DOXETAXEL IN PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER PATIENTS: CLINICAL EFFICACY AND QUALITY OF LIFE

Thitiya Sirisinha[1], Suwanee Sirilertrakul[2], Manmana Jirajarus[2] and Vorachai Ratanatharathorn[1]

[1]Medical Oncology Unit, Department of Medicine, [2]Nursing Department, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract. Docetaxel (Taxotere) is one of the most active new generation chemotherapy agents against advanced non-small cell lung cancer (NSCLC). This study aimed to determine the activity, toxicity and impact on the quality of life (QOL) in patients treated with docetaxel after failure with first-line platinum-based combination chemotherapy. Twenty-one patients with advanced NSCLC who had previously received the platinum-containing regimen were treated with docetaxel 75 mg/m^2 every 3 weeks. QOL was assessed at intervals during the treatment period using the Functional Assessment of Cancer Treatment - Lung (FACT-L). Of the 21 patients enrolled, 16 were able to be evaluated for response and 20 were included in the toxicity analysis. The median age was 57 (range, 39-75 years). A median of 3 cycles was given (range, 1-9). Of the 16 evaluatable patients, there was one partial response (6.3%) and 4 with stable disease (25%). The median survival time was 8.1 months and the 1-year survival rate was 25%. Myelosuppression and peripheral neuropathy were the major toxicities. Grade 3/4 neutropenia and paresthesia occurred in 6 patients (30%) and 3 patients (15%), respectively. There was no significant improvement or deterioration in the overall FACT-L, TOI (Trial Outcome Index) and lung cancer symptom scores during the treatment. Symptom improvement was noted, in particular for shortness of breath and weight loss in the majority of patients. It is concluded that docetaxel is a well tolerated second-line treatment for recurrent NSCLC. Of particular importance was that the treatment did not negatively impact the overall quality of life, on the contrary, did palliate some of the lung cancer related dash symptoms in many patients.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death globally, including in Thailand. Most patients present late in their disease courses and treatment is, in general, non-curative. After years of debate regarding the role of systemic chemotherapy in advanced NSCLC, the result of a large meta-analysis has shown conclusively that this treatment modality can prolong survival (Non-small Cell Lung Cancer Collaborative Group, 1995). For patients with advanced NSCLC, the use of the older generation platinum-based regimen yielded an absolute improvement in one-year survival of 10% compared to supportive care alone. With several newer and more active agents, such as the taxanes, gemcitabine and vinorelbine, higher response rates and one-year survival rates were noted in randomized studies of these drugs in comparison with supportive care (Helsing *et al*, 1998; Thongprasert *et al*, 1999; Ranson *et al*, 2000; Roszkowski *et al*, 2000; Sandler *et al*, 2000). The role of second-line chemotherapy in this disease has been unclear, in light of the mixed results in several early phase II studies using a variety of drugs (Fossella *et al*, 1997; Gridelli *et al*, 1999). One agent that has been extensively evaluated and had shown quite consistent results in this setting is docetaxel.

Docetaxel (Taxotere^R) is a semi-synthetic taxane extracted from the needles of the European yew tree, *Taxus bacata.* It has potent antitumor activity against NSCLC *in vitro* (Bissery *et al*, 1991). In a randomized trial, patients treated in the docetaxel arm demonstrated a superior survival as well as improvement in disease-related symptoms (Roszkowski *et al*, 2000).

Correspondence: Dr Thitiya Sirisinha, Oncology Unit, Department of Medicine, Ramathibodi Hospital, Rama VI Road, Bangkok 10400, Thailand.
Tel: ++66 (0) 2201-1671; Fax: ++66 (0) 2643-5648
E-mail: ratsh@mahidol.ac.th

