Original Article

Chemotherapy for advanced lung cancer: A 5-year experience

Rajappa S, Gundeti S, Talluri MR[1], Digumarti R
Departments of Medical Oncology and [1]Internal Medicine, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500 016, India

Correspondence to: Dr. Rajappa Senthil, E-mail: siddharth142@sify.com

Abstract

BACKGROUND: Lung cancer is an important cause of cancer related deaths worldwide. There are few publications from India on treatment outcomes for non-small cell lung cancer (NSCLC). This study was done to analyze the response rates (RR), progression free survival (PFS), overall survival (OS), one and two-year survival of patients with advanced NSCLC treated with chemotherapy. **MATERIALS AND METHODS:** Data of all patients who received chemotherapy for stage IIIB and IV NSCLC between the years 2002-2006 was analyzed. Only patients who received at least two cycles of chemotherapy and had a radiological response evaluation were eligible for assessment of outcome parameters. **RESULTS:** There were 294 patients who received chemotherapy. Of these 194 (66%) were evaluable for outcome parameters. The RR, median PFS, OS, one and two-year survivals were 35.4%, six months (range, 2-70), seven months (range, 2-72), and 29.8% and 9.7% respectively. On univariate analysis, the strongest predictors for overall survival were female gender, absence of smoking and performance status (PS) (P = 0.0057, 0.0013, 0.0074). On multivariate analysis, only PS (P = 0.0387) was significant. The survival of patients treated with I generation platinum based doublet was not different from those treated with a II generation doublet (P = 0.45). The overall survival of patients who took II line chemotherapy was superior to those who did not receive it (P = <0.0001). **CONCLUSIONS:** Treatment outcomes for patients with advanced NSCLC continue to be poor. The II generation platinum doublets were not superior to I generation doublets. Chemotherapy at disease progression significantly improves survival.

Key words: Chemotherapy, lung cancer, platinum doublet

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of death due to cancer worldwide.[1] In the recent years, there has been a dramatic increase in the incidence of lung cancer in the developing countries, including India.[2-4] Most patients present at an advanced stage where the disease is incurable and the intent of treatment is palliative.[5]

Over the past three decades, there have been steady improvements in the treatment of advanced NSCLC. The median survival of patients with advanced NSCLC treated with platinum based chemotherapy continues to be dismal at 7-9 months.[6] With the addition of monoclonal antibodies, the median survival has improved to 12.5 months.[7]

At progression, second line chemotherapy for NSCLC has resulted in improvements in quality of life and overall survival.[8] With the advent of tyrosine kinase inhibitors, there has been renewed interest in this area especially with trials showing that patients from Asia are more likely to benefit than their Western counterparts.[9]

There is scant literature with regard to outcomes for Indian patients with advanced NSCLC.[10,11] Previously published studies report a survival of 27 weeks for patients with advanced NSCLC treated with platinum

based chemotherapy compared to 10.3 weeks for the supportive care group. Also, the median survival for a small group of 11 patients who received Docetaxel and Cisplatin was superior to those who received Mitomycin, Ifosfamide and Cisplatin.[10]

This marginal improvement in outcomes with newer generation platinum doublets (Gemcitabine/Paclitaxel/Docetaxel/Vinorelbine + platinum) comes with a major increase in the cost of therapy, which is beyond the reach of most Indian patients. Same is the case with II line chemotherapy at progression. Hence, we felt it was relevant to analyze in a larger group of patients, if there were any differences in the outcomes between patients treated with I versus II generation platinum doublets, and, if II line chemotherapy led to improved survival.

The primary objectives of this analysis were to study the response rate, median progression free survival (PFS), overall survival (OS), 1 and 2-year survival of patients with stage IIIB and IV lung cancer treated with platinum-based chemotherapy.

The secondary objectives were to study adverse events, to compare the outcomes for patients treated with I versus II generation platinum doublets and the effect of II line chemotherapy on OS.

Materials and Methods

Data from medical records of patients with stage IIIB and IV NSCLC who received platinum based doublet chemotherapy during the years 2002-2006 were collected.

The diagnosis of NSCLC was confirmed either by fine needle aspiration or a biopsy. The staging investigations included a contrast enhanced computed tomography scan (CT) of the chest and upper abdomen. A bone scan and CT scan of the brain were done whenever appropriate. Other investigations before therapy included complete blood counts, liver and renal function tests. Other biochemical tests were done wherever indicated.

