

RESEARCH ARTICLE

Survival Analysis in Advanced Non Small Cell Lung Cancer Treated with Platinum Based Chemotherapy in Combination with Paclitaxel, Gemcitabine and Etoposide

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Abstract

Background: The wide spectrum of clinical features in advanced stages of non-small cell lung cancer (NSCLC) probably contributes to disparities in outcomes because of different prognostic variables significant for stage IIIB/IV patients. Hence the aim of this study was to check for favorable response of patients to various chemotherapeutic combinations with respect to patient survival in stage IIIB and stage IV NSCLC disease. We selected those patients for our study who were receiving treatment with paclitaxel, gemcitabine or etoposide in combination with platinum based drugs. **Materials and Methods:** Seventy-two patients who visited the hospital from June 2009 to November 2012 with confirmed diagnosis of lung cancer were included, and data were collected for follow up and classified according to treatment received with respect to patients' regimen and response, and overall survival. This study analyzed tumor variables that were associated with clinical outcome in advanced NSCLC patients who were undergoing first-line chemotherapy for stage IIIB/IV NSCLC. **Results:** Comparative data on various parameters like age, gender, stage, histology, site of disease, metastatic site and chemo-regimens was analyzed; these parameters predicted variable significant improvement for overall survival ($p \geq 0.05$). One and two year survival rates were 20.8% and 15.3%. **Conclusions:** In this study we found slight improvement in survival rates in NSCLC and clinical outcomes with one combination (carboplatin+paclitaxel). Overall there were only marginal differences in survival rates for other chemo-regimens evaluated in this study.

Keywords: Non small cell lung cancer - chemotherapy - metastatic cancer - survival

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Introduction

Lung cancer is the leading cause of morbidity and mortality globally. In clinical practice, it is classified as small cell carcinoma or non-small cell carcinoma of the lung (NSCLC). At diagnosis, the majority of patients have either locally advanced, unresectable disease (stage III; approximately 44%) or metastatic disease (stage IV; approximately 35%) (Sandler et al., 2006). The more common sites of metastatic disease include liver, bones, adrenal, brain, and contra lateral lung (Bülzebruck et al., 1992). It has poorer prognosis despite best possible chemo/biological therapies (Pirker et al., 2009). Palliative therapy with appropriate agents [pemetrexed/ Gemcitabin/ etoposide with platinum doublet/EGFR TKI] is the treatment of choice (Mark et al., 2003; Ciuleanu et al., 2009), and radiation therapy (RT) is usually given to palliate specific symptoms (Koo et al., 2011). In locally advanced or metastatic lung cancer cases (stage IIIB/IV) chemotherapy treatment for non-small-cell lung cancer

(NSCLC) has favorable effects on patient survival and quality of life (Pfister et al., 2004). Cis-diamminedichloro-platinum(II) was first shown to have antitumor activity in 1969 (Rosenberg et al., 1969) and has subsequently become a pivotal component of many therapeutic regimens against a wide variety of solid tumors along with carboplatin for the first line treatment because of the better response (Goffin et al., 2010). The combination of one or more agents like paclitaxel, gemcitabine with a platinum compound has resulted in high response rates and prolonged survival of one year in phase 2 studies in NSCLC (Crino et al., 1997; Cullen et al., 1999). However, there have been few comparisons of these newer chemotherapy regimens, which are now used frequently, with each other. An international collaborative meta-analysis by Stewart 1995 showed the median survival time for patients with untreated metastatic NSCLC is only 4-5 months; with a survival rate at one year for only 10% with earlier chemotherapy regimens but with second-generation regimens (e.g., cisplatin and etoposide) the survival rates

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have improved by 20-25% in one year. However, a meta-analysis has demonstrated that, with best supportive care chemotherapy results showed slightly better improvement in survival rates of patients with advanced NSCLC (Crinò et al., 2010). Even though patients have similar characteristics with respect to stage, symptoms with the same chemotherapeutic regimen in advanced NSCLC the outcome among these patients varied with each other may be because it is a heterogeneous disease (Darwish et al., 1995). Additionally, some patients experienced weight loss and some had a significant number of co-morbidities because of treatment related toxicity. These are generally managed by neoadjuvant therapy followed by radiotherapy with the treatment associated with a variety of side effects. This wide spectrum of clinical features of patients with stage IIIB/IV NSCLC probably contributes to disparities in outcomes seen in different clinical trials.

