RESEARCH COMMUNICATION

Effect of Change in Symptoms, Respiratory Status, Nutritional Profile and Quality of Life on Response to Treatment for Advanced Non-small Cell Lung Cancer

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Abstract

Introduction: Quality of life (QOL), and pulmonary and nutritional parameters are important outcome measures during treatment of lung cancer; however, the effect of chemotherapy on these factors and their relationship with clinical response is unclear. Methods: Patients with non-small cell lung cancer (NSCLC) were evaluated for symptom profile, nutritional status (using anthropometry), pulmonary functions by spirometry and six minute walk distance (6 MWD), and QOL using the WHO-QOL Bref 26 questionnaire, before and after chemotherapy. Results: Forty-four patients were studied (mean (SD) age, 55 (10) years, 75% males). The majority (98%) had stage III or IV disease and 72% were current / ex-smokers with median pack-years of 27.0 (range, 0.5-90). Some 61% had a Karnofsky Performance Scale (KPS) 70 or 80. The commonest symptoms were coughing, dyspnea, chest pain, anorexia and fever (79%, 72%, 68%, 57% and 40%, respectively). The mean (SD) 6 MWD was 322.5 (132.6) meters. The mean (SD) percentage forced vital capacity (FVC %), and forced expiratory volume in one second (FEV1 %) were 64.7 (18.8) and 57.8 (19.4), respectively. The mean (SD) QOL scores for the physical, psychological, social, and environmental domains were 52.9 (20.5), 56.1 (17.9), 64.5 (21.8), 57.1 (16.6), respectively. Fourteen patients (32%) responded to chemotherapy. Non-responders had significantly higher baseline occurrence of fever, anorexia, and weight loss, higher pack-years of smoking and poorer KPS compared to responders. Overall, chemotherapy caused significant decline in the frequency of coughing, dyspnea, chest pain, fever, anorexia, weight loss, and improvement in hemoglobin and albumin levels. There was no significant improvement in pulmonary functions, nutritional status, or QOL scores after treatment. Conclusions: Lung cancer patients have a poor QOL. Although chemotherapy provides significant symptomatic benefit, this does not translate into similar benefit in respiratory and nutritional status or QOL. Patients with constitutional symptoms, higher smoking burden, and poor KPS are less likely to respond to chemotherapy. Management of NSCLC must include strategies to improve various aspects of QOL, nutritional status and pulmonary reserve to achieve comprehensive benefit.

Key Words: Lung cancer - quality of life - chemotherapy - nutrition

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Introduction

Lung cancer is the commonest cancer worldwide and leading cause of cancer-related death, resulting in over 1 million deaths annually (Parkin et al., 2005). In spite of the emergence of newer treatment regimens, benefits in traditional end points such as survival have been marginal at best (Lassen et al., 1995). There is thus a compelling need to focus on other aspects of this disease. In this context, quality of life (QOL) is an important treatment outcome and has been the focus of several studies in the past few years (Naughton et al., 2002, Montazeri et al., 2001; 2003). However, most QOL trials have been conducted in the developed world and there is scant data from the developing countries (Mohan et al., 2007a).

Majority of patients with lung cancer have multiple symptoms such as dyspnea, cough, hemoptysis, pain and anorexia, (Cooley, 2000) and the total symptom burden has an important bearing on the overall QOL (Mohan et al., 2007a). In addition, QOL has been closely linked with symptom prevalence and intensity in patients with lung cancer (Bernhard and Ganz, 1991; Montazeri et al., 2001). Dyspnea and other respiratory symptoms have a negative effect on QOL in COPD and other chronic lung diseases, but data on lung cancer are sparse. Several other factors, such as age, gender, extent of tobacco use, and comorbid conditions influence the respiratory status in patients with lung cancer.

Physiological measures of disease impairment, particularly spirometric measures of lung function as well

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as walk tests have been correlated with functional health and well being in several QOL studies in patients with chronic lung disease (McGavin et al., 1978; Mungall and Hainsworth, 1979; Mahler and Wells, 1988; Mahler et al., 1992) and may also be useful in patients with lung cancer. Their improvement after chemotherapy can translate into better QOL.