In addition, it has also been evaluated in the second-line setting after platinum-failure and a convincing activity was noted and proven to benefit many patients, both in terms of survival and quality of life (QOL) (Fossella *et al*, 2000; Gandara *et al*, 2000; Shepherd *et al*, 2000). In spite of these findings, the treatment comes with the cost of adverse side effects which the patients have to endure. Hence, QOL is an important aspect to be considered in the assessment of treatment for advanced cancer. For NSCLC, there have been many reports indicating that despite the side effects of chemotherapy, patients who received palliative chemotherapy fared better in their overall QOL compared to those receiving only supportive care (Helsing *et al*, 1998; Thongprasert *et al*, 1999; Roszkowski *et al*, 2000). Even with the use of second-line chemotherapy for those who have failed prior treatment, exclusive of docetaxel, similar data were obtained (Fossella *et al*, 2000; Shepherd *et al*, 2000). We reported here, a single institution experience in the treatment of platinum-failure NSCLC using docetaxel with respect to its clinical efficacy as well as the impact on QOL in these patients.

PATIENTS AND METHODS

Patients and drug administration

Eligibility criteria for this study included patients with the diagnosis of advanced non-small cell lung cancer who has progressed while, or after, receiving at least one platinum-containing regimen. Additional inclusion criteria included age 18 years or older, an ECOG score of 0-2, the presence of evaluable or measurable disease, and adequate hematologic, hepatic, and renal function. Patients with uncontrolled brain metastases or neuropathy were not eligible.

Docetaxel was administered at a dose of 75 mg/m^2 every 3 weeks. Premedication was with dexamethasone 8 mg twice daily, given on day -1, 0 and 1 of each treatment cycle. Treatment was continued until disease progression or unacceptable toxicity. Dose reduction or delay was allowed for grade 3 neuropathy or any grade 4 toxicity, until they resolved. Those with treatment delays longer than 2 weeks were removed from the study.

Response and toxicity assessment

Pre-study evaluation included a complete history and physical examination with performance status assessment, complete blood count (CBC) and a serum liver function test. Baseline tumor measurement was performed either by CXR, CT scan or other radiographic methods appropriate for each case. CBC and toxicity assessment were performed every week and liver function testing was done before each cycle. All toxicities were graded using the National Cancer Institute common toxicity criteria, version 2.0

Patients were assessed for tumor response every 2 to 3 cycles at the discretion of the treating physicians or at the time of suspected disease progression. Patients who received less than 2 cycles were considered to be non-assessable for response. Treatment response determination was done in accordance with WHO criteria (Miller *et al*, 1981). Complete response was defined as the disappearance of all radiographic or clinically apparent tumors; partial response was defined by a greater than 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Stable disease was defined as no change of more than 25% of the baseline tumor size and no new lesions. Progressive disease was defined as more than 25% increase in any measurable lesions or an appearance of a new lesion. After disease progression, each patient was followed either in the clinic or by phone contact every 1 to 2 months until death.

Quality of life assessment

Patients were requested to complete the Thai version of the Functional Assessment of Cancer Therapy - Lung (FACT-L, version 4) QOL questionnaire (Ratanatharathorn *et al*, 2001) at baseline and before each cycle. A follow-up assessment was not done after withdrawal from the study. The FACT-L has a total of 36 items measuring 4 general and one lung cancer symptom subscales. The general subscales include, Physical Well - Being (PWB) (7 items), Social/ Family Well-Being (SWB) (7 items), Emotional Well-Being (EWB) (6 items) and Functional Well - Being (FWB) (7 items). The Lung Cancer Subscale (LCS) comprises 7 specific items that

assess common symptoms reported by lung cancer patients, and 2 items which ask about concern for hair loss and regret for smoking. These last 2 items are not scored. Scoring of the questionnaire was performed according to the guidelines provided by Dr David Cella (Cella, 1997). Total scores can range from 0 to 136, the higher scores indicate a better QOL. A Trial Outcome Index (TOI) was calculated by combining the Physical Well-Being, Functional Well-Being and Lung Cancer Subscale. This is considered to be the most clinically relevant aggregation of QOL dimensions that reflect the effects of the treatment for NSCLC (Cella *et al*, 1995).

Statistical methods

The primary study endpoint was survival with secondary endpoints being response rate, toxicity and QOL. Overall, survival was calculated from the day of enrollment until death using the Kaplan-Meier method. Baseline QOL and changes in QOL over time were studied. Analysis of the change in the QOL score during treatment was performed using repeated measurement ANOVA and multiple comparisons by the S-N-K test.

