Original Article

Impact of chemotherapy on symptom profile, oxidant-antioxidant balance and nutritional status in non-small cell Lung Cancer

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ABSTRACT

Background: Lung cancer is associated with an oxidant-antioxidant imbalance that is implicated in tumor progression. However, the association of this imbalance on disease burden and treatment response is unclear. The effect of chemotherapy on oxidative stress, antioxidant status, and nutritional profile in patients with advanced nonsmall cell lung cancer (NSCLC) was prospectively evaluated. **Subjects and Methods:** Patients with confirmed cytological/histological diagnosis of NSCLC were recruited. Performance status was determined using the Eastern Cooperative Oncology Group grading and the Karnofsky Performance Scale. Skin fold anthropometry was done for nutritional assessment. All patients received chemotherapy with intravenous carboplatin and paclitaxel at three-weekly intervals. Response was assessed after four cycles by repeat imaging. Plasma levels of total antioxidant status (TAS), malondialdehyde (MDA), and glutathione peroxidase (GPx) levels were estimated using commercially available kits, and the change was correlated with clinical outcome, response to chemotherapy, performance status, and nutritional profile. **Results:** Thirty-five cases were studied (92% males), with a mean (SD) age of 56.2 (9.3) years. Following treatment, majority of patients demonstrated stable disease ($n = 15$ [42%]), followed by partial response (29%), progressive disease (22%), and complete remission (6%). Significant improvement occurred in respiratory symptoms. Body fat declined while subscapular skinfold thickness and 6-min walk distance increased. Spirometric values and performance status remained unchanged. GPx levels declined significantly while no notable change was observed in MDA and TAS levels. **Conclusions:** Chemotherapy for NSCLC improves symptoms, nutritional status, and exercise capacity but worsens the antioxidant status.

KEY WORDS: Lung cancer, nutritional profile, oxidant-antioxidant status

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INTRODUCTION

Lung cancer is the most common malignancy worldwide and the most common cause of cancer-related death.[1,2] Oxidant-antioxidant imbalance is proposed as a possible mechanism for the development and propagation of lung cancer.[3,4] Elevated levels of thiobarbituric acid reactive substances (a marker of oxidative stress) and reduced activity of antioxidant enzymes have been detected in the blood of lung cancer patients.[5] In addition, surgical removal of the lung tumor has led to increased total body antioxidant status, implying a possible association between the presence of lung cancer cells and circulating antioxidant levels.[6] The administration of chemotherapy is

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also associated with increased free radicals and decreased antioxidants.[7,8] This oxidant-antioxidant imbalance plays a role in the side effects of chemotherapy drugs as well,[9] for example, cisplatin-induced nephrotoxicity.[10]

Nutritional assessment is an important outcome variable in most lung cancer trials.[11,12] In lung cancer, weight loss, malnutrition, and skeletal muscle depletion indicate poor treatment response and contribute to morbidity and mortality.[13-15] However, the inter-relationship between oxidant-antioxidant balance and malnutrition, as well as their association with various clinical parameters, including response to treatment is unclear as yet. This study thus aims to look at the effect of chemotherapy on oxidative stress, antioxidant status, and nutritional profile in patients undergoing treatment for advanced nonsmall cell lung cancer (NSCLC).

SUBJECTS AND METHODS

This prospective, observational study was carried out over a period of 3 years from February 1, 2011, to January 31, 2014. Patients with confirmed cytological/histological diagnosis of NSCLC were screened. All the patients were staged according to the American Joint Committee on Cancer (7th edition) tumor-node-metastasis classification and those eligible for chemotherapy (Stage IIIB and IV) were recruited after obtaining informed consent.[16] Patients with any other serious medical or psychiatric condition or those who had received any prior chemotherapy were excluded from the study.

All patients were evaluated twice during the study period, once before and once at the completion of the fourth cycle of chemotherapy. Symptoms were quantified using the Lung Cancer Symptom Scale (LCSS), which consists of six symptom items and three general items, each ranging from zero (no symptoms) to 100 (worst).[17] Patient demographics, clinical history, physical examination, and smoking history were obtained using a structured pro forma. Based on their smoking status, patients were grouped as current smokers, former smokers (those who had quit smoking for at least the last 6 months), or nonsmokers (lifetime smoking index <100). The extent of smoking was measured by calculating the smoking index (smoking index = [number of cigarettes/bidis smoked per day] × [years as a smoker]) (bidi: A small hand-rolled often flavored cigarette made chiefly in India). Performance status was determined using the Eastern Cooperative Oncology Group (ECOG) grading, as well as the Karnofsky Performance Scale (KPS), which consists of an 11-point scale ranging from zero (dead) to 100 (asymptomatic with normal activities) and categorizes a patient according to the ability to carry out routine work.[18,19] The 6-min walk test was administered according to the American Thoracic Society (ATS) 2002 guidelines and spirometry was performed using the FLOWHANDDY ZAN 100 USB machine (Germany) in accordance to the ATS 1995 recommendations.[20,21] Prior ethical clearance was obtained from the Institute Ethics Committee. Tissue was tested for mutations in epidermal growth factor receptor (EGFR); patients who tested positive for activating EGFR mutations were prescribed targeted therapy with gefitinib and excluded from subsequent analysis.