Nutritional status as computed by anthropometric measurements is an important variable in cancer patients as it is affected because of anorexia and poor nutritional intake. Hence better baseline nutritional status or improvement of nutritional status after chemotherapy can correlate with better QOL. Patients with higher nutritional status are also more likely to tolerate chemotherapy with lesser adverse effects.

Although the importance of QOL as a treatment outcome has been recognized by the American Society of Clinical Oncology and the United States Food and Drug Administration, its relationship to response to platinum-based therapy has not been clearly evaluated. The effect of treatment on respiratory functions, nutritional profile and QOL has shown conflicting results. There may be certain differences between responders and non-responders to chemotherapy in lung cancer which also need to be explored. Hence, this study was done with the following objectives (a) to assess QOL of lung cancer patients and its response to chemotherapy, (b) to evaluate the effect of medical treatment on clinical profile, as well as pulmonary and nutritional status, and (c) to determine the possible factors associated with poor response to therapy.

Patients and Methods

Subjects

This prospective observational study assessed the clinical symptoms, respiratory status, nutritional profile, and QOL of patients with newly diagnosed patients with NSCLC at baseline and one month after completion of treatment. All the patients were staged according to the American Thoracic Society TNM classification after thorough clinical evaluation, chest x-ray and computerized tomography scan (CT) of chest and abdomen (Mountain, 1997). Patients with other types of lung cancer (eg, mesothelioma, carcinoid, lung metastasis) were excluded. Also excluded were patients with any other serious medical or psychiatric illness. The hematological, renal and hepatic profiles were of included patients were normal, and informed consent was obtained from all.

Symptoms and Clinical Characteristics

A detailed history and physical examination was carried out and information on respiratory symptoms (cough, dyspnea, chest pain, hemoptysis) and systemic symptoms (anorexia, weight loss, fever) and their duration was obtained. The extent of smoking was measured by calculating the number of pack-years smoked. Performance status was determined using the Karnofsky Performance Scale (KPS) (Schaafsma and Osoba, 1994) which consists of an 11-point scale ranging from 0 (dead) to 100 (asymptomatic with normal activities) and categorizes a patient according to the ability to carry out routine work.

Pulmonary Functions and Other Indices of Respiratory Status

The quantification of dyspnea and exercise capacity were done using the Medical Research Council (MRC) scale (Bestall et al., 1999), single breath count (SBC) and breath holding time (BHT) (Davidson et al., 1974). For SBC, the patient was instructed to count numbers during the time of breath holding as fast as possible in their native language. Exercise capacity was measured using the six-minute walk test (6MWT) (Brooks et al., 2003). The level of dyspnea was assessed before and after the test using the visual analog scale (VAS) (Mador and Kufel, 1992). This scale comprises of a 10 centimeter long vertical line with an anchor point at each extreme denoting none and maximum breathlessness.

Measurement of lung function was performed using rolling seal electronic spirometer (Morgan S232, UK) with determination of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, peak expiratory flow rate (PEFR), and maximum mid-expiratory flow rate (FEF 25-75). Values were selected from the best of three efforts having the greatest sum of FVC and FEV1. Predicted normal values were taken from the work of Crapo and colleagues (1981). Spirometry was specifically omitted in patients with recent (within 3 weeks) chest infection, recent (within three months) myocardial infarction or heart failure or recent major surgery (within three months). Spirometry was interpreted as normal, obstructive or restrictive ventilatory abnormality according to the criteria described by the ATS (Koyama et al., 1998).

Quality of Life (QOL)

World Health Organization Quality of Life (WHOQOL-Bref)-Hindi questionnaire was used for the evaluation of QOL. This 26-item questionnaire has been tested and validated in Hindi, the local language of the study region. WHOQOL was designed as an international cross-culturally comparable quality of life assessment instrument (Saxena et al., 1998). It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns.