RESULTS

Patient characteristics

There were 21 patients enrolled in the study. Table 1 lists the patient characteristics in the trial. The median age was 57 (range, 39-75 years). There were 16 male and 5 female patients, all with an ECOG performance status of 0-1. Seventeen of 21 patients had stage IV disease at study enrollment. One patient had stage II disease at final review. Histology included adenocarcinoma in the majority (13 patients, 62%), with the remainder being squamous cell carcinoma in 5 patients, poorly differentiated carcinoma in 2 patients and one with large cell carcinoma. All patients had previously received at least one platinum-based course of chemotherapy. Among the patients, 5 had received paclitaxel before protocol enrollment (data not shown). Response to previous chemotherapy was: 6 partial responses, 4 with stable disease and 10 with progressive disease.

Of the 21 patients enrolled, 16 were evaluable for response and 20 were evaluable for toxicity. One patient received the study drug for a presumed liver metastasis, which was later confirmed to be a hepatic cyst, and was excluded from the response analysis. One patient developed sudden death at home after the first cycle, 2 patients had early disease progression after the first cycle and one patient was withdrawn due to intolerability to the side effects of the treatment following the first treatment.

Treatment delivery and toxicity

A total of 74 cycles of docetaxel were administered, with a median number of treatments per patient of 3 (range, 1-9 cycles). Treatment was fairly well tolerated and the details of the adverse effects are listed in Table 2. Two pa-

Table 1
Patient characteristic (n=21).

Characteristics	N (%)
Male/ Female	16/5
Age, years	
Median (range)	57 (39-75)
ECOG	
0	6 (28.5)
1	15 (71.5)
Histologic subtype	
Adenocarcinoma	13 (62)
Squamous cell carcinoma	5 (23)
Poorly differentiated carcinoma	2 (10)
Large cell carcinoma	1 (5)
Stage	
II	1 (5)
IIIA/IIIB	3 (14)
IV	17 (81)
Numbers of prior chemotherapy regimen	
1	18 (86)
2	3 (14)
Best response to previous chemotherapy	
Partial response	6 (29)
Stable disease	4 (19)
Progressive disease	10 (48)
Not applicable[a]	1 (5)
Previous radiotherapy	
Yes	10 (48)
No	11 (52)

[a] = No evidence of metastasis at final review.

Table 2
Summary of toxicity.

Toxicity	All grade		CTC grade 3/4	
	No. of patients/total no.	%	No. of patients/total no.	%
Leukopenia	14/20	70	3/20	15
Neutropenia	12/20	60	6/20	30
Anemia	19/20	95	3/20	15
Myalgia	20/20	100	1/20	5
Arthralgia	17/20	85	0/20	0
Paresthesia	17/20	85	3/20	15
Fatigue	20/20	100	2/20	10
Mucositis	9/20	45	0/20	0
Diarrhea	12/20	60	0/20	0
Alopecia	16/20	80	0/20	0
Nausea	13/20	65	1/20	5
Vomiting	6/20	30	0/20	0
Fluid retention	3/20	15	0/20	0

Abbreviation: CTC = Common toxicity criteria.

Table 3
FACT-L descriptive statistics.

QOL subscale	Patients (n)	Score		
		Mean	SD	Range
Total FACT-L score				0-136
Baseline assessment	17	80.68	15.51	41-99
Assessment 2	17	78.29	17.51	46-100
Assessment 3	12	84.38	12.49	66-109
Assessment 4	9	86.72	13.68	69-108
TOI				0-84
Baseline assessment	17	45.94	10.48	18-60
Assessment 2	17	44.06	13.57	16-61
Assessment 3	12	49.00	9.25	39-67
Assessment 4	9	51.89	8.28	41-66
Lung cancer subscale				0-28
Baseline assessment	17	15.35	2.67	11-20
Assessment 2	17	16.59	3.94	6-21
Assessment 3	12	17.42	3.12	12-24
Assessment 4	9	18.00	3.12	14-24

Abbreviation: FACT-L= Functional assessment of cancer therapy-lung; QOL = Quality of life; TOI = Trial outcome index; SD= Standard deviation.