An informed consent was taken from all patients before administration of chemotherapy and the institutional ethics committee approved the study. Patients were treated with various regimens administered intravenously ranging from I generation platinum based doublets like Cisplatinum (75mg/m^2)/carboplatin (AUC 5) Day 1 + etoposide (100mg/m^2 Days 1-3) (EP) or II generation regimens like gemcitabine (1250 mg/m2 Day 1 and 8) + cisplatinum (75mg/m^2 Day 1)/carboplatin (AUC 5 Day 1) (GC) and Paclitaxel (175 mg/m^2 Day 1) + cisplatinum (75 mg/m^2 Day 1)/carboplatin (AUC 5 Day1) (TC). Patients were also given radiotherapy either as definitive loco regional therapy in stage IIIB or with palliative intent for the primary or metastatic sites in stage IV.

Patients were given a maximum of 6 cycles of chemotherapy. Response evaluation was performed after every 2-3 cycles of chemotherapy by clinical examination and CECT chest and upper abdomen.

The following response criteria were used

A complete response (CR) was defined as disappearance of all the lesions on radiology. Partial response (PR) was defined as a decrease of 30% in the sum of the longest diameters of all target lesions. Stable disease (SD) was defined as patients who did not fit into either partial response or progressive disease. Progressive disease (PD) was defined as an increase of 20% in the sum of the longest diameters of the target lesions or appearance of a new lesion at any time during or after therapy.

Those patients who had at least two cycles and had a contrast enhanced CT scan for response evaluation were eligible for assessment of outcome parameters namely response rate (RR), progression free survival (PFS), overall survival (OS), one year and two year survivals.

Progression free survival (PFS) was defined as the time from start of chemotherapy to the time that progressive disease was documented, death or lost for follow-up. Overall survival was defined as the time from start of chemotherapy to death due to any cause.

Univariate and multivariate analysis was done to assess the effect of age, sex, smoking status, performance status, stage, treatment with a I or II generation platinum doublet on overall survival. Patients were also compared for all outcome parameters with respect to whether they were treated with a I or II generation platinum doublet.

The effect of II line chemotherapy on the overall survivals was also assessed. The adverse events that were documented in the case files were also archived.

Statistical methods

GraphPad software QuickCals online calculator was used to calculate the *P* values for the categorical and continuous variables. For continuous variables, the *P* value was calculated using the unpaired t test to compare the means. For categorical data like stage, smoking, sex, performance status and response rates, the

2-tailed *P* value was calculated using Fisher's exact test and 2×2 contingency table.

Data of patients who did not receive at least two cycles of chemotherapy or a response evaluation were censored for outcome parameters namely response rates, PFS, OS, one and two-year survival. Graph Pad Prism software for windows Version 4, 2003 was used to plot the Kaplan Meier curves for PFS and OS. Univariate analysis for OS was done by plotting Kaplan Meier curves and the log rank test was used to calculate *P* values. Logistic regression analysis for multivariate analysis for OS was carried out using Met calc. demo version statistical software using the same independent variables after coding. A *P* value < 0.05 was considered as statistically significant.

Results

Patient characteristics

Between the years 2002-2006, a total of 294 patients received chemotherapy for stage IIIB and IV NSCLC. The median age of patients was 58 years (range, 16-88) with a male: female ratio of 4:1.The baseline characteristics of all patients are in Table 1.

Of this, 169 patients took >4 cycles, 18 patients - 3 cycles and 7 patients - 2 cycles amounting to a total of 194 (66%) patients who had taken at least two cycles of chemotherapy and had radiological response evaluation. These patients were eligible for evaluation of outcome parameters-RR, median PFS, OS, one and two-year survival. One hundred patients (44%) were not eligible for outcome parameter analysis as they had received less than two cycles or were lost for follow-up without having a radiologic response evaluation.