The WHOQOL instruments were developed collaboratively in a number of centers worldwide, and have been widely field-tested. The WHOQOL-Bref instrument comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment with 4-6 questions in each pertaining to that particular aspect, all based on the patients' status over the past four weeks and rated on a five-point scale. The maximum score possible in each was 20, with a maximum total score of 80. Patients were asked to read and answer the questions on their own. In case of linguistic or other difficulties, the questionnaire was administered by interview.

Treatment

All patients were treated with a standard chemotherapy

Table 1. Patient Characteristics

Variable		% of Total
Age (years) *		55.1(±10.4)
Gender	Males	75.0
	Females	25.0
Current/ ex-smokers**		72.7
Pack Years#		27.0 (0.5-90)
Disease Stage	Stage III	65.9
	Stage IV	34.1
KPS#		80 (50-90)
Duration of Symptoms (months)#		5.3 (1-12)
Response to treatment	CR	2.3
	PR	29.5
	SD	40.9
	PD	27.3

*Mean Value (± Standard Deviation)**Patients who were current/ex-smokers (n=32)# Median Value (Range)

regimen consisting of Cisplatin infusion of 30 mg/m2 on days 1-3 along with 1 hour infusion of Etoposide 130 mg/m2 on days 1-3, the cycle being repeated every three weekly for 4 cycles. The disease was reassessed after the fourth cycle by symptoms, and CT scan of chest and abdomen. Response was categorized as complete responders (CR), partial responders (PR), stable disease (SD), and progressive disease (PD). Patients with CR and PR were classified as responders, whereas SD and PD were grouped as non-responders. Radiotherapy was administered either for curative or palliative purposes. The doses used were 45-50 Gy in 23-25 fractions, and 8 Gy single fraction to 20 Gy / 5 fraction respectively.

Statistical Analysis

Data were managed on an Excel spreadsheet. Descriptive analysis of WHOQOL-Bref scale scores, demographic data and clinical parameters was carried out. Quantitative variables were summarized by mean and standard deviation or median and range and categorical variables were summarized by frequency (percentage). Paired students't-test and McNemar's test were respectively used for quantitative and categorical variables while comparing QOL scores, clinical parameters, pulmonary function tests and nutritional status before and after chemotherapy. Student's t-test was used to compare means among two groups and chi-square test was employed for two-way tables. In this study, p- value less than 0.05 was considered as statistically significant. All the statistical tests done in this study were two tailed. STATA 9.0 version for Windows (STATA Corporation, College Station Road, Houston, Texas, USA) was used for data analysis.

Results

A total of 44 patients with advanced (Stage III or IV) NSCLC who completed the clinical evaluation and QOL questionnaire at both times, before and 1 month after chemotherapy, were included in the final analysis. The baseline characteristics are shown in Table 1. Majority were males and current/ex-smokers with mean duration of symptoms of about 5 months. Cough and shortness of breath were the commonest symptoms observed. Approximately one third of patients responded to chemotherapy. Eleven patients experienced toxicity related to chemotherapy; however, none of them required any discontinuation of treatment or dose modification.

Table 2. Comparison of Various Parameters before and after Chemotherapy (n=44)