Although different prognostic variables have been described for advanced stage NSCLC (Reboul et al., 1996) by different authors these results did not show any improvement for stage IIIB/IV. There are very few reports addressing this issue in our patient population. One such chemotherapy regimen using Cisplatin with Etoposide has been widely used in our country because of its synergistic action (Cardenal et al., 1999), in spite of the availability of these drugs, like Gemcitabine, Vinorelbine, Gefitinib etc. Because of the therapeutic efficacy of these drugs were clinically proven and it became affordable for a majority of Indian patients, except those who are under poor socio economic status. According to published clinical trial data a combination of cisplatin plus gemcitabine has been found to be superior to the previous combination of cisplatin plus etoposide (Schiller et al., 2002). In another study drug combination using cisplatin with gemcitabine, vinorelbine, paclitaxel or docetaxel in advanced-stage NSCLC patients have been tried, but all of the combinations demonstrated nearly the same effect on tumor dimensions and patient survival (Ostros et al., 2005). Some meta-analyses suggested that the gemcitabine plus platinum drug combination has a small survival advantage over other combinations. According to one meta-analysis of advanced-stage NSCLC, overall survival was 9 months, median progression-free survival (PFS) was 5.1 months, and the 1-year survival rate was 40% for gemcitabine-based treatments (Cullen, 2005). An earlier study by Sandler et al. (2010) concluded that bevacizumab plus carboplatin and paclitaxel (BCP) versus carboplatin and paclitaxel (CP) alone in advanced chemo-naïve adenocarcinoma of NSCLC patients indicated that OS was better in BCP patients compared to those treated with chemotherapy alone (14.2 vs 10.3 months). Other options are also available for NSCLC patients for better treatment and better response rate by using the EGFR status. Where EGFR mutations are important predictive factor for first-line treatment with EGFR - TKI therapy (Gefitinib), which improves the response rates, quality of life, and median progression-free survival (by 2-5 months) with first-line Gefitinib therapy compared with standard platinum-doublet chemotherapy in patients with EGFR mutation-positive NSCLC (Mitsudomi et al., 2010; Zhou et al., 2011; Han et al., 2012).

Socioeconomic status of individuals also influences the patients treatment options because gemcitabine with platinum combination (Bidoli et al., 2007) is less expensive than other combinations like paclitaxel or vinorelbine.

Therefore, in this study our aim was to determine the patients' tumor variables that are associated with improved outcome in advanced lung cancer cases that were undergoing first-line chemotherapy for stage IIIB/IV NSCLC treatment with cisplatin and etoposide, carboplatin and paclitaxel, gemcitabine and carboplatin.

Materials and Methods

Patients' details

In this retrospective study of a total of 72 patients, with the confirmed diagnosis of lung cancer (pathologically, histologically/cytologically confirmed) between June 2009 to November 2012, was undertaken for a follow up of survival statistics. The disease was determined clinically through FNAC, malignant cytology in pleural effusion, bronchoscopy.

Medical records/through our questionnaire

Demographic details of the patient's age, gender, contact information, smoking status, the dates of first visit and diagnosis were also recorded. Apart from this patients' histology, site of disease, stage of the disease were also recorded.

The baseline laboratory parameters, were also recorded for complete hematology (WBC, RBC, Hb and Platelets counts). Liver Function Test and Renal Function test with subsequent visit to identify adverse events/drug induced toxicity.

Locally advanced and metastatic cases

Locally advanced disease was defined as tumor confined to one hemithorax, but including mediastinum, ipsilateral supraclavicular lymph nodes and ipsilateral pleural effusions (Stage IIIB). Diseases beyond this stage were classified as extensive (Stage IV). A Bone Scan confirmed their bone metastasis and were evaluated for other relevant investigations to determine the extent of local metastases which included CT scans chest, abdomen and pelvis (CAP) and CT brain.

Details of the treatment

The treatment details received i.e., chemotherapy (CT) at initial date and the type of treatment such as: etoposide+cisplatin; carboplatin+paclitaxel; Gemcitabine+carboplatin; were recorded. The number of cycles from the dates of initiation and completion of treatment were also recorded. Standard criteria were used to assess radiological response (RECIST- Response Evaluation Criteria in Solid Tumors) to treatment as complete response (CR), partial response (PR), progressive disease (PD) and no response (NR) (Miller et al., 1981).

