

Pharmacoeconomic benefit of cisplatin and etoposide chemoregimen for metastatic non small cell lung cancer: An Indian study

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ABSTRACT

Background: The incidence of lung cancer is rising in developing countries like India. Due to unaffordability among the low socioeconomic status (SES) patients, there is a significant delay in seeking appropriate medical treatment due to which a high proportion of patients present in an advanced/metastatic stage and the outcomes are poor. **Objective:** In this study, we studied the progression-free survival (PFS) and the pharmacoeconomic benefits with the cisplatin plus etoposide (EtoP) chemo regimen and compared it with the current generation chemo regimen. **Materials and Methods:** We performed a retrospective analysis of metastatic nonsmall cell lung cancer patients who received one or more cycles of platinum-based chemotherapy between 2011 and 2014. **Results:** Of the 304 patients, 56.6% of the patients were of the low SES. Of the low socioeconomic group patients, 67.45% and 31.4% received etoposide and paclitaxel platinum doublet combination regimen as first line, respectively. The mean PFS with the etoposide, paclitaxel, pemetrexed, and gemcitabine platinum-based doublet regimens were 9.35, 10, 10.76, and 9.83 months, respectively. Kaplan–Meier survival curve analysis showed a statistically significant initial survival with the first line EtoP cisplatin regimen for the initial 6 months of starting chemotherapy in comparison with the other regimens. **Conclusions:** This study showed a substantial pharmacoeconomic benefit with the cisplatin and etoposide chemo regimen in the lower socioeconomic group of patients. We believe that this is the first pharmacoeconomic study on metastatic non small cell lung treatment of great relevance to countries with limited resources.

KEY WORDS: Cisplatin and etoposide, lower socioeconomic status, metastatic nonsmall lung cancer, pharmacoeconomics

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INTRODUCTION

Lung cancer has been the most common cancer in the world for the past several decades. Fifty-eight percentage of all lung cancer cases are expected to occur in the less developed countries. The rise in lung cancer incidence in developing countries like India, together with the fact that the overall 5 years survival of patients is less than 15 percent, underscores the magnitude of the lung cancer epidemic.^[1,2] There is a significant delay in seeking appropriate medical attention due to which a higher proportion of lung cancers

in developing countries present with the advanced/metastatic stage. Furthermore, unaffordability for the standard chemotherapy regimens and targeted therapy among the lower socioeconomic status (SES) patients results in poorer outcomes of such patients. Cisplatin-based chemotherapy is the standard in metastatic nonsmall cell lung cancer (NSCLC) patients. We studied the outcomes with the cisplatin plus etoposide (EtoP) regimen, a first

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How to cite this article: Kamath MP, Lakshmaiah KC, Babu KG, Loknatha D, Jacob LA, Babu SM. Pharmacoeconomic benefit of cisplatin and etoposide chemoregimen for metastatic non small cell lung cancer: An Indian study. Lung India 2016;33:154-8.

Access this article online	
Quick Response Code: 	Website: www.lungindia.com
	DOI: 10.4103/0970-2113.177448

generation chemotherapy regimen in metastatic NSCLC patients, and compared it with the outcomes of other current standard chemotherapy in our regional cancer institute. The study also tried to find out if the outcomes with that of the EtoP regimen was cost-beneficial and whether this chemo regimen can be revisited for the treatment of metastatic NSCLC in resource-limited settings.

Aims

We did a retrospective study of outcomes with the standard platinum-based regimens including the EtoP regimen in metastatic NSCLC patients presenting to our institute. The study looked at the cost-benefit ratio of treating metastatic NSCLC in the low socioeconomic group of patients with the EtoP regimen. We looked at whether there was a meaningful outcome benefit in comparison with the world data on the outcome with best supportive care (BSC).