Variable	Pre-Chemo*	Post-chemo*	p-value#
Symptoms			
Coughing	79.6	61.4	0.021
Shortness of breath	72.7	50.0	0.012
Chest pain	68.2	47.7	0.007
Hemoptysis	22.7	13.6	0.157
SVC obstruction	4.6	4.6	1.000
Fever	40.5	9.5	<0.001
Anorexia	57.1	38.1	0.005
Weight Loss	61.9	35.7	<0.001
Pulmonary function			
FVC%	65.2±18.7	65.5±18.5	0.903
FEV1%	58.0±19.6	56.2±19.7	0.591
PEFR%	45.2±19.7	42.8±22.9	0.388
FEF%	44.8±25.6	44.2±25.6	0.887
Indices of Pulmonary reserve			
6MWD (meters)	331±128.2	331±166	0.972
VAS for Dyspnea (cm)			
Resting	0.4±1.14	0.7± 1.68	0.056
After exercise	2.1±2.33	2.7±2.73	0.094
BHT (seconds)	20.9±12.1	18.6±11.6	0.239
SBC	34.7±17.8	33.8±19.0	0.603
Nutritional Status			
BMI	22.2± 4.0	21.7 ± 4.2	0.096
Waist circ (cm)	83.8±12.0	83.4 ± 12.0	0.521
Hip circ (cm)	90.5± 8.9	91.0 ± 9.0	0.472
Mid arm circ (cm)	23.1± 3.8	23.3 ± 3.8	0.426
Biceps SFT (mm)	8.3± 4.5	8.4 ± 4.2	0.845
Triceps SFT (mm)	12.2 ± 6.0	12.4 ± 5.4	0.671
Subscap SFT (mm)	14.4 ± 7.1	14.5 ± 6.6	0.856
Suprailiac SFT (mm)	17.3 ± 8.6	18.5 ± 9.1	0.072
Lab parameters			
Hemoglobin (g/dL)	12.5 ± 1.6	11.1 ± 1.51	<0.001
Albumin (g/dL)	4.0 ± 0.43	3.79 ± 0.62	0.031
Quality of Life scores			
D1-Physical	52.9 ± 20.5	51.0 ± 21.4	0.509
D2-Psychological	56.1 ± 18.0	54.8 ± 18.6	0.652
D3-Social	64.5 ± 21.8	62.2 ± 20.6	0.383
D4-Environmental	57.1 ± 16.6	57.9 ± 18.5	0.716

* Presented as Mean ± SD for continuous variables and frequency percentage for categorical variables.#Calculated using the t-test for continuous variables and the McNemar test for categorical variables

There was significant improvement in the frequency of cough, shortness of breath, chest pain, fever, anorexia, and weight loss after treatment (Table 2) There was no significant difference in respiratory profile, nutritional status, or QOL.

Poor KPS (<70), and the presence of constitutional symptoms such as fever, anorexia, and weight loss were significantly associated with non-responsiveness to treatment (Table 3).

Discussion

The results of this study indicate that patients with lung cancer have a poor QOL, which is dependent on

Table 3. Comparison of Variables before and after Chemotherapy among Responders and Non-responders

Variable		Responders		Non-responders		p-value			
		Pre-*	Post-*	Pre-*	Post-*	1vs2)$	(3vs4)$	(1vs3)#	(2vs4)#
Poor KPS (<70)[1]		0.0	14.3	36.7	36.7	-	*	0.009	*
Smokers[1]		92.9	NA	63.3	NA	-	-	0.041	-
Symptoms	Coughing[1]	64.3	64.3	86.7	60.0	*	0.008	*	*
	SOB[1]	71.4	42.9	73.3	53.3	*	*	*	*
	Chest-pain[1]	50.0	28.6	76.7	56.7	*	*	*	*
	Hemoptysis[1]	21.4	14.3	23.3	13.3	*	*	*	*
	SVCO[1]	0.0	0.00	6.7	6.7	-	*	*	*
	Fever[1]	14.3	0.00	56.7	16.7	-	<0.001	0.008	*
	Anorexia[1]	21.4	21.4	73.3	43.3	*	0.004	0.001	*
	Weight Loss[1]	28.6	21.4	76.7	43.3	*	0.002	0.002	*
Pulmonary functions	FVC %[2]	64.4	74.2	65.8	61.9	*	*	*	0.028
	FEV1 %[2]	54.2	60.9	59.4	54.3	*	*	*	*
	PEFR %[2]	51.2	54.1	44.3	38.1	*	*	*	0.041
	FEF %[2]	40.9	47.2	47.3	42.9	*	*	*	*
Pulmonary reserve	6MWD[2]	366	415	301	327	*	*	*	*
	VAS rest[2]	0.04	0.14	0.59	1.00	*	*	0.034	*
	VAS exercise[2]	1.41	2.22	2.44	2.92	*	*	*	*
	BHT[2]	21.4	22.6	20.6	16.8	*	*	*	*
	SBC[2]	36.6	34.9	33.8	33.3	*	*	*	*
Nutritional Status	BMI[2]	22.3	22.4	22.1	21.3	*	0.024	*	*
	Waist[2]	83.6	83.5	83.9	83.3	*	*	*	*
	Hip[2]	90.6	90.6	90.5	91.1	*	*	*	*
	MUAC[2]	21.9	22.6	23.6	23.7	*	*	*	*
	Biceps SFT[2]	8.6	8.2	8.2	8.4	*	*	*	*
	Triceps SFT[2]	11.8	12.7	12.3	12.2	0.009	*	*	*
	Subscapular SFT[2]	15.1	15.6	14.1	14.0	*	*	*	*
	Supra-iliac SFT[2]	19.1	21.0	16.5	17.4	0.002	*	*	*
Laboratory parameters	Hemoglobin[2]	12.6	10.9	12.5	11.3	0.024	<0.001	*	*
	Albumin[2]	4.1	4.1	4.0	3.7	*	0.024	*	*
QOL Scores	Physical[2]	59.2	61.2	50.0	46.3	*	*	*	0.029
	Psychological[2]	62.6	62.2	53.0	51.4	*	*	*	0.039
	Social[2]	70.6	71.9	61.7	57.6	*	*	*	0.031
	Environmental[2]	55.1	58.6	58.0	57.6	*	*	*	*