Table 1: Demographic characteristics (n = 294)

Character	N (%)
Age in years (median)	58 (16-88)
Males	59 (16-88)
Females	53 (18-87)
Sex ratio	4:1
Males	235 (80)
Females	49 (20)
ECOG performance status	
< 2	191 (65)
≥ 2	103 (35)
Smoking/tobacco use	
Males	188/235 (80)
Females	3/49 (5)
Stage	
IIIB	170 (58)
IV	124 (42)

Treatment results for all patients

Sixty-nine patients had at least a CR or PR for an overall response rate of 35.4% [Table 2]. There were 64 (32.9%) patients who progressed while on therapy. The median PFS was six months (range, 2-70) and OS was seven months (range, 2-72) [Figures 1 and 2]. The one-year and two-year survivals were 29.8% and 9.7% respectively. The median PFS and OS of the

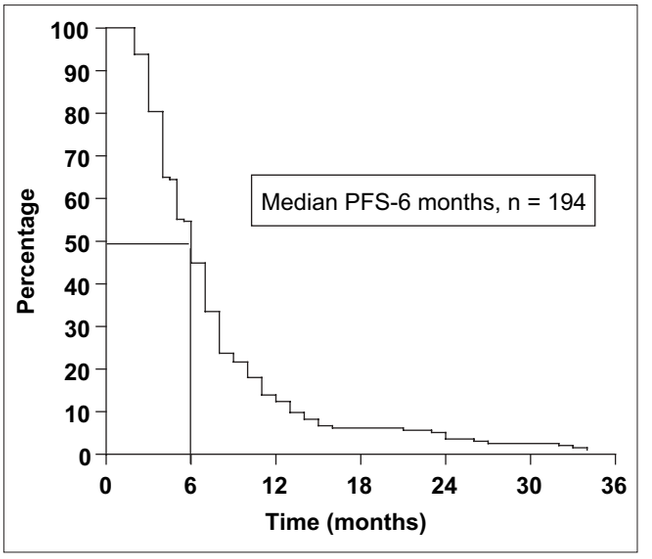

Figure 1: Kaplan Meier estimates of progression free survival (PFS) for all patients

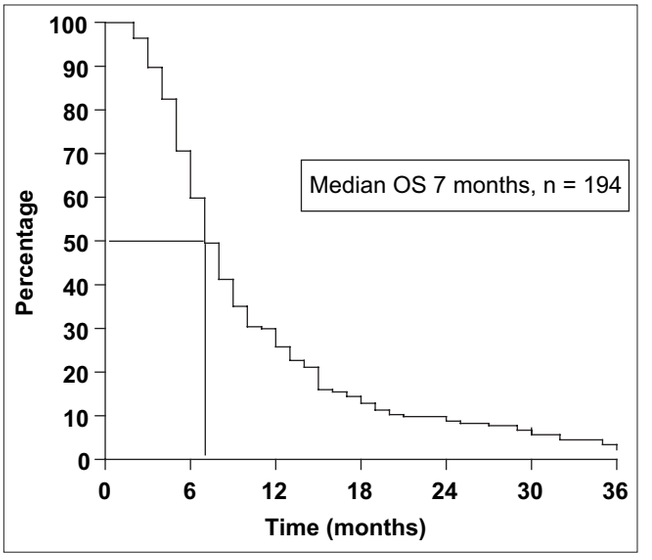

Figure 2: Kaplan Meier estimates of overall survival (OS) for all patients

169 patients who received >4 cycles of chemotherapy were seven months (range, 3-70) and eight months (range, 4-72) respectively.

Univariate and multivariate analysis of variables for overall survival

Univariate analysis was performed for age (<50 vs >50 years), gender (male vs female), smoking status (yes vs no), stage (IIIB vs IV) and performance status (PS, 0-1 vs 2) for overall survivals [Table 3].

On univariate analysis, the strongest predictors for overall survival were female gender, absence of history of smoking and PS (P = 0.0057, 0.0013, 0.0074). Age, stage, and treatment regimens did not predict significantly for overall survival (P = 0.2758, 0.2556, 0.8353). However, in the multivariate analysis, only PS (P = 0.0387) was significant.

Table 2: Treatment outcomes for all patients (n = 194)

Parameter	N (%)
Complete response	6 (3.0)
Partial response	63 (32.4)
Stable disease	61 (31.4)
Progressive disease	64 (32.9)
PFS (months)	6 (2-70)
OS (months)	7 (2-72)
1 year OS (%)	58/194 (29.8)
2 year OS (%)	19/194 (9.7)

PFS - Progression free survival, OS - Overall survival

Characteristics and outcomes for patients treated with i and ii generation platinum doublet regimens

The baseline clinical characteristics and outcome measures of patients who were treated with I versus II generation platinum doublet regimen were comparable [Table 4]. The difference in the RR, median PFS and OS were not significant (P = 1.0, 0.64, 0.45) [Figures 3 and 4]. The one and two-year survivals for those who received I generation regimen were 33.3% and 11.1%, and that for the II generation regimens were 28.2% and 9.1% respectively (P = 0.5 and 0.79). Similarly, the difference in the median OS of patients who received EP, compared to GC or TC were not significant (P = 0.61) [Figure 5].