Table 4
Changes in FACT-L lung cancer subscales with docetaxel (n= 17).

Symptom or observation	No. of patients		
	Better	Stable	Worse
Shortness of breath	9	5	3
Weight loss	10	5	2
Clear thinking	3	10	4
Coughing	5	9	3
Hair loss	4	9	4
Good appetite	2	11	4
Tightness in chest	5	11	1
Easy breathing	4	9	4

tients withdrew from the protocol due to excessive toxicity. The main side effects were myelosuppression and peripheral neuritis. Myelosuppression was moderate; six patients (30%) developed grade 3/4 neutropenia, 3 patients (15%) had grade 3 anemia and two of them required packed red cell transfusions. Three patients had febrile neutropenia. In no cases was thrombocytopenia observed. Paresthesia was common (17 of 20 patients) and in 3 patients (15%) this was grade 3. Two of the 3 patients who developed grade 3 neuropathy did so after having receiveing 7 and 9 cycles of docetaxel. Other common toxicities included myalgia/arthralgia, fatigue, diarrhea, mucositis, alopecia and nausea, which were seen in over half of the treated patients. Most of them were of mild intensity. Fluid retention were observed in 3 of 20 cases and consisted of mild peripheral edema. No patients experienced a hypersensitivity reaction to the study drug. There were no treatment-related deaths in this study.

Tumor response and survival

Among the 16 patients evaluable for response, there was one partial response (6.3%) documented after 6 cycles of therapy. An additional 4 patients (25%) attained stable disease. Two patients developed sudden death after 2 cycles, before formal radiographic assessments were done, and the definitive diagnosis of the causes of death were not available to the investigators. The remaining 11 patients had disease progression as their best response and all were seen within the first 3 cycles of treatment.

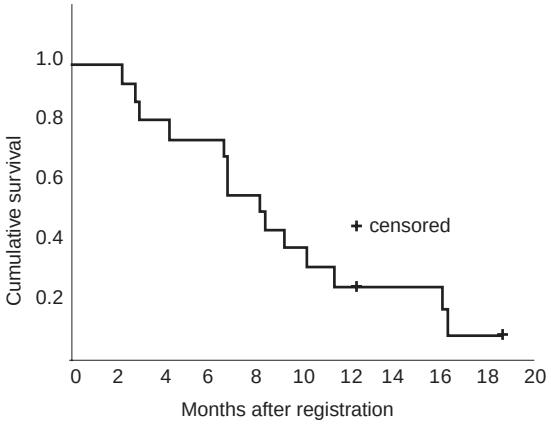

Fig 1–Kaplan-Meier estimates of overall survival.

There was no correlation between previous response to first-line treatment and response to docetaxel (data not shown). All 6 patients who had a partial response to their earlier regimen progressed while receiving docetaxel.

Sixteen patients were included in the analysis of survival. The median follow-up time was 8.1 months. Fourteen patients had died (87.5%) and the remaining 2 patients were still alive at last follow-up. The median survival time was 8.1 months (range, 2.1-18.6 months) (Fig 1). The 1-year survival rate was 25% (95% confidence interval, 7.8-47.2%)

Quality of life

Of the 21 patients registered, only 17 completed the baseline FACT-L questionnaire (81%). The reason for this incompleteness in data collection was that the Thai version of the FACT-L was not fully validated at the time the therapeutic part of this trial was begun. Among those with baseline QOL data, complete assessments were available for 17 patients (100%) at pre-cycle 2 (week 4), 12 patients (70%) at pre-cycle 3 (week 7) and 9 patients (53%) at pre-cycle 4 (week 10). As the majority of the patients (16 patients, 76%) received 3 cycles or less of docetaxel and the protocol did not require continued assessment of QOL after treatment was stopped, only 3 patients (who received extended treatment) had completed more than 4 FACT-L assessments.