[1]: Categorical variables presented as frequency percentage, [2]: Continuous variables presented as mean value.* : p-value did not reach statistical significance (p>0.05), $: Calculated using paired t-test for continuous variables and McNemar test for categorical variables. #: Calculated using independent t-test for continuous variables and chi-square test for categorical variables. : p-value not computed because the test value is constant.

several patient-dependent as well as disease-dependent variables. The mean age of our study group was comparable to that seen in other Indian studies (Mohan, 2007) but less than that seen in most western data (Svobodnik, 2004, Prasad, 2004).

The patients in this study showed significant reduction in the frequency of cough, dyspnea, chest pain and systemic symptoms like fever, anorexia, weight loss. Interestingly, the reduction in occurrence of fever, anorexia and weight loss of the whole stduy group was almost entirely contributed by the improvement among non-responders. Patients who responded to chemotherapy had significantly lower baseline (pre-chemotherapy) incidence of these three symptoms and better KPS compared to non-responders; this relationship lost statistical significance when both the groups were compared after treatment. Various chemotherapeutic regimes used previously have also demonstrated improvement in constitutional symptoms such as fever, fatigue, anorexia, and weight loss (Buccheri and Ferrigno, 2001; Khalid et al., 2007).

Weight loss is a common symptom of lung cancer, found in up to 38% of patients, and is closely linked to survival (Buccheri and Ferrigno, 2001; Khalid et al., 2007). The etiology of weight loss is poorly understood and may be due to decreased food intake. The presence of fever, especially during the course of chemotherapy, has a major effect on survival independent of the performance status (Ide, 2001). Similarly, KPS has been often used as a surrogate marker for assessing response to treatment in several lung cancer clinical trials. KPS is a good predictor of QOL and prognosis in lung cancer (Aaronson et al., 1993; Buccheri and Ferrigno, 1994; Buccheri et al, 1995) and correlates well with increasing symptom burden and symptom severity (Hopwood, 1995). Compared with best supportive care, chemotherapy offers symptom control not only in patients with objective response, but also in some cases with relative stable disease. An evaluation of disease-related symptom improvement using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire in 216 patients with lung cancer who received oral Geftinib showed rapid symptom improvement that correlated with tumor response and survival. In the TAX 326 trial, the largest prospective evaluation of QOL in NSCLC using validated instruments, patients in the docetaxel-cisplatin arm reported greater improvement in pain control, weight loss, and performance status as compared to Vinorelbin-cisplatin treated patients. In the present study, the number

of patients with poor KPS (<70) was significantly greater among non-responders, implying thereby that patients who have a poor baseline KPS have less probability of responding. However, KPS per se did not change after treatment either in responders or non-responders.

