

Second-Line Chemotherapy in Advanced Non-Small Cell Lung Cancer (NSCLC): Single Institution Experience

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Background: Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 80-85 %.

Methods: In this retrospective hospital based study, 424 NSCLC patients "stage IIIb-IV" were enrolled to analyze the prognostic factors and survival after receiving second-line chemotherapy.

Results: From 424 NSCLC patients, 236 (55.7%) had stage IIIb-IV disease. The majority (70%, 165/236) of these patients received best supportive care only and 30% (71/236) received first-line chemotherapy. Second-line chemotherapy was administered in 11.9% (28/236) patients after first-line chemotherapy. The median age of patients who received second-line was 58 years. The majority were males (64%). Sixty four percent had stage IV, 57% had an Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, 72% had a body mass index of >18.5 kg/m² and 57% had history of smoking. The median overall survival was 13 months (95% CI: 6.82-19.18). The first-line chemotherapy was platinum-based combination in all patients, and docetaxel was the second-line treatment in half of the patient. The most common side effects were hematological (93%) and gastrointestinal (78%). Higher risk of mortality was accompanied with age 40-60 years (HR: 5.53, 95% CI: 1.29-23.7, p = 0.022) and stage IV (HR: 3.65, 95% CI: 1.21-11.06, p = 0.022). Multivariate analysis revealed that stage IV had higher risk of mortality than stage IIIb (HR: 3.75, 95% CI 0.969-14.535, p = 0.056). The platinum-taxane combination added 3 months in the median survival (13 vs. 10 months, p = 0.4).

Conclusion: Stage IV and age between 40-60 years had a higher risk of death in NSCLC.

Keywords: Non-small cell lung cancer, Advanced, second-line chemotherapy

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INTRODUCTION

Lung cancer accounts for 14% of all new cancer ranking the second in both sexes. Non-small cell lung cancer (NSCLC) accounts for 80-85% of cases¹. Locally advanced non operable lung cancer carries a poor prognosis².

In recent years, more focus on the genetic background of lung cancer opened the way for more targeted treatments with minimal side effects. The presence of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or ROS1 gene rearrangement, allow the use of biological agents as afatinib, erlotinib, or gefitinib and crizotinib in the first-line treatment³.

It is Important to be aware that this genetic alterations are present in only small percentage of patients. Therefore, for most eligible patients, doublet cisplatin based chemotherapy, with antibodies against vascular endothelial growth factor remains the mainstay of treatment⁴.

In second-line treatment, docetaxel, pemetrexed and erlotinib revealed better progression free survival and time to progression. Third line treatment is not routinely

recommended. Erlotinib is advised if it is not taken before^{5,6}.

Immunotherapy is a new advent that flares the field of treatments in lung cancer. It shows signs of future success and minimal toxicity. This includes PD-1/PD-L1 blockades, nivolumab, pembrolizumab. However this needs longer follow up especially when combined with other agents⁷⁻¹⁰.

This study was conducted in patients with locally advanced inoperable and metastatic NSCLC receiving second-line chemotherapy. Assessment of tolerability and response to treatment as well as disease free survival and overall survival were analyzed.

METHODS

This retrospective hospital based study was approved by Ethics Committee of the Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK).

Eligibility criteria included histopathological diagnosis of NSCLC, stage IIIb-IV, initiation of second-line chemotherapy upon disease progression or stationary course disease and receiving at least 3 cycles of chemotherapy during the first-line treatment.

The following data were collected: age, gender, common symptoms, modalities of diagnosis, histology, TNM stage according to AJCC/UICC TNM staging system (7th edition), the Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, body mass index, smoking status, co-morbidities, date of diagnosis, date of death or last follow up and chemotherapy given.

Overall survival (OS) was defined as the time from the first diagnosis of NSCLC to the date of death or the date of last follow-up. The Kaplan-Meier method was used for survival analysis and multivariate Cox proportional hazard analysis was performed to identify independent predictors of death. A *p* value of < 0.05 was considered significant. The analyses were performed with SPSS software (Statistical Package for the Social Sciences IL USA.).