Radiotherapy

Out of 194, 92(47.4%) patients received radiation therapy. Sixty-nine (35.5%) patients received RT for loco-regional disease and 27 (14%) received RT for extra thoracic disease (brain and bone).

II Line chemotherapy

Of the 194 patients who were evaluable for outcome measures, 40 (20.6%) took second line chemotherapy. Majority of them - 24 (60%) were treated with

Table 3: Univariate analysis of treatment variables (n = 194)

Variable	N (%)	PFS (months)	OS (months)	*P* for OS (log rank test)
Age				
<50 years	61 (31.5)	7 (2-70)	8 (2-72)	0.2758
>50 years	133 (68.5)	6 (2-42)	7 (2-52)	
Gender				
Female	50 (25.8)	7 (2-70)	9 (3-72)	0.0057
Male	144 (74.2)	6 (2-42)	7 (2-52)	Smoking
Smoking				
No	79 (40.7)	7 (2-70)	9 (4-72)	0.0074
Yes	115 (59.3)	5 (2-42)	7 (3-52)	Stage
Stage				
IV	104 (53.6)	6 (2-42)	7 (2-52)	0.2556
IIIB	90 (46.4)	6 (2-70)	7.5 (2-72)	
PS				
0 and 1	124 (63.9)	6 (2-70)	8 (2-70)	0.0013
2 and 3	70 (36.1)	5 (2-24)	6.5 (2-32)	

PFS - Progression free survival, OS - Overall survival, PS - Performance status

Table 4: Characteristics and outcomes of patients - I vs II generation regimens (n = 194)

	I Generation (n = 63)	II generation (n = 131)	*P* value
Age (range)	52 (27-73)	56 (18-85)	0.55
Gender (%)	F: 18 (28.5)	F: 32 (24.4)	0.59
	M: 45 (71.5)	M: 99 (75.6)	
Smoking (%)	Yes: 33 (52.4)	Yes: 82 (62.5)	0.21
Stage (%)	IIIB: 31 (49.2)	IIIB: 59 (45)	0.76
	IV: 34 (50.8)	IV: 72 (55)	
PS	0-1:43 (68)	0-1:81 (62)	0.42
	2:20 (32)	2:50 (38)	
Response rate (CR + PR) %	22 (35.6)	47 (36)	1.0
DFS (months)	6 (2-70)	6 (2-34)	0.64
OS (months)	7 (2-72)	8 (2-42)	0.45
1 Year OS (%)	21 (33.3)	37 (28.2)	0.5
2 year OS (%)	7 (11.1)	12 (9.1)	0.79

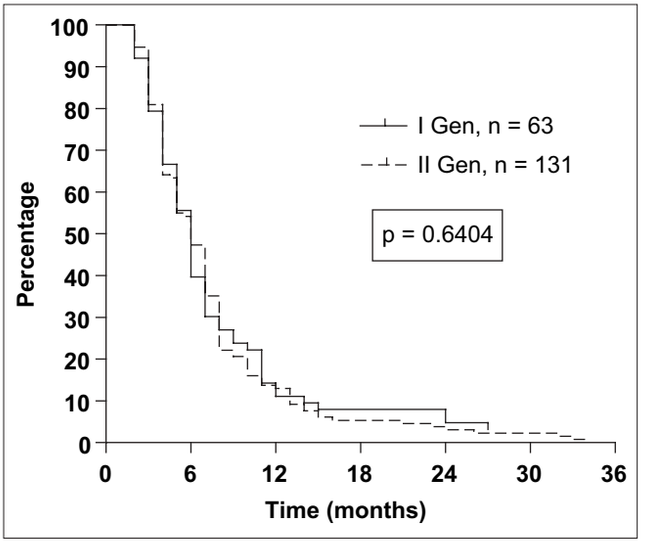

Figure 3: Kaplan-Meier estimates of progression free survival (PFS) for I versus II generation platinum doublets