The post-treatment FVC% and PEFR% values were significantly higher in the responders, although baseline (pre-treatment) values did not significantly differ. The extent of residual lung function is a major determinant of a patient's performance capacity and particularly relevant in the context that spirometric abnormalities are common in lung cancer, since a significant proportion of patients have concomitant COPD (Maas et al., 2003; Mohan et al., 2007). While some studies have demonstrated improved lung functions following chemotherapy (Maas et al., 2003; Pinson and Klatersky, 1998), others have shown deterioration (Gopal et al., 2003) and some have been equivocal (Groen et al., 1995). In our study, although not significant, there was an obvious improvement in lung functions after treatment in responders and a clear decline among non-responders. Improvements in lung function are explained by tumor response, whereas declining function may be due to poor treatment response or treatment related pulmonary toxicity.

Before treatment, responders had significantly lower dyspnea VAS scores, so that the baseline severity of dyspnea may also be a potential marker for response to chemotherapy in advanced NSCLC. We did not find any significant difference in other objective parameters of respiratory status/pulmonary reserve such as six minute walk distance, VAS (post-exercise), single breath count and breath holding time. These results imply that constitutional symptoms like fever, anorexia, weight loss probably show greater improvement after treatment of lung cancer rather than significant objective increase in other parameters of respiratory profile.

No significant improvement was noted in the nutritional profile among patients after treatment. A previous study demonstrated persistent, albeit variable weight loss in lung cancer patients on treatment (Brown, 1998). The mean BMI and waist circumference of our patient group reduced after treatment whereas the SFT and hip circumference increased, possibly indicating a redistribution of body fat; however, this change not achieve statistical significance. Triceps and suprailiac skin fold thicknesses, however, increased significantly in patients who responded to treatment.

Both hemoglobin and serum albumin levels were significantly lower post-chemotherapy in the study-group as a whole. This may be due to the toxic effects of the chemotherapeutic drugs on the hematopoietic cells and gut epithelium leading to malabsorption. The decrease in hemoglobin was significant for both responders and non-responders, though serum albumin concentration was significantly reduced only in non-responders.

QOL measurements form an essential part of all cancer related clinical trials, more so in lung cancer where response is poor and survival benefit marginal and hence difficult to assess. QOL correlates well with tumor response and survival independently of other known prognostic factors such as age and extent of disease, hence are often used as surrogate markers of evaluating treatment efficacy (Montazeri et al., 2001; Moinpour et al., 2002). Improvement in QOL usually reflects symptomatic benefit and better performance status. Trials evaluating QOL variations in response to chemotherapy have found conflicting, and often indeterminate results. Some studies have shown worsening, whereas others have demonstrated benefit or equivocal results (Ganz et al., 1989; Bonomi et al., 2000; Spiro et al., 2004; Belani et al., 2006). Although our patients did not show significant change in QOL scores of any domain following treatment, we found significantly higher scores in the physical, psychological and social domains after treatment in responders vis-à-vis non-responders. Similar association between QOL change with objective tumor response as been observed in other recent studies as well (Zhou, 2008). While improvement in the physical domain can be explained by alleviation of constitutional symptoms, the psychological and social domain merits further attention. It is possible that the improvement in symptoms encouraged greater interaction between the patient and his social circle such as family, relatives, and friends. Both pre-chemotherapy QOL (except environment domain) and post-chemotherapy QOL were better among responders than non responders, although not reaching statistical significance. Hence, contrary to a previous report by Montazeri et al(2001), baseline QOL did not help predict patients' response to therapy; however, following treatment, QOL was better in responders compared to non-responders, indicating the possible utility of post-treatment QOL assessments in evaluating response.

Our study was limited by the small numbers of patients that were followed up. Obtaining prospective data was difficult due to the high rates of attrition among patients. Studies with a larger sample size need to explore these findings further as they may have a direct bearing on the treatment and its outcomes of lung cancer patients. Also such studies may yield statistical significance to the trends and differences noted in our study and bring forth other clinical, respiratory and nutritional parameters directly associated with response to treatment in lung cancer.

In conclusion, the findings of this study indicate that treatment of NSCLC provides significant symptomatic benefit; however, this does not translate into similar benefit in respiratory indices, nutritional status or in QOL. Patients with good baseline performance status and absence of constitutional symptoms are more likely to respond to treatment.

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