RESULTS

Among 424 cases of NSCLC patients, the majority was stage IIIb-IV (55.7%, 236/424). Of them 71(30%) received chemotherapy and the rest (70%, 165/236) were subjected to best supportive care including 28% receiving palliative radiotherapy. Second-line chemotherapy was feasible in 39.4% (28/71) of patients taking first-line chemotherapy and to 11.9% (28 /236) of stage IIIb-IV disease (Figure 1).

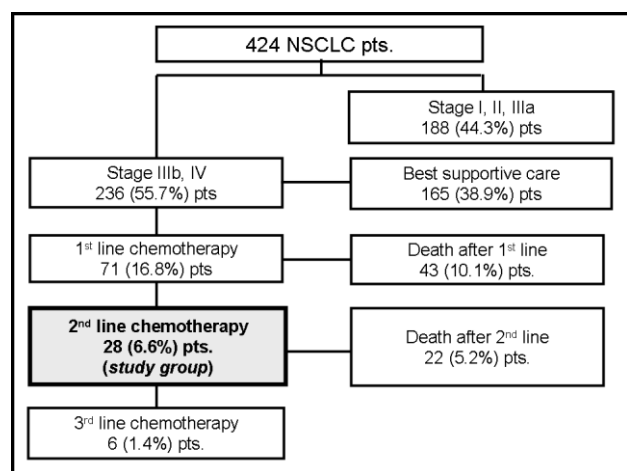


Figure 1: Flow diagram of treatment received by stage IIIb/IV non-small cell lung cancer patients

The clinical characteristics of the 28 patients are listed in Table 1. The median age for all patients was 58 years (range, 37-69 years) and the majority were males (64%) and had a BMI of >18.5 kg/m² (72%), history of smoking (57%). The most common co-morbidity was hypertension (21%) and the most common symptoms at presentation were cough (93%) and dyspnea. The most common site of distant metastasis was brain in 21% of patients followed by bone in 7%.

Details of chemotherapy regimens are listed in Table 2. The first-line chemotherapy was platinum-based combination in all patients with a median number of five cycles. As the first-line treatment, half of the cases received carboplatin-gemcitabine combination.

Table 1: Clinico-epidemiological characteristics of 28 patients with stage IIIb-IV NSCLC receiving second-line chemotherapy

	No.	%
Gender		
Male	18	64.3
Female	10	35.7
Age		
<40	4	14.3
40-60	16	57.1
>60	8	28.6
Performance status		
1	6	21.4
2	14	50
3	2	7.1
Unknown	6	21.4
Smoking		
Yes	16	57.1
No	12	42.9
Body mass index		
Underweight	4	14.3
Normal	2	7.1
Overweight	8	28.6
Unknown	14	50
Co-morbidities		
Hypertension	6	21.4
Diabetes	2	7.1
Common symptoms		
Cough	26	92.9
Chest pain	16	57.1
Dyspnea	20	71.4
Hemoptysis	6	21.4
Mode of biopsy		
CT guided	20	71.4
US guided	6	21.4
Bronchoscopy	2	7.1
Histopathology		
Adenocarcinoma	18	64.3
Squamous cell	10	35.7
Stage		
IIIb	10	35.7
IV	18	64.3
Palliative treatment		
Medical	20	71.4
Radiotherapy	8	28.6

All 28 patients had disease progression and received second-line chemotherapy with a median number of three cycles. Single agent docetaxel was given to 50% of the patients. The majority of patients (22/28, 78%) had died during the course of second line treatment while 6 (21%) progressed and managed to receive third line

chemotherapy in the form of single agent vinorelbine (4 patients) or paclitaxel (2 patients).