Follow up cases/survival data

All the patients were contacted by telephone for

response and follow up. The survival data was obtained either from the patients themselves, or their relatives. For those dead, the date of death was recorded and was used to calculate survival data. For those patients, where survival information was not obtained, the interval between the date of diagnosis and the date of last follow up was used to calculate survival duration (Maestu et al., 1997).

Statistical analysis

Data of the present study was analysed by MedCalc® software, demo version, 10.0.2.0. Multiple Comparisons were used to compare continuous variables. The $p < 0.05$ was considered significant. Survival curves were constructed using the Kaplan–Meier method, and differences analysed by the log-rank test.

Results

Patient and disease characteristics

From June 2009 to November 2012, 72 patients those who were diagnosed as Non small cell lung cancer with confirmed pathology and cytology/histological formed our study group.

All these patients were diagnosed as stage III B and Stage IV. Of the 72 patients with advanced NSCLC, 54 were males (75%) and 18 were females (25%) with a male: female ratio of 3.23:1 (Table 1). Twenty nine patients (40.277%) were below the age of 50 years and forty three patients were (59.722%) above age of 50 years at diagnosis. Mean age was 54.43 ± 10.306 (SD) years (range 34–78). Of these patients 25 (34.72%) were stage IIIB and 47 were (65.28%) in stage IV metastatic disease. The most common histology observed in our study was adenocarcinoma (34, 47.22%), while squamous cell carcinoma (25, 34.722%) and others types included Bronchio, Alveolar and large cell carcinoma, this accounted for 13, and 18.05% respectively. The majority of stage IV (n=47) patients had metastasis of single organ,

higher incidence of bone (skeletal) (12, 25.53%), followed by brain (06, 12.77%), liver (02, 04.26%) and other sites (27, 57.44%) (Table 1). Of these metastasis cases two patients showed two or more organs were affected.

Treatment strategies

Thirty-six patients were treated with Gemcitabine+Carboplatin, 27 were treated with Carboplatin+Paclitaxel and 09 patients were treated with Cisplatin+Etoposide (Table 2).

Adverse events

General cumulative toxicities like neuropathy and alopecia were noticed in all treatment regimens and non-cumulative toxicities were hematological (febrile neutropenia, thrombocytopenia, and anemia) and gastrointestinal (diarrhea, vomiting) problems were observed. Neutropenia in Grade III and IV of was similar in all arms of treatment such as 13.83% in Gemcitabine+Carboplatin, 18.5% in Carboplatin+Paclitaxel and 22.22% in Cisplatin+Etoposide group. Elevated creatinine was observed in one patient in each group of Gemcitabine+Cisplatin and Cisplatin+Etoposide treatment.

Response and outcome of therapy

Univariate analysis of prognostic factors was performed on all treated patients with survival data for age groups, gender, stage, Histology, Locally advances versus Metastasis (Table 1) and chemo-regimen (Table 2) but, these parameters did not predict the overall survival ($p=0.3105, 0.9137, 0.7905, 0.0905, 0.4469$ followed by 0.4780) significantly.

Response of patients to chemo regimens undertaken

Among all these cases two patients showed metastasis to brain (5.56%) and five cases showed (13.88%) disease progression (PR) when treated with

Table 1. Patients Characteristics and Treatment Out Come

Variable	No. of Patients	Median Survival in Months	SD	95% CI	Correlation Coefficiency -r	p value	
Age	<50 years	29	9.17	5.42	-0.3432-0.2237	-0.1212	0.3105
	>50 years	43	7.953	6.405			
Gender	Male	54	8.52	5.37	-0.2439-0.2193	-0.013	0.9137
	Female	18	8.33	3.97			
Stage	IIIB	24	8.66	5.23	-0.2616-0.2013	-0.031	0.7905
	IV	48	8.33	4.88			
Histology	Adenocarcinoma	34	5.82	4.472	-0.4134-0.03217	-0.201	0.09
	Squamous cell carcinoma	25	9.68	5.82			
	other	13	8.61	4.46			
Stage of the Diseases	Locally advanced (IIIB)	25	8.72	5.12	-0.3160-0.1437	-0.09104	0.4469
Metastatic (IV)	Brain	6	9.5	4.5			
	Bone	12	8.33	5.597			
	Liver	2	14.5	6.36			
	Other	27	7.55	4.51			