The FACT-L, lung cancer subscale and TOI scores at baseline and at assessment 2-4 are summarized in Table 3. The mean baseline FACT-L score was 80.7 (range; 40.7-99.0) from a possible score of 0-136. There was a trend for the mean total FACT-L, TOI and lung cancer subscale scores to increase with time during subsequent assessments. An analysis using repeated measures of ANOVA, comparing baseline scores with the first 3 cycles of treatment showed no significant improvement or deterioration regardless of disease response categories. There was no correlation between the baseline QOL score and survival (data not shown).

Individual patient analysis revealed that of the 10 patients with progressive disease, 3 had significant improvements in their FACT-L scores (and corresponding improvement in their lung cancer subscales); three had a worse FACT-L score and 4 had stable scores. The only patient who had a partial response to docetaxel had a stable FACT-L score after 3 cycles of therapy, which later improved following cycle 6, when she had a documented response. Table 4 lists the changes in lung cancer symptoms recorded on the FACT-L questionnaires for all 17 evaluatable patients.

DISCUSSION

Recently, there has been an expanding body of evidence showing the beneficial effects of second-line chemotherapy in advanced NSCLC. Despite many phase I and II studies using various agents, only docetaxel has emerged as the single drug that has consistently been shown, in randomized trials, to improve survival when compared with supportive care or other second-line regimens (Fossella *et al*, 2000; Shepherd *et al*, 2000). This gain in survival, although very modest (2.9 months), is encouraging, given the lack of benefit from other treatments in the past. In this study, we found no differences between the toxicity profiles of this and other studies (Fossella *et al*, 2000; Roszkowski *et al*, 2000; Shepherd *et al*, 2000). Fatigue was seen universally in all the patients in this study, with only 10% being grade 3/4. In a study by Shepherd *et al* (2000) and Roszkowski *et al* (2000), severe asthenia was reported in 20-28% in the docetaxel arm and

23-28% in the control arm with any grade of asthenia seen in 55-60%. It is impossible to conclude from our single-arm study design if fatigue is entirely a 'treatment-related' side effect or 'disease-related' in the population of advanced lung cancer patients. Other commonly seen side effects with this drug included diarrhea, stomatitis and neurosensory abnormalities, but again, most were of grade 1/2.

The results of our current study confirm a fairly low rate of response, with a partial response of only 6.3%; with a median survival comparable to the other two landmark studies in the same setting. The goal of palliative chemotherapy, in this disease, was not merely to prolong survival but also to improve the symptoms experienced by the patients, and therefore is the relevant issue that needs to be addressed. It has been noted by many investigators that a higher proportion of patients gain symptomatic benefits than is suggested by the objective tumor response rate (Ellis *et al*, 1995; Thatcher *et al*, 1997). In general, symptoms recorded by physicians are underestimated compared to the patients' own rating (Stephens *et al*, 1997) emphasizing the importance of QOL assessment in cancer patients where palliation is the goal.

QOL measurements provide a direct measure of patient benefits as perceived by the patient themselves, which is different from the traditional endpoints used in clinical studies, such as response rates or survival. It is the balance between symptom palliation and treatment-related side effects, together with other non-physical aspects of life. Survival with NSCLC is limited, and the treatment itself, whether it be radiotherapy or chemotherapy, can produce untoward side effects that many physicians and patients feel would jeopardize their remaining QOL. It is prudent that the treatment offered should take into account not only the 'medical benefit' but also the patient's perception of the benefit before one accepts or rejects that treatment. This issue was taken seriously by the Oncologic Drugs Advisory Committee of the US Food and Drug Administration and recommended that for new anticancer drugs to be approved, a beneficial effect on QOL should also be demonstrated, in addition to the usual clinical efficacy (Beitz *et al*, 1996).

More than 50 different instruments have been used to quantify QOL in lung cancer patients (Montazeri *et al*, 1998). We chose the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) as a tool for QOL assessment in this study. It is a comprehensive but brief and reliable means of measuring the QOL domains relevant to the patients' values (Cella *et al*, 1993, 1995). In addition, it is one of the few cancer-related instruments in the Thai language that has been adequately validated (Sanguanmitra *et al*, 1993; Ratanatharathorn *et al*, 2001). It can be completed by the patients themselves and thus is suitable for use in a busy outpatient oncology clinic.