All patients were administered a doublet chemotherapy regimen consisting of carboplatin AUC 6 intravenous (IV) on day 1 plus paclitaxel 200 mg/m^2 IV on day 1, at three-weekly intervals. This regimen was chosen primarily because these drugs were available free for the patients in our hospital for majority of their treatment course. Patients were put on other regimens such as carboplatin-gemcitabine; their numbers, however, were few and hence were not included for analysis. Response to chemotherapy was assessed at the end of four cycles by repeat computed tomography scan and as per the Response Evaluation Criteria In Solid Tumors criteria version 1.1 which is a set of published rules that define when cancer patients improve ("complete responders [CR] or partial responders [PR]"), stay the same ("stable disease" [SD]), or worsen ("progressive disease" [PD]) during treatments.[22] CR and PR were together classified as "responders" while SD and PD clubbed as "nonresponders." The overall response rate (ORR) was defined as the sum of CR and PR, and disease control rate (DCR) was defined as the sum of CR, PR, and stable disease.

Measurement of oxidative stress

Blood samples were collected in heparinized vials by sterile venipuncture before the institution of chemotherapy and at the end of the fourth cycle. Plasma was prepared by immediate centrifugation for 10 min at 1600 x*g* and 4°C and was immediately stored at −20°C until further use. Total antioxidant status (TAS), malondialdehyde (MDA), and glutathione peroxidase (GPx) levels were estimated using commercially available kits according to the manufacturer's protocol in the plasma collected. The normal limits of these were taken as: TAS, ref. range1.30–1.77 mmol/l; MDA ref range <1.5 units; GPx ref range: 4171–1088 IU/l. The change in TAS, MDA, and GPx between pre- and post-treatment was calculated and correlated with clinical outcome, response to chemotherapy, performance status, and nutritional profile.

Assessment of nutritional profile

All patients were weighed, their waist and hip measurements were taken, and the mid-upper arm circumference and skinfold thickness (biceps, triceps, subscapular, suprailiac) were measured before the start of chemotherapy and at the end of the fourth cycle. Basal metabolic rate (BMR), total body water (TBW), fat mass, and fat-free mass (FFM) were calculated by bioelectric impedance method using Tanita TBF-300 body composition analyzer, Tanita Corp., IL, USA.

Statistical analysis

Data were managed on Excel spreadsheets. Descriptive statistics was used to determine the frequency of symptoms, ECOG and KPS. Mean and SD were calculated for

continuous variables. When the F-value indicated significant differences between group means, *post hoc* pairwise multiple comparisons were performed using Bonferroni method. Pearson's correlation coefficient was computed to assess relationship between two quantitative variables. $P < 0.05$ was considered as significant. All the statistical tests done in this study were two-tailed. STATA 11.0 version for Windows (STATA Corporation, College Station Road, Houston, Texas, USA) was used for data analysis.

RESULTS

During the study period, 47 subjects with NSCLC were recruited at baseline before initiation of chemotherapy. Of these, 35 subjects completed four cycles and were ultimately included for analysis. The remaining patients either died before completing four cycles or were advised discontinuation in view of worsening performance status. The final study group included 32 males (91%), with a mean (SD) age of 56.2 (9.3) years and median symptom duration of 510 days (range, 42–620 days). For the smokers, the median smoking index was 224 (range, 0-1150). The most common symptoms were chest pain (83%), cough (77%), shortness of breath (77%), loss of weight (54%), and weakness (54%). Majority had Stage IV disease (63%), followed by Stage IIIB (20%), and Stage IIIA (17%). Nineteen patients (54.3%) had a KPS score between 80 and 100, and 16 patients (45.7%) between 50 and 70. Twenty-one patients (60%) had an ECOG performance Grade I, 12 (34.3%) had Grade II, and 2 (5.7%) had Grade 0. A pre- and post-chemotherapy comparison of various clinical characteristics is shown in Table 1.