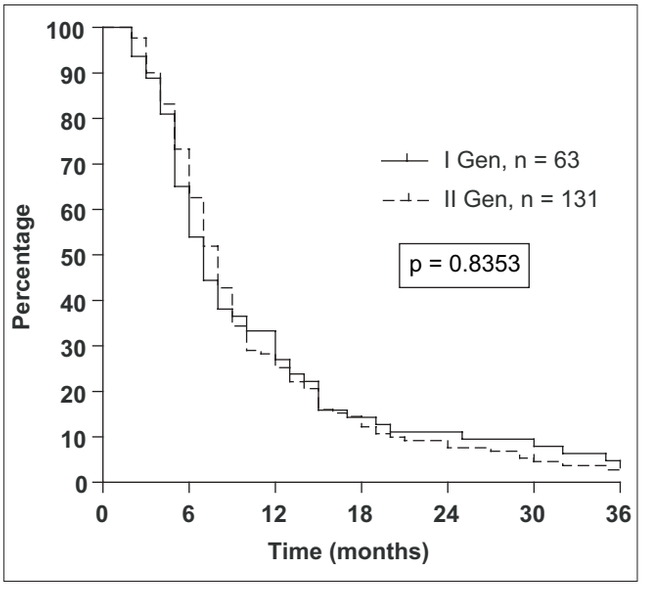

Figure 4: Kaplan Meier estimates of survival (OS) of I versus II generation platinum doublets

Gefitinib, 12 (30%) with Docetaxel and 4 (10%) with Gemcitabine and carboplatin. The overall survival of patients who took II line chemotherapy was 15 months compared to 7 months of those who did not receive II line chemotherapy (P = <0.0001) [Figure 6].

Adverse events

The common adverse events were fatigue (12%), vomiting (8%), Gr 3 or 4 anemia and neutropenia (5% each), neuropathy (3%) and febrile neutropenia (2.4%). Thrombosis occurred in four patients, anaphylaxis to paclitaxel in two patients. Severe depression occurred in two patients and one of them committed suicide.

Discussion

The outcome parameters analyzed were response rates, progression free survival, overall survival and the one and two-year survivals. There is increasing evidence that most objective responses and maximal palliation of symptoms occur during the first two cycles of chemotherapy.[12-15] Longer duration of therapy is associated with minimal increments in response and increased morbidity.[12,13] Hence, in our study, all patients who received at least two cycles of chemotherapy and had objective response evaluation were evaluable for outcome parameters.

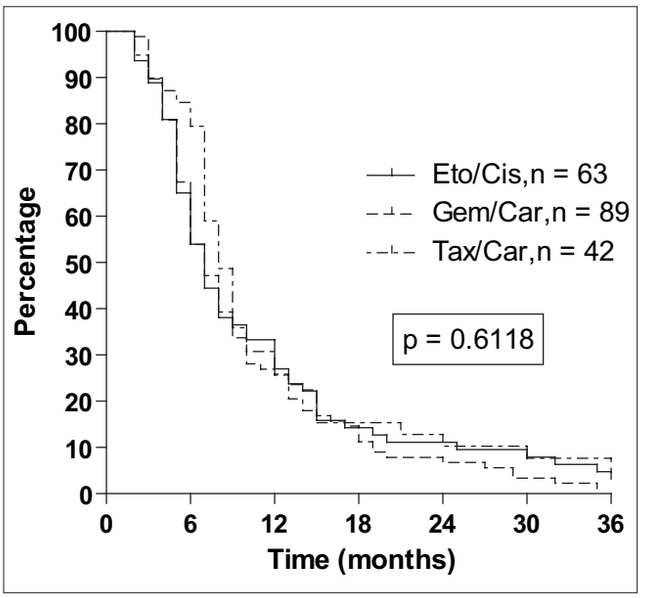

Figure 5: Kaplan-Meier estimates for survival-comparison of chemotherapy regimens (Eto-Etoposide, Tax-Paclitaxel, Gem-Gemcitabine, Cis-Cisplatinum, Car-Carboplatinum)