Table 2: Systemic chemotherapy in 28 NSCLC patients

Chemotherapy regimen	1 st line	2 nd line	3 rd line
	n (%)	n (%)	n (%)
Cisplatin + Gemcitabine	8 (28.6)	2 (7.1)	
Cisplatin + Navelbine	4 (14.3)	2 (7.1)	
Carboplatin + Gemcitabine	14 (50)	2 (7.1)	
Carboplatin + Navelbine	2 (7.1)		
Carboplatin + Paclitaxel		8 (28.6)	
Docetaxel		14 (50)	
Navelbine			4 (14.3)
Paclitaxel			2 (7.1)

During chemotherapy, the most common adverse effect was hematological (93%) in the form of anemia, neutropenia and thrombocytopenia. Followed by gastrointestinal toxicity in the form of nausea and vomiting observed in 78% of the patients.

A minority of our patients (7%) complained of renal toxicity in the form of high serum creatinine and urea. Most of the patients had received palliative treatment (71.4%), of which 28% had received palliative radiotherapy (whole brain irradiation in 21% and bone irradiation in 7%).

After a median follow up of 40 months, the median OS was 13 months (95% CI: 6.82-19.18) shown in Figure 2.

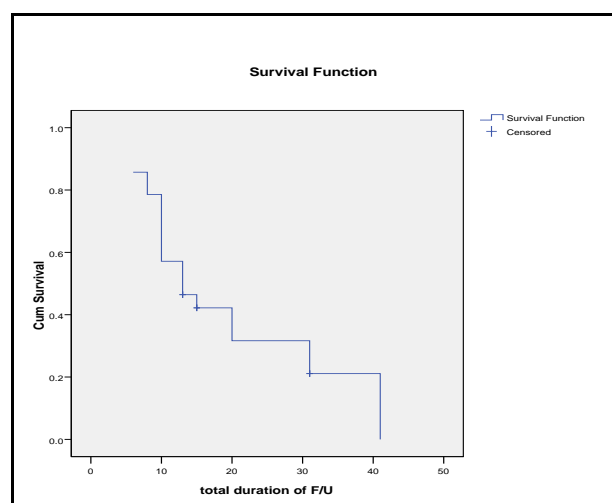


Figure 2: Kaplan-Meier curve: overall survival

Cumulative survival probabilities were estimated using the Kaplan-Meier curve for second-line therapy in patients treated with Platinum/Taxanes in one arm and Platinum + other regimen in the other one. The

Platinum/Taxanes arm added 3 months for the median survival period (13 month vs. 10 months, p-value: 0.4) shown in Figure 3.

Patients who received palliative treatment had worse survival (13 vs. 20 months; p-value = 0.886).

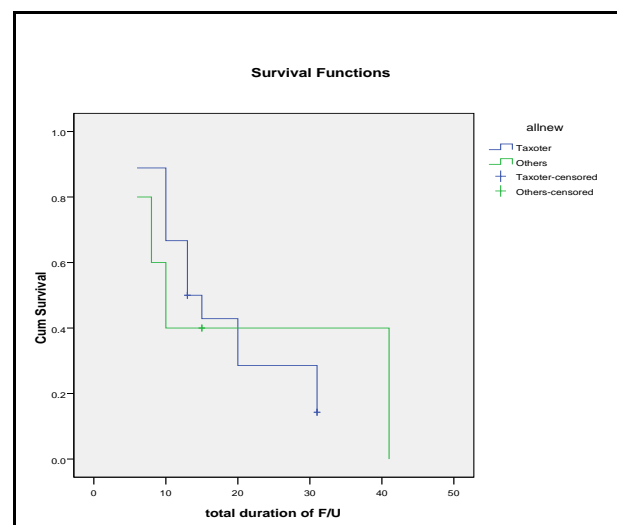


Figure 3: Kaplan Meier overall survival according to second-line chemotherapy: docetaxel vs. others

The relation between variables and survival of patients is shown in Table 3. The univariate analysis revealed higher risk of mortality accompanied with the age group 40-60 and stage IV. While in the multivariate analysis, stage IV had a higher risk of mortality (3.752) than stage III.

DISCUSSION

Our results showed that patients with advanced NSCLC have a higher risk of death mainly with stage IV disease and age between 40-60 years. Better prognosis was shown in cases of non-squamous histology, good nutritional status and in patients received platinum based as first-line treatment followed by taxanes.