The mean baseline FACT-L score in our study population was 80.7 (from a possible score of 0-136), which is somewhat low compared to a previously reported score in the SWOG 9509 study (Moinpour *et al*, 2002). Because different versions of the FACT-L were used in the SWOG study and in our study, the score was transformed according to the scoring guideline (Cella, 1997), and after adjusting the score, the mean baseline score in our patient population was 85.1, compared to 96.0-97.2 for the SWOG data. Such a finding is not unusual, given the fact that these patients had failed prior treatment (50% with disease progression as their best response to first-line therapy) and therefore were expected to have a lower QOL score compared to those treated at first diagnosis. In addition, this finding also points toward a less highly-selected population, which may be more relevant to everyday practice.

We decided to use a comparison score at week 11 because it provided sufficient time to observe clinical changes without excessive missing data due to death or disease progression. For this population, the compliance rate was 53% at the above time-point, which reflects the difficulty in collecting QOL data in physically compromised NSCLC patients. Overall, the longitudinal analysis of the total FACT-L score showed neither significant deterioration nor improvement with docetaxel. In order to investigate the short-term changes in the physical aspects of the QOL

which may have been affected most by the treatment given, we used the Trial Outcome Index (TOI) as a surrogate, as it was considered to be the best summary indicator of the physical component of QOL (Cella *et al*, 1995). Again, there was no significant decline in this particular parameter in spite of the side effects of the drug. Moreover, the change in the Lung Cancer Subscale (in particular, shortness of breath and weight loss) also indicated that palliation was achieved, even in the absence of an objective response in most patients.

There are not many reports of QOL data in the setting of second-line chemotherapy for NSCLC. The other 2 studies with this information were TAX 317 and TAX 320 which compared docetaxel with the best supportive care (Shepherd *et al*, 2000) or vinorelbine/ifosfamide (Fossella *et al*, 2000). Using different QOL tools from ours [Lung Cancer Symptom Scale (LCSS) and EORTC-QLQ-C30], both trials demonstrated trends in better QOL, favoring the docetaxel-treated arm. While these data showed only a modest trend in improvement in QOL, it is still encouraging not to see any decline in the overall well-being of these patients, whose disease state was progressing.

In this study, the completion of the FACT-L questionnaire was quite satisfactory during the first 10 weeks of enrollment. However, due to the study design, which did not require patients who withdrew from the study (regardless of the reason for withdrawal) to continue with the FACT-L assessment upon follow-up, we were unable to quantify the proportion of patients who might have a rapid decline in their QOL after disease progression. It would be worthwhile to try to collect additional QOL data, even after the patients had failed treatment, to visualize the impact of the treatment and the disease itself on each patient, although this would require more of the patients' time and effort to do so. The decreasing compliance rate over time in many other studies in patients with NSCLC (Giaccone *et al*, 1998; Bonomi *et al*, 2000; Moinpour *et al*, 2002) underscores the difficulty of performing QOL studies in advanced malignancy. It is well-recognized that missing data on the QOL in terminally-ill patients due to deterioration in health status can overestimate the results and we cannot exclude that possibility being responsible for our findings.

This study demonstrated the feasibility of using the QOL assessment in a clinical trial of advanced stage lung cancer in Thai patients, although an inherent difficulty in collecting serial assessments does exist, as stated earlier. Nevertheless, when resources allow their inclusion in the trial, the QOL and other non-clinical outcomes can assist the physicians and patients in a more comprehensive evaluation of the treatment regimens.

In spite of the limitations of this small study, it is reasonable to conclude that docetaxel is tolerable to patients in an out-patient setting, as second-line chemotherapy for advanced NSCLC. There was little or no substantial negative effect on the total QOL, to the extent that the patients and health care providers were expecting.

ACKNOWLEDGEMENTS

We are grateful to Umaporn Udomsubtakul, a researcher from the Research Center at Ramathibodi Hospital, for her statistical assistance, without whom this work would not be possible.