A significant reduction was observed in the LCSS scores for shortness of breath, cough, sputum, hemoptysis, and chest pain after four cycles of chemotherapy compared to pretreatment values. No significant difference was observed in KPS/ECOG, pulmonary functions, BMI, BMR, impedance, FFM, TBW, or anthropometric values (except subscapular skinfold thickness). However, significant improvement was noted in the 6-min walk distance. Among body composition parameters, body fat percentage showed significant decline following treatment.

Plasma GPx levels declined significantly while no notable change was observed in MDA and TAS levels [Table 1].

At the completion of four cycles of chemotherapy, majority of patients documented stable disease (43%), followed by PR (28%), PD (23%), and CR (6%). Based on this, 12 patients (34%) were classified as responders and 23 (66%) as nonresponders. The ORR and DCR of the study group were 35% and 77%, respectively. No significant correlation was seen between the baseline levels of TAS, MDA, and GPx with response to treatment. Similarly, no difference in these parameters was observed between responders and nonresponders.

Table 1: Clinicolaboratory characteristics (*n*=35)

Variable	Prechemotherapy	After fourth cycle of chemotherapy	*P*
Symptoms			
Cough*	50 (0-75)	0 (0-100)	0.001
Sputum*	25 (0-75)	0 (0-100)	0.001
Shortness of breath*	50 (0-75)	25 (0-100)	0.001
Hemoptysis*	0 (0-75)	0 (0-100)	0.001
Chest pain*	50 (0-100)	25 (0-75)	0.02
Loss of weight*	0 (0-75)	0 (0-75)	0.03
6-min walk distance (m)	355.0 (96.9)	394.6 (76.9)	0.02
Nutritional assessment			
BMI (kg/m^2)	21.0 (3.1)	20.7 (3.3)	0.22
Basal metabolic rate (kJ/day)	5278.9 (1096.2)	5409.0 (760.1)	0.27
Body fat (%)	17.1 (6.9)	15.3 (6.9)	0.01
Fat mass (kg)	10.4 (5.4)	9.6 (5.4)	0.07
Fat-free mass (kg)	48.1 (7.8)	45.6 (10.4)	0.15
Bicep (mm)	5.6 (2.8)	5.5 (2.7)	0.86
Triceps (mm)	9.2 (3.9)	9.6 (4.6)	0.3
Subscapular (mm)	11.7 (4.4)	12.2 (5.2)	0.04
Suprailiac (mm)	11.7 (6.4)	10.3 (5.9)	0.63
MAC[§] (cm)	22.6 (4.8)	22.9 (4.5)	0.77
MDA[‖] (nmol/ml)	55.5 (12.4)	57.7 (13.4)	0.19
TAS[**] (mmol/ml)	1.8 (0.4)	1.7 (0.3)	0.09
GPx[††] (nmol/min/ml)	305.0 (57.9)	257.6 (42.6)	0.001

*Values expressed as median (range); All other values expressed as mean (SD). [§]MAC: Mid arm circumference, [‖]MDA: Malondialdehyde, **TAS: Total antioxidant status, [††]GPx: Glutathione peroxidase. BMI: Body mass index, SD: Standard deviation

DISCUSSION

Our findings suggest that after four cycles of chemotherapy, mean levels of GPx decreased significantly while no significant changes were observed in MDA and TAS. There was a significant improvement in symptoms and exercise capacity as assessed by the distance walked in 6 minutes. A significant deterioration of the nutritional profile as evidenced by the decline in body fat and subscapular skinfold thickness was also observed.

GPx-1 is the major antioxidant enzyme in lung lining fluid and acts to prevent the initiation of cancer by reactive oxygen species-mediated DNA damage and is a powerful scavenger of harmful reactive oxygen and nitrogen free radical compounds.[23] Previous studies suggest that GPx-1 is altered in several types of cancer cells and its overexpression propagates antitumorigenic effect by eliminating oxidants.[24]

MDA is one of the most frequently measured biomarkers to indicate the level of overall lipid peroxidation.[25] TAS is defined as the sum of endogenous and food-derived antioxidants in the extracellular fluid of an individual and provides a better-integrated index of antioxidant activity, as compared to one based on simple summation of measurable antioxidants.[26]

In majority of previous reports, assessment of the antioxidant status in lung cancer has been carried out by measuring various vitamins and individual antioxidant

enzymes such as superoxide dismutase (SOD), catalase, and GPx. Malignant pleural exudates have demonstrated increased lipid peroxidation and lower antioxidant status than nonmalignant fluids.[27] A recent study conducted in 58 NSCLC patients receiving platinum-based chemotherapy found results similar to our study by demonstrating that patients had significantly elevated prechemotherapy levels of reactive oxygen metabolites (ROM) compared with normal healthy subjects; postchemotherapy, ROM production was suppressed in responders but not in nonresponders.[28] The effect of chemotherapy on antioxidant status was evaluated in 12 patients with SCLC by measuring plasma levels of total radical antioxidant parameter (TRAP), Vitamins C and E.[29] Significant decline in plasma TRAP and Vitamin C levels was observed 8 h after initiation of chemotherapy. However, this study had some important drawbacks, in that sample size was small and patients were not stratified according to treatment received or smoking status. A meta-analysis was conducted after including all studies that investigated antioxidant levels in cancer patients receiving chemotherapy.[30] This analysis eventually suggested that chemotherapy lowered TAS but accepted that the available evidence was limited and results too inconsistent to be extrapolated to individual cancers.