The poor prognosis of squamous histology and male gender agrees with Di Maio et al ¹¹, whereas patients with poor performance status, advanced clinical stage, poor response to first-line chemotherapy, were males and the non-adenocarcinoma histology had worse outcome.

The bad prognosis obtained among patients of the age group 40-60 years was statistically significant in the univariate analysis, however, was contradictory to previous studies comparing adults to older ages. Some studies showed no difference in time to progression and OS between younger and elder patients (>70years) ^{12, 13}. Others obtained a higher risk of death in patients aged 65 and older ones ^{14, 15}. This discrepancy may be attributed to the small sample size of the current study.

The multivariate analysis in this study showed that patients with stage IV disease had a higher risk for death than stage IIIb which is consistent with other studies, whereas the initial clinical stage affects the success of second-line chemotherapy ^{11, 14}.

Table 3: Prognostic factors by Cox regression analysis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
< 40	Reference			Reference		
40-60	5.53	1.29 - 23.76	0.022	0.32	0.09 - 1.15	0.080
> 60	1.48	0.48 - 4.63	0.498	0.46	0.46 - 0.09	0.348
Gender						
Male	Reference					
Female	1.33	0.52 - 3.42	0.554			
Stage						
III	Reference			Reference		
IV	3.65	1.21 - 11.06	0.022	3.75	0.97 - 14.54	0.056
Palliative treatment						
No	Reference					
Yes	1.3	0.53 - 3.2	0.567			
Histological type						
Adenocarcinoma	Reference					
Squamous cell	0.59	0.22 - 1.58	0.295			
Body mass index						
Normal	Reference					
Underweight	1.68	0.27 - 10.53	0.578			
Overweight	0.73	0.13 - 4.04	0.721			

From our study we observed that patients who had received platinum based as first-line treatment followed by taxanes containing regimen as second-line treatment had a better prognosis than others. The taxanes added 3 months to the median survival which was statistically insignificant. Alike some studies reported increase in time to progression (10.6 vs. 6.7 weeks; $p < 0.001$) and median overall survival (7.0 vs. 4.6 months; $p = 0.047$) in patients receiving docetaxel *versus* best supportive care¹⁶. Noteworthy, Pemetrexed have been approved in second-line treatment with good tolerability but less effective in squamous histology when compared with docetaxel¹⁷⁻¹⁹.

Recently, docetaxel, erlotinib and gefitinib are considered as second-line options for NSCLC patients. Pemetrexed is given only to the non-squamous histology. As for *ALK* rearrangement who experience progression after crizotinib, chemotherapy or ceritinib is given in the second setting. Third line Chemotherapy treatment includes erlotinib if erlotinib or gefitinib were not given. There is limited data to support routine third line^{5, 6}.

Most of our patients (71.4%) received tramadol or morphine as palliative treatment A minority had palliative radiotherapy (28%), in the form of either whole brain irradiation (21%) or bone irradiation (7%).

Overall survival analysis indicates that when palliative treatment was initiated patients tend to have a higher risk for death. This can be justified by poor performance of these patients and accompanied with the advanced stage of disease whereas 28% was metastatic. Body mass index (BMI) is known to reflect the nutritional status, which is an important factor affecting the response to treatment and progression. Although it is

not significant, our findings demonstrated that patients with a lower BMI had higher risk of death, which is comparable to Dahlberg et al²⁰.

Our study was limited by being a single institutional retrospective study. Another limitation was the small number of cases. Moreover, molecular testing was not performed. Consequently, target therapy and immunotherapy were not offered to this group of patients.

Conclusion

Advanced NSCLC had a higher risk of death mainly with stage IV disease and age between 40-60 years. Non-squamous histology, good nutritional status and platinum-based first-line treatment followed by taxanes had better prognosis and outcome.

The poor response of second-line chemotherapy in NSCLC encourages introduction of targeted therapy and immunotherapy in this category of patients.

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