MATERIALS AND METHODS

We did a retrospective analysis of metastatic NSCLC patients presenting with Eastern cooperative oncology group (ECOG) performance status (PS) ≤ 2 , who received at least one cycle of chemotherapy, in the Department of Medical Oncology between 2011 and 2014. Demographic data, smoking history, SES, ECOG PS, histological subtype, and treatment regimen details were collected. Patients were classified as nonsmokers (smoked < 100 cigarettes), light smokers (10–100 packs years), and heavy smokers (more than 100 pack years). In our center, patients with an annual income of less than or equal to Rs. 10,000 from rural or urban areas are registered as those belonging to the low SES and those with an annual income of more than Rs. 10,000 are registered as those belonging to the high SES. This procedure has been established by the government to enable the provision of subsidized treatment for patients with low SES. Patients started on first-line targeted therapy with small molecules and patients receiving only BSC, and no chemotherapy were excluded from the analysis. The progression-free survival (PFS) with the first line regimens namely the EtoP (IV Etoposide 100 mg/m², d1-d3 plus cisplatin 100 mg/m², d1, q3 weekly), PacP (IV Paclitaxel 175 mg/m², d1 plus cisplatin 75 mg/m² or carboplatin area under curve [AUC] 5, d1, q3 weekly), GemP (IV Gemcitabine 1250 mg/m², d1, d8 plus cisplatin 75 mg/m² or carboplatin AUC 5, d1, q3 weekly) and the PemP (IV pemetrexed 500 mg/m², d1 plus cisplatin 75 mg/m² or carboplatin AUC 5, d1, q3 weekly) regimens were studied. PFS was defined as the time from treatment initiation until objective clinical tumor progression or death due to any cause. A simplified cost-benefit ratio was calculated in which the cost of six cycles of chemo regimen inclusive of hospitalization charges was divided by the product of median PFS and the median number of cycles received. The major toxicities with the four chemotherapy regimen were recorded. The data were analyzed using SPSS Version 22 software by IBM software. All patients received supportive care measures

which included analgesics, symptom relief medications, psychosocial support and management of comorbidities, which were provided free of cost to all the low and high SES patients.

RESULTS

A total of 304 patients were retrospectively studied. The characteristics of results are outlined in Tables 1-4 and Figure 1.

Table 1: Baseline characteristics

Variables	Nonsmokers	Smokers	P (test used)
Number of patients	111	193	$< 0.001^*$ (Chi-square test)
Median age	47	59	$< 0.001^*$ (Mann-Whitney U-test)
Sex (%)			
Females	95.9	4.1	$< 0.001^*$ (Chi-square test)
Males	17.4	82.6	
SES (%)			
Low	36.6	63.4	Not significant
High	36.4	63.6	
ECOG PS (%)			
1	39.2	60.8	Not significant
2	33.1	66.9	
HPE (%)			
AC	40.9	59.1	Not significant
SCC	32.0	68.0	

* $P < 0.05$ significant. ECOG PS: Eastern co-operative oncology group performance status, SES: Socioeconomic status, SCC: Squamous cell carcinoma, AC: Adenocarcinoma, HPE: Histotype on pathological examination

Table 2: Distribution of patients receiving chemotherapy

First line CT	HPE		χ^2	P
	AC	SCC		
EtoP				
n	52	80	93.009	$< 0.001^*$
Percentage	39.40	60.60		
PacP				
n	41	44		
Percentage	48.20	51.80		
GemP				
n	0	26		
Percentage	0	100		
PemP				
n	61	0		
Percentage	100	0		

*Statistically significant. EtoP: Etoposide, GemP: Gemcitabine, PacP: Paclitaxel, PemP: Pemetrexed, CT: Chemotherapy, SCC: Squamous cell carcinoma, AC: Adenocarcinoma, HPE: Histotype on pathological examination

Table 3: Mean and median PFS with chemotherapy

First line CT	Mean				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower	Upper			Lower	Upper
EtoP	9.35	0.28	8.80	9.91	6.00			
PacP	10.01	0.96	8.13	11.88	8.75	1.08	6.63	10.00
GemP	9.83	0.60	8.65	11.00	9.00	0.35	8.32	9.68
PemP	10.76	0.82	9.17	12.36	9.00	0.47	8.08	9.92