Table 2. Chemo Regimen and Over All Survival Rate

Variable	No. of Cases	Over all Survival in months	95% CI for r	Correlation Coefficiency -r	p value
Gemcitabine+Carboplatin	36	7.5	-0.1497-0.3105	0.08496	0.478
Carboplatin+Paclitaxel	27	10.18			
Cisplatin+Etoposide	9	7			

Table 3. Chemo Regimen and Over All Survival Rate

Covariate	Standard Error	Hazard Ratio (HR)	95%CI for HR	p value
Age	0.5142	0.9163	0.3362-2.497	0.8651
Histology	0.2864	0.7931	0.4537-1.3862	0.4182
Sex	0.5648	1.8621	0.6190-5.6018	0.271
Stage	0.5061	0.698	0.2602-1.8724	0.698
Regimen	0.4334	1.174	0.5041-2.7325	0.7118

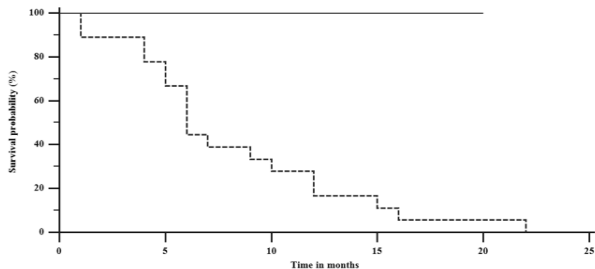


Figure 1. Overall Survival of All Patients

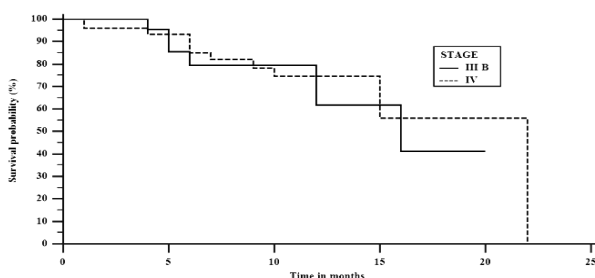


Figure 2. Survival According to Stage (IIIB vs IV)

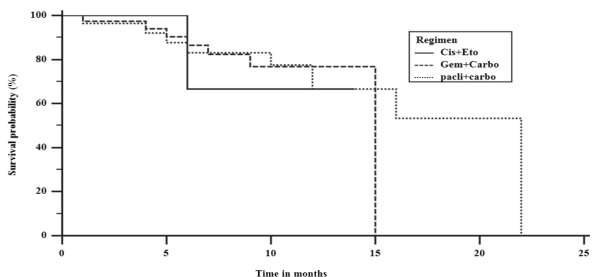


Figure 3. Survival Rate for Chemotherapeutic Regimen

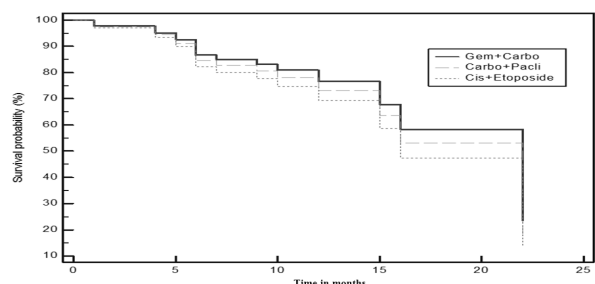


Figure 4. Multivariate Analysis by Cox Proportional Hazard Model Showing the Survival Rates in Three Different Regimens

Gemcitabine+Carboplatin, six patients (22.22%) showed disease progression (PD) treated with Carboplatin+Paclitaxel, also these patients showed pleural effusion, multiple nodules in both lungs and lymph nodes, one patient showed bone metastasis (3.7%) on treatment. Two patients (22.22%) continued to show disease progress on treatment treated with Cisplatin+Etoposide in both lungs. Rest of the patients in the three chemo regimen groups, fall into the category of partial response/stable disease. The overall survival for one and two year survival

period was 20.8% followed by 15.27% and median survival was 8.49 months (Figure 1), this appears to be significant in clinical terms of overall survival of such cases. Multivariate analysis was performed for the variants included in univariate analysis by Cox proportional hazard. The results of multivariate analysis are shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that there is no significance for any covariates where p showed >0.05.