In our study group, the low baseline levels of antioxidants may be due to the effect of lung cancer itself. It has been previously shown that cancer patients have lower levels and activity of antioxidants such as SOD and catalase than controls, even before initiating treatment.[31]

The worsening of antioxidant status after chemotherapy may be either due to the oxidative stress generated by the chemotherapy drugs, due to tumor progression, or both. Many classes of anti-neoplastic agents including the platinum coordination complexes, most alkylating agents, epipodophyllotoxins, and camptothecins are known to generate high levels of oxidative stress.[32] Poor dietary intake of antioxidants may be another contributing factor for low TAS levels although this was not assessed in our study. In fact, the impact of dietary intake and supplementation with various antioxidants and nutrients on their circulating levels has not been conclusively demonstrated in cancer.

Impaired intestinal absorption could be a possible cause of the worsening oxidant-antioxidant status following chemotherapy; however, it seems unlikely since the mean body weight did not significantly change in our study group after chemotherapy. In addition, no evidence of hepatic derangement or intestinal malabsorption was observed, which otherwise could have explained the low baseline antioxidant levels. Other causes, such as cisplatin which induced renal proximal tubular damage and decreased renal tubular reabsorption of water-soluble antioxidants such as uric acid, may also have contributed to the lowered antioxidant status but could not be assessed as part of this study.

The median age of our patients was similar to previous studies done in Indian population.[33] Although performance status did not change markedly, significant improvement in clinical symptoms was observed in our patients following treatment. This observation contrasts with previous studies, where symptomatic improvement was accompanied by a concomitant enhancement in performance status.[13] In addition, significant increase was observed in the 6-min walk distance, implying improvement in exercise capacity. The improvement in exercise capacity in the form of 6-min walk distance, following treatment, has been observed in previous studies as well and shows a good correlation with performance status and survival. No significant change was observed in spirometric parameters among our patients, implying discordance between subjective symptom severity with objective measures of pulmonary function. No correlation was found between the oxidant-antioxidant status and the exercise capacity or the anthropometric parameters.

Malnutrition is an important cause of morbidity and mortality in lung cancer and may have an impact on the clinical course. Weight loss is a common symptom of lung cancer and closely linked to survival.[11] Our study demonstrated a significant decline in body fat after four cycles of chemotherapy, implying thereby a worsening of postchemotherapy nutritional status.

Assessment of body fat and body composition following chemotherapy has not been extensively studied and published reports show contrasting results. A previous study in NSCLC patients undergoing chemotherapy demonstrated a significant increase in triceps and suprailiac skin fold thicknesses after four cycles.[13] In our patient group, the mean BMI and waist circumference reduced, albeit nonsignificantly, after treatment whereas the hip circumference and subscapular thickness increased, possibly indicating a redistribution of body fat. Similar results were found in an earlier publication by our group, wherein chemotherapy resulted in improvement in symptoms, nutritional profile, and quality of life.[13] The low fat following chemotherapy could be due to poor diet, due to the disease itself, or both. Larger studies including dietary assessment may be useful to resolve this issue.

This study was limited by its small sample size and hence, was not adequately powered to detect the differences in the oxidant-antioxidant status between different stages of lung cancer. A detailed dietary intake was not available for analysis, and a matched control group was lacking. For reasons mentioned previously, our predominant chemotherapy regimen was carboplatin-paclitaxel and thus we could not compare changes in antioxidant status between two different drug regimens. Studies with a larger sample size need to explore these findings further as they may have a direct effect on the clinical course and treatment outcomes. In spite of these shortcomings, the above results may provide useful insights into the trends in oxidant-antioxidant balance in patients with lung cancer

and their association with various clinical and nutritional parameters.

CONCLUSIONS

The findings of this study indicate that platinum-based doublet chemotherapy for advanced NSCLC is associated with a decline in the antioxidant status but improves symptoms; however, this does not translate into similar benefit in respiratory indices or nutritional status.

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Conflicts of interest

There are no conflicts of interest.

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