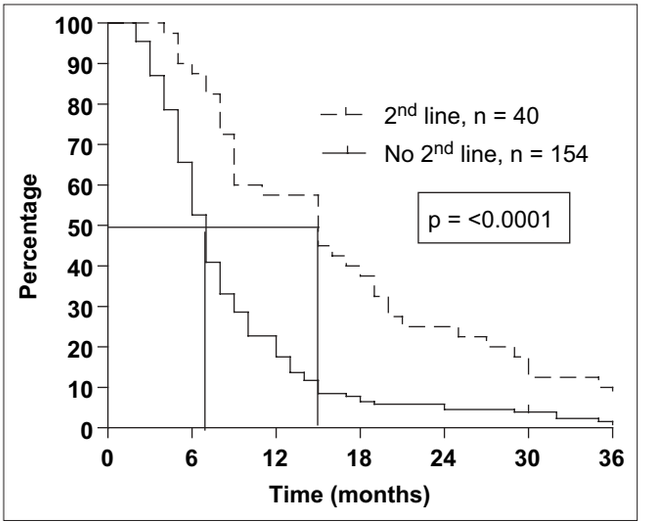

Figure 6: Kaplan Meier estimates of survival for II line chemotherapy

Of the 294 patients who received chemotherapy, there were 194 patients who were evaluable for assessment of outcome parameters. One hundred of them who had no radiological response evaluation or were lost to follow-up before two cycles were completed were censored for analysis. The objective response rate (CR + PR) of 35.4% was comparable to the 21% to 46% reported with various platinum based doublets (2, 16-19). The median PFS and OS for all evaluable patients in our series is lower than the 7.8-11.3 months reported for various II generation platinum based doublets. However, the median OS for patients who received >4 cycles at eight months is comparable to both previously reported Indian and western studies.[2,10,16] The one and two-year survivals in our study were similar to the 25-40% and 6-12% reported in the literature.[2,16-19] Our findings are consistent with previous reports where PS is the most important predictor for OS.

The probable reasons for the poorer OS may be that lesser number of patients went on to take II line chemotherapy -20.6% in our study compared to 45% reported from the west[20], more patients in our study belonged to PS 2 (35.6%) and some patients received <4 cycles of chemotherapy. In our study, PS and second line chemotherapy were important predictors for OS. Most western trials randomized only patients who had PS 0-1 and selective patients with PS 2.[2,16,17]

The superiority of the newer II generation combinations (GC/TC) over the I generation regimens (EP) has not been consistently proven in randomized clinical trials. In a randomized study comparing EP to two arms with different doses of Paclitaxel (135 and 250 mg/m^2) with cisplatin, the median survival and one-year OS was significantly better in the Paclitaxel arms at 9.9 months and 38.1% compared to 7.6 months and 31.8% in the EP arm.[21] There was no difference in the quality of life between the arms. However, other trials comparing EP to TC or GC showed superior responses to the TC/GC arms but no significant differences in the response rates, median PFS, OS, one and two-year survivals or QOL.[22] In our study, there was no difference in outcomes for patients treated with I or II generation doublets. Except that it needs to be administered over three days, EP is cheaper than and as good as the newer drugs for NSCLC.

Second line chemotherapy with Pemetrexed, Docetaxel or Erlotinib has been shown to prolong disease free survival, overall survival and quality of life in patients with NSCLC.[8,23] In our series, only 40 (20.6%) of all patients who were eligible for outcome evaluation went on to receive II line chemotherapy at progression. We are unable to explain the definite reasons for the small number of patients taking II line therapy. It may probably be due to deterioration in PS, lack of adequate finances, being lost for follow-up or the patients' perception that the marginal gains in PFS or OS may not justify the costs and adverse event profiles of the therapies. The median overall survivals of patients who received II line chemotherapy was 15 months compared to the seven months who did not receive the same which is consistent with reported literature.[8,23]

The pitfalls of the study are retrospective in nature, with very little data on the adverse events of chemotherapy and the lack of information on the quality of life.

Since the data collected was retrospective, patients were not reviewed routinely for mid-cycle blood counts and documentation was inadequate in the case files, there is under-reporting of both hematologic and non-hematologic adverse events. Quality of life is an important parameter for patients being treated for stage IV cancer. However, it is important to develop QOL questionnaires that are relevant for Indian patients and validate them. This will help us make a more realistic assessment of QOL rather than accept what the western literature reports.

The findings of our study have significant implications for clinical practice. The outcome of patients receiving chemotherapy for advanced lung cancer is similar to that reported from the west. Since social and financial issues are important factors that determine both compliance to therapy and follow-up, cheaper and patient-friendly regimens need to be used for therapy. Considering the fact that the I generation platinum doublet of cisplatin and etoposide is cheaper and as good as the newer regimens, it not yet time to abandon it. Patients should be explained the importance of being on follow-up so that symptomatic relapses can be detected and treated with II line chemotherapy leading to improved survival.

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