many third-line treatments in non-small cell lung cancer stage IIIB/IV have involved the use of high-cost chemotherapy or new targeted therapies, which only slightly improve progression-free survival and tolerance.

What this study adds ?

Treatment with carboplatin/etoposide as third-line chemotherapy in non-small cell lung cancer stage IIIB/IV prolonged progression-free survival and maintained patients' quality of life at a lower cost.

Potential conflicts of interest

None.

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เปรียบเทียบคุณภาพชีวิตของผู้ป่วยมะเร็งปอดชนิด Non-small cell ระยะ IIIB หรือ IV โดยใช้ยาเคมีบำบัด Carboplatin ร่วมกับ Etoposide เป็นขนานที่สามเทียบกับรักษาตามอาการ

เจษฎา มณีชวขจร, สิทธิโชค หทัยสงวน

ภูมิหลัง: มะเร็งปอดระยะที่สามบีและสี่ส่วนใหญ่จะได้รับยาเคมีบำบัดขนานแรกที่ประกอบด้วย paclitaxel หรือ gemcitabine combination และได้รับขนานที่สองด้วยยา docetaxel แต่หลังจากโรคลุกลามในขนานสองแล้วส่วนใหญ่จะไม่ได้รับการรักษาด้วยยาเฉพาะ เนื่องจากยาในขนานที่สามมีราคาค่อนข้างสูงรวมไปถึงกลุ่มยา target ใหม่ ๆ

วัตถุประสงค์: การศึกษานี้ได้ใช้ยาเคมีบำบัด carboplatin ร่วมกับ etoposide ที่เคยใช้เป็นยารักษามะเร็งปอดในขนาดแรก นำมาเปรียบเทียบกับรักษาตามอาการโดยเปรียบเทียบคุณภาพชีวิตและผลการรักษา

วัสดุและวิธีการ: เป็นการศึกษาแบบ prospective study โดยรวบรวมผู้ป่วยมะเร็งปอดชนิด non-small cell ระยะสามบีและสี่ 47 ราย ที่ให้การรักษาด้วยยาเคมีบำบัด carboplatin ร่วมกับ etoposide หรือให้การรักษาตามอาการที่มารับการรักษา ณ หน่วยงานโรคมะเร็ง กลุ่มงานอายุศาสตร์ โรงพยาบาลราชวิถี ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2548 ถึง วันที่ 31 ธันวาคม พ.ศ. 2555 โดยศึกษาถึงข้อมูลพื้นฐานประชากร ประเมินคุณภาพชีวิตด้วยแบบสอบถาม functional assessment of cancer therapy-lung cancer (FACT-L) และประเมินผลการรักษาเปรียบเทียบระหว่างกลุ่มที่ได้รับยาเคมีบำบัด carboplatin ร่วมกับ etoposide และกลุ่มที่รักษาตามอาการ

ผลการศึกษา: ผู้ป่วยทั้งหมด 47 ราย แบ่งเป็นกลุ่มที่ได้รับยาเคมีบำบัด carboplatin ร่วมกับ etoposide 27 ราย และรักษาตามอาการ 20 ราย ลักษณะทั่วไปและลักษณะทางคลินิกใกล้เคียงกันและคุณภาพชีวิตทั้งสอบกลุ่มไม่แตกต่างกันก่อนการรักษา ผลการรักษาพบว่าผู้ป่วยกลุ่มที่ได้รับยาเคมีบำบัดมีระยะเวลาที่โรคสงบ (PFS) ที่ 2 เดือนเพิ่มขึ้น 88.9% เทียบกับ 75.0% (p-value <0.001) ในผู้ป่วยที่รักษาตามอาการและมีคุณภาพชีวิตไม่แตกต่างกันหลังรักษา

สรุป: การรักษามะเร็งปอดขนานสามด้วยยาเคมีบำบัด carboplatin/etoposide สามารถชะลอการลุกลามของโรคเทียบกับการรักษาตามอาการ และไม่ทำให้คุณภาพชีวิตลดลง