Discussion

Paclitaxel and gemcitabine are promising new chemotherapeutic agents in the treatment of advanced NSCLC in combination with platinum based chemotherapy. The aim of chemotherapy for treating advanced NSCLC is to decrease disease symptoms, and this practice is being followed by many clinicians who are concerned about the toxicity of the chemotherapeutic agents that may adversely affect patients’ quality of life and performance status. Advanced stages (IIIB and IV) of lung cancer have a poor prognosis and a median survival time of only 6-8 months (Carr et al., 1994) because of the toxic alkylating agents that actually result in shortened survival time (Masters and Vokes, 1995). But now with newer cisplatin-based regimens the scenario is changing. Latest promising clinical trial reports suggest that with third generation platinum agents which contain combination therapies including Gemcitabine, Vinorelbine or taxanes, a better response of 30-40%, and median survival of 8-10 months or 1 year has been reported in approximately 35% of patients with advanced non-small cell lung cancer. Our findings confirm that poor prognosis in patients diagnosed with stage IIIB and IV NSCLC, with a median overall survival time of 8.66 and 8.33 months (Figure 2).

The present study consists of small number of cases, even though the results showed the overall survival rates was a gradual improvement in the cases as per the phase III trials, these results are in agreement with the reports of Scagliotti et al. (2002). But there were marginal differences in overall survival between patients who received one of the three regimens Gemcitabine+Carboplatin and Carboplatin+Paclitaxel and Cisplatin+Etoposide. But median survival varied within these groups of patients who received carboplatin and paclitaxel, the median survival was 10.18 months, 7.5 months in gemcitabine+carboplatin and 7 months in Cisplatin+etoposide regimen (Table 2). The results of our study were in comparison with those reported by Scagliotti (2012) in their “clinical trial-ChEST”, with a significant improvement in both disease free survival (DFS) (HR=0.51) and overall survival rate (HR=0.42) in patients with clinical stage IIB-IIIA NSCLC using preoperative gemcitabine plus cisplatin. However there was better improvement in Carboplatin+Paclitaxel regimen in the overall survival rate among the three treatment groups. Our results are also similar with those reported by Socinski et al. (2012) where the authors found no significant improvement with nab-paclitaxel arm versus standard paclitaxel arm.

When we compared non metastasis cases versus metastatic cases the overall survival was not significant

as $p=0.95$, and there was no single 'best' regimen for metastatic setting (Figure 3). These patients with stage-III and stage IV disease status were also given the same treatment as there was no benefit of any other systemic chemotherapy as the prognosis of these patients was similar to that of patients with stage IV NSCLC. Our findings were consistent with other published data (Schiller et al., 2002) that there is no beneficial chemo regimen with respect to stage, as it was confirmed with all the three regimens in our studies as well as of those reported by Srisam-ang et al. (2005) and Gridelli et al. (2010). A very recent study by Nørøxe et al. (2013), reported that when carboplatin and vinorelbine were compared together with bevacizumab and without bevacizumab, the results were not favorable even including bevacizumab. Since the effect of maintenance bevacizumab on OS was not established but it has been proven as being favourable on PFS for only performance status 1 (PS) patients and suggest that patients with PS- 2 should not receive this treatment.

In our study, some of the variants showed prognostic significance for OS in univariate analysis, multivariate analysis and the hazard ration did not reach statistical hazard model where $p=0.7316$ (Figure 4). This might be due to the small number of patients and difference of treatment choice (Table 2).

In conclusion, the findings in the present study revealed that the overall survival in NSCLS patients varied with each type of treatment. These findings were based on statistical methods such as multiple covariant analyses by MedCalc® software, Kaplan–Meier method and other relevant methods. Despite improvements with combined therapies as seen in this study, cancer is the leading cause of death worldwide. Many patients experience severe, unnecessary symptoms during treatment as well as at the end of life. Hence it is suggested that more attention has to be given for palliative care which is an approach that focuses on communication and quality of life, including treatment of physical, psychosocial, and spiritual suffering. It is concluded that among the treatment regimens which comprised of three combinations of chemo drugs along with a platinum based drug we observed small increase in survival status but not much improvement.

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