EtoP: Etoposide, GemP: Gemcitabine, PacP: Paclitaxel, PemP: Pemetrexed, SE: Standard error, CI: Confidence interval, PFS: Progression free survival, CT: Chemotherapy

Table 4: Major toxicity with chemotherapy

Major toxicity	EtoP		PacP		GemP		PemP	
	n	Percentage	n	Percentage	n	Percentage	n	Percentage
Bleeding	1	1.28	3	5.36	1	8.33	3	7.69
Diarrhoea	17	21.79	12	21.43	1	8.33	6	15.38
Febrile neutropenia	34	43.59	20	35.71	5	41.67	16	41.03
Hepato toxicity	0	0.00	5	8.93	3	25.00	1	2.56
Pneumonia	19	24.36	11	19.64	2	16.67	11	28.21
Renal toxicity	7	8.97	5	8.93	0	0.00	2	5.13
Total	78		56		12		39	

EtoP: Etoposide, GemP: Gemcitabine, PacP: Paclitaxel, PemP: Pemetrexed

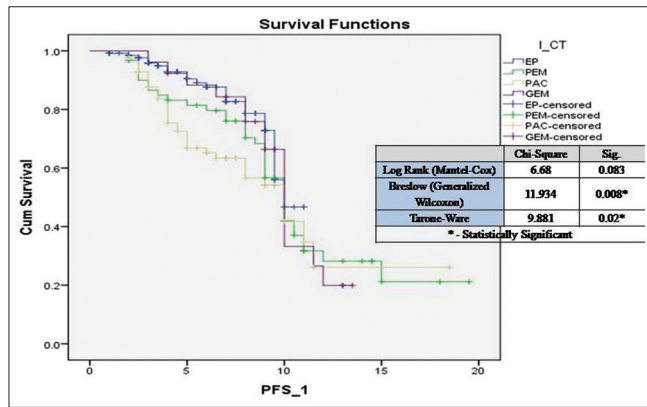


Figure 1: Kaplan–Meier estimates of progression free survival of the chemotherapy regimens

Age and gender

55.6% of the patients belonged to the age group 41–60 years while 31.9% patients were of the age between 61 and 80 years. 75.7% (n = 230) of the patients were male. 63.48% of the patients were smokers while nonsmokers formed 36.51% of the patients [Table 1].

Socioeconomic status

56.6% of the patients were of the low SES, and 44.4% were of the high SES. The distribution of smokers in both the low and high SES was similar at 63.6% [Table 1].

Performance status and nonsmall cell lung cancer histology

56.3% of the patients presented with ECOG PS1 and 43.8% patients presented with ECOG PS2. Both the PS1 and PS2 group patients had an equal number of smokers. Of the 304 patients, equal numbers of patients had adenocarcinoma (AC) and squamous cell carcinoma (SCC) histology. 62% of the nonsmokers patients were of the AC histology while SCC histology was more common in smokers (54.30%) [Table 1].

The most common sites of metastasis were pleura, contralateral lung, bone and adrenal metastasis; the proportions of the metastatic sites were similar in both the AC and SCC histology groups.

Treatment received

One hundred and thirty-two patients received EtoP regimen of which 60.60% were of SCC histology; 85 patients received PacP regimen of which almost equal number were of AC and SCC histology. Sixty-one patients with AC histology received PemP regimen and 26 patients with SCC histology received GemP regimen [Table 2].

Of the low SES group patients 67.45% and 31.4% received EtoP and PacP as first-line chemotherapy, respectively. Of the high SES group patients, 12% received first line EtoP regimen.