REFERENCES

Beitz J, Gnecco C, Justice R. Quality-of-life end points in cancer clinical trials: the US Food and Drug Administration perspective. *J Natl Cancer Inst Monogr* 1996: 7-9.

Bissery MC, Guenard D, Gueritte-Voegelein F, Lavelle F. Experimental antitumor activity of taxotere (RP 56976, NSC 628503), a taxol analogue. *Cancer Res* 1991; 51: 4845-52.

Bonomi P, Kim K, Fairclough D, *et al.* Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2000; 18: 623-31.

Cella D. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT Scales)- Version 4. Evanston, IL: Center on Outcomes, Research and Education, Evanston Northwestern Healthcare and Northwestern University, 1997.

Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995; 12: 199-220.

Cella DF, Tulsky DS, Gray G, *et al.* The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol* 1993; 11: 570-9.

Ellis PA, Smith IE, Hardy JR, *et al.* Symptom relief with MVP (mitomycin C, vinblastine and cisplatin) chemotherapy in advanced non-small-cell lung cancer. *Br J Cancer* 1995; 71: 366-70.

Fossella FV, DeVore R, Kerr RN, *et al.* Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000; 18: 2354-62.

Fossella FV, Lee JS, Hong WK. Management strategies for recurrent non-small cell lung cancer. *Semin Oncol* 1997; 24: 455-62.

Gandara DR, Vokes E, Green M, *et al.* Activity of docetaxel in platinum-treated non-small-cell lung cancer: results of a phase II multicenter trial. *J Clin Oncol* 2000; 18: 131-5.

Giaccone G, Splinter TA, Debruyne C, *et al.* Randomized study of paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. The European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 1998; 16: 2133-41.

Gridelli C, Perrone F, Gallo C, *et al.* Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. *Anticancer Res* 1999; 19: 4535-8.

Helsing M, Bergman B, Thaning L, Hero U. Quality of life and survival in patients with advanced non-small cell lung cancer receiving supportive care plus chemotherapy with carboplatin and etoposide or supportive care only. A multicentre randomised phase III trial. Joint Lung Cancer Study Group. *Eur J Cancer* 1998; 34: 1036-44.

Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47: 207-14.

Moinpour CM, Lyons B, Grevstad PK, *et al.* Quality of life in advanced non-small-cell lung cancer: results of a Southwest Oncology Group randomized trial. *Qual Life Res* 2002; 11: 115-26.

Montazeri A, Gillis CR, McEwen J. Quality of life in patients with lung cancer: a review of literature from 1970 to 1995. *Chest* 1998; 113: 467-81.

Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer : A meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995; 311: 899-909.

Ranson M, Davidson N, Nicolson M, *et al.* Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2000; 92: 1074-80.

Ratanatharathorn V, Sirilerttrakul S, Jirajarus M, *et al.* Quality of life, Functional Assessment of Cancer Therapy-General. *J Med Assoc Thai* 2001; 84: 1430-42.

Roszkowski K, Pluzanska A, Krzakowski M, *et al.* A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* 2000; 27: 145-57.

Sandler AB, Nemunaitis J, Denham C, *et al.* Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2000; 18: 122-30.

Sanguanmitra P, Juthapan W, Thongprasert S. Validity and reliability of the modified Functional Living Index Cancer (T-FLIC) and the modified Quality of life (T-QOL) questionnaires [Abstract]. Bangkok, Thailand: The 11th Asian Pacific Cancer Conference, 1993: 121.

Shepherd FA, Dancey J, Ramlau R, *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18: 2095-103.

Stephens RJ, Hopwood P, Girling DJ, Machin D. Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? *Qual Life Res* 1997; 6: 225-36.

Thatcher N, Hopwood P, Anderson H. Improving quality of life in patients with non-small cell lung cancer: research experience with gemcitabine. *Eur J Cancer* 1997; 33 (suppl 1): S8-13.

Thongprasert S, Sanguanmitra P, Juthapan W, Clinch J. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) versus BSC plus chemotherapy. *Lung Cancer* 1999; 24: 17-24.