Totally, 80.3% of the patients receiving EtoP regimen completed 3 or more cycles of chemotherapy. 78.75% of EtoP patients with SCC histology and 82.7% of EtoP patients with AC histology completed 3 or more cycles of chemotherapy. 83.52% of the patients receiving PacP regimen completed ≥3 cycles. Ninety-five percentage and 100% of patients receiving PemP and GemP, respectively completed ≥3 cycles. Five patients of the high socioeconomic group were able to afford for PemP maintenance after first line PemP. The EtoP and PacP groups received a median of 4 cycles of chemotherapy each. The PemP and GemP groups received a median of 5 cycles each.

The mean PFS with the EtoP regimen, the PacP, the PemP and the GemP regimen were 9.35, 10, 10.76, and 9.83 months respectively, with the standard error between 0.28 and 0.96. The median PFS with the EtoP, PacP, PemP, GemP regimens were 6, 8.75, 9, and 9 months, respectively. The median PFS in the PemP + maintenance group was 14.5 months (range 10.5–19.5 months) [Table 3]. The median PFS with the EtoP regimen was 5 and 5.5 months for the AC and SCC histology, respectively. The median PFS with the PacP regimen was 5.5 and 5.3 months for the AC and SCC histology, respectively.

The major toxicities observed during treatment common to all the four regimens were febrile neutropenia, pneumonia, neutropenic colitis, and in decreasing order. GemP regimen had the highest frequency of hepatotoxicity [Table 4].

Kaplan–Meier survival curve analysis was done to compare the survival distributions with the four chemotherapy regimen used at the first line. Breslow (generalized Wilcoxon) test and Tarone-Ware test showed a statistically significant initial survival with the first line EtoP regimen for the initial 6 months of starting chemotherapy in comparison with the other regimens [Figure 1].

The cost of each cycle of chemotherapy including day care ward admission charges at our center is Rs. 1500 for EtoP, Rs. 4500 for PacP, Rs. 7500 for GemP and Rs. 15,000 for PemP. For the EtoP regimen, patients were admitted for 3 days whereas patients receiving the PacP, GemP, and PemP regimens were given chemotherapy at daycare ward only and discharged the same day. The median

number of days of hospitalization for management of the major chemotherapy-related toxicities with the EtoP, PacP, GemP, and PemP regimens were 5, 4, 3, and 3 days, respectively. There was no significant difference w.r.t the duration of hospitalization between the four regimens. The cost-benefit ratio for the EtoP, PacP, GemP, and PemP was 375, 771, 1002, and 1998, respectively.

DISCUSSION

Chemotherapy has proven to be of benefit in stage IV NSCLC. Platinum-based chemo regimen has become the established standard of care in the treatment of metastatic NSCLC. Rapp *et al.* in 1988 concluded in their report that cisplatin-based chemo regimen improved survival in metastatic NSCLC patients.^[9] While cisplatin may be having a slightly higher response rate than carboplatin, the toxicity with cisplatin, especially nonhematologic, is worse.^[4]

Since 1990's, several randomized controlled trials have shown that chemotherapy of good ECOG PS patients with stage IV NSCLC significantly prolongs survival and alleviates disease-related symptoms compared with BSC alone.^[5,6] Recent studies have demonstrated a median survival of approximately 10–12 months for patients with nonsquamous histology, and 9–10 months for squamous carcinoma with current standard chemo regimens.^[7,8]

The outcome of metastatic NSCLC with the older and now inexpensive cisplatin plus etoposide treatment regimen was studied since 1980's.^[9,10] A significant benefit with cisplatin-containing regimens, including the EtoP regimen, was seen over BSC alone. Over the next few years, several randomized trials demonstrated a significant superiority in efficacy of newer platinum doublet regimens such as PacP, GemP and PemP.^[11-13] The cost of these newer regimens is not afforded by the low SES group patients. While the costs of these current generation regimens are higher, the magnitude of benefit over the older regimen is still modest. In resource-limited settings, the poorer patients cannot afford for the current standard regimens.

“Pharmacoeconomics” is one of the most important topics concerning today's cancer therapy in the developing countries. Pharmacoeconomics is a scientific discipline that compares the difference in the value of one pharmaceutical drug or drug therapy compared to another for their benefit in a particular health condition.^[14] It is a branch of health economics which looks at the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, efficacy or enhanced quality of life) of a pharmaceutical product thereby estimating the cost-benefit ratio of the drug. Pharmacoeconomic studies are helpful in optimal healthcare resource allocation and are relevant in resource-limited settings.

A large number of lung cancer patients in India are of the low SES group. These patients not only present with advanced stage disease but also delay treatment due to

the high costs involved. Therefore, the challenge for today's cancer therapy in developing countries like India is to devise treatment strategies which will enable a large number of patients to avail treatment at affordable costs and obtain a substantial benefit.^[15]

In our study, we looked at the outcomes with the EtoP regimen for the treatment of metastatic NSCLC. We then compared it with the currently used standard regimens with respect to outcomes.

The proportions of AC and SCC histology were almost equal in our study. Almost three-fourths and two-thirds of all the AC and SCC histology patients respectively were smokers. Almost two-thirds of the low SES patients and 12% of the high SES patients received EtoP chemotherapy. Each cycle of EtoP regimen is 3 times, 5 times and 10 times cheaper than PacP, GemP, and PemP regimen, respectively. This made the EtoP regimen affordable for the low SES patients. The affordability for EtoP probably ensured a good compliance rate (~80% patients completed ≥ 3 cycles) which in combination with disease response provided a substantial benefit to the low SES patients who otherwise would have been forced to opt for BSC due to unaffordability. In our study, the mean PFS with EtoP regimen was 9.35 months which is significantly better than historical data with EtoP regimen in which the median survival ranged between 5 and 7 months.^[9,16-18] This may either indicate a better tolerability for EtoP in our patients or may be attributed to improved supportive care measures given along with chemotherapy. The median PFS seen with the other commonly used regimens such as PacP, GemP and PemP regimen were 8.75 m, 9 m and 9 m, respectively, which were higher than many previous studies including an Indian study.^[19,20] The median PFS were similar for both the AC and SCC histology treated with the EtoP regimen. The median PFS were similar for both the AC and SCC patients treated with the PacP regimen. Five patients in our study took maintenance treatment with PemP. While the number may be small to conclude, the median PFS/survival was 14.5 months (range 10.5–19.5 months) which is similar to the data with the large trial on maintenance pemetrexed.^[21] The median PFS with EtoP was 6 months; almost 18% ($N = 23/132$) of the patients had clinical progression after which they took second line treatment. The median survival of patients taking second-line chemotherapy after EtoP regimen was 11 months which is a significant benefit.

Kaplan–Meier survival curve analysis was done to compare the survival distributions with the four chemotherapy regimen used at the first line. Breslow (generalized Wilcoxon) test and Tarone–Ware test showed a statistically significant initial survival with the first line EtoP regimen for the initial 6 months of starting chemotherapy in comparison with the other regimens. All patients throughout treatment were given BSC as per existing standards. Perhaps, the BSC measures are better today than those existing at that time which may also be

contributing toward a better survival in these patients. The cost-benefit ratio was the most favorable for the EtoP regimen followed by that for the PacP, GemP and PemP regimens. This ratio means that each additional month of PFS with the EtoP regimen costed Rs. 375/cycle, corresponding to Rs. 771/cycle for PacP regimen, Rs. 1002/cycle for the GemP regimen and Rs. 1998/cycle for the PemP regimen. This difference in the cost-benefit ratio is of great importance, especially to the patient not affording for today's standard treatment but still keen on treatment for palliation.

CONCLUSION

This study also shows the substantial benefit with cisplatin plus etoposide chemo regimen in the lower socioeconomic group of patients. The outcomes with the four chemotherapy regimen were comparable with the previously published data. We believe that this is the second Indian study to compare the outcomes with the available chemo regimens and first Indian pharmacoeconomic study on lung cancer treatment. The outcome of this study may encourage the usage of low-cost effective regimens for treatment of NSCLC irrespective of histology in the lower economic sections of the society, offering them a meaningful benefit over no treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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