

RESEARCH COMMUNICATION

Prognostic Factors for Second-line Treatment of Advanced Non-small-cell Lung Cancer: Retrospective Analysis at a Single Institution

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Abstract

Background: Platinum-based chemotherapy for advanced non-small cell lung cancer (NSCLC) is still considered the first choice, presenting a modest survival advantage. However, the patients eventually experience disease progression and require second-line therapy. While there are reliable predictors to identify patients receiving first-line chemotherapy, very little knowledge is available about the prognostic factors in patients who receive second-line treatments. The present study was therefore performed. **Methods:** We retrospectively reviewed 107 patients receiving second-line treatments from August 2002 to March 2012 in the Dicle University, School of Medicine, Department of Medical Oncology. Fourteen potential prognostic variables were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival. **Result:** The results of univariate analysis for overall survival (OS) were identified to have prognostic significance: performance status (PS), stage, response to first-line chemotherapy, response to second-line chemotherapy and number of metastasis. PS, diabetes mellitus (DM), response to first-line chemotherapy and response to second-line chemotherapy were identified to have prognostic significance for progression-free survival (PFS). Multivariate analysis showed that PS, response to first-line chemotherapy and response to second-line chemotherapy were considered independent prognostic factors for OS. Furthermore, PS and response to second-line chemotherapy were considered independent prognostic factors for PFS. **Conclusion:** In conclusion, PS, response to first and second-line chemotherapy were identified as important prognostic factors for OS in advanced NSCLC patients who were undergoing second-line palliative treatment. Furthermore, PS and response to second-line chemotherapy were considered independent prognostic factors for PFS. It may be concluded that these findings may facilitate pretreatment prediction of survival and can be used for selecting patients for the correct choice of treatment.

Keywords: Non-small cell lung cancer - prognostic factors - second-line treatment

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Introduction

Lung cancer is the most common among cause of cancer deaths in both men and women in world. NSCLC represent between 80% to 85% of all the diagnosed lung cancers cases (Boyle et al., 2005). At the time of diagnosis, In two-third of patients with lung cancer is diagnosed in locally advanced or metastatic disease. The median survival time for advanced disease is 5.8 to 12.6 months and the overall 5-year survival rate among this patient population is still less than 10% (Shepherd, 1993; Hotta et al., 2007).

Systemic chemotherapy with the platinum-based doublets are still considered the first choice, which presents a modest survival advantage (Schiller et al., 2002; Azzoli et al., 2009). However, patients with advanced

NSCLC eventually experience disease progression and require second-line therapy. For second-line therapy ASCO and NCCN guidelines suggest docetaxel, pemetrexed, or erlotinib (Azzoli et al., 2009). Second-line therapy provides the median survival time of 5-8 months in selected patients (Hanna et al., 2004; Ciuleanu et al., 2012).

In spite of the clinical benefit of second-line treatments is often to observe toxic side effects. While there are reliable predictors to identify patients receiving first-line chemotherapy, very little knowledge is available about the prognostic factors in patients who receive second-line treatments. Prognostic factors are not sufficiently predictive of second-line treatment efficacy, while it may be concluded help that the choice of a treatment should be based according to prognostic factors.

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Table 1. The General Characteristics of the Patients

Characteristic	No. of patients (%)
Sex:	
Male	81 (75.7)
Female	26 (24.3)
Age, median (range)	54 (28-76)
Age:	
<65	91 (85.0)
≥65	16 (15.0)
Performance status:	
0-1	74 (69.2)
2-3	32 (29.9)
Unknown	1 (0.9)
Smoking history:	
Current or former	58 (54.2)
Never	20 (18.7)
Unknown	29 (27.1)
Weight loss:	
Yes	57 (53.3)
No	19 (17.7)
Unknown	31 (29.0)
DM:	
Yes	10 (9.3)
No	97 (90.7)
HT:	
Yes	15 (14.0)
No	92 (86.0)
Stage:	
IIIB	48 (44.9)
IV	59 (55.1)
Histology:	
Adenocarcinoma	48 (44.9)
Squamous	32 (29.9)
Large-cell carcinoma	4 (3.7)
Not specified	23 (21.5)
First-line chemotherapy regimen:	
GC	38 (35.5)
DC	29 (27.1)
PC	29 (27.1)
Others	11 (10.3)
Second-line chemotherapy regimen:	
TKIs	15 (14.0)
Docetaxel	20 (18.7)
Vinorelbin	4 (3.8)
Platinum-based doublets	68 (63.5)
Third-line chemotherapy regimen:	
Yes	23 (21.5)
No	84 (78.5)
Median OS (months)	6 (1-38)
Median PFS (months)	3 (1-18)

GC, Gemcitabine plus cisplatin; DC, Docetaxel plus cisplatin; PC, Paclitaxel plus cisplatin; TKIs, Tyrosine kinase inhibitor

The aim of this study was to investigate the prognostic factors for survival in patients with advanced NSCLC who patients receiving second-line treatments.

Materials and Methods

Patient Population

We retrospectively reviewed 107 patients receiving second-line treatments from August 2002 to March 2012 in the Dicle University, School of Medicine, Department of Medical Oncology.

They met the following inclusion criteria; 1) they had histologic or cytologic diagnosis of Stage IIIB or IV NSCLC; 2) they were 18 years or older in age; 3) receiving first-line platinum-based doublets chemotherapy; 4) they had to have measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST).

Factors Analyzed

Fourteen potential prognostic variables were chosen on the basis of previously published clinical trials. The variables were divided to categories: age (<65 or

Table 2. Univariate Analysis by Categorical Variable

Variable	Survival Time			PFS		
	Log-rank test value	Degrees of freedom	p	Log-rank test value	Degrees of freedom	p
Sex	0.2	1	0.59	1.7	1	0.18
Age	0.02	1	0.86	0.4	1	0.52
Stage	8.6	1	0.003	0.2	1	0.58
Smoking history	2.7	1	0.09	2.9	1	0.08
Performance status	15.7	1	<0.001	10.7	1	0.001
Histology	0.2	1	0.58	0.07	1	0.78
Weight loss	1.8	1	0.17	0.2	1	0.61
DM	0.4	1	0.51	4.8	1	0.02
HT	0.1	1	0.68	0.01	1	0.98
Response to first-line chemotherapy	10.4	1	0.001	2.3	1	0.001
Response to second-line chemotherapy	7.5	1	0.006	12.5	1	<0.001
Second-line chemotherapy	3.8	1	0.14	-	-	-
Third-line chemotherapy	1	1	0.3	-	-	-
Number of metastasis	6.5	1	0.01	0.6	1	0.42

≥ 65), gender (male or female), PS (0-1, 2-3), stage at diagnosis (IIIB or IV), histology (adenocarcinoma or non-adenocarcinoma), weight loss ≥5% with previous 3 months (present or absent), DM (present or absent), hypertension (HT) (present or absent), smoking history (present or absent), response to first-line chemotherapy (present or absent), response to second-line chemotherapy (present or absent), second-line chemotherapy (Erlotinib or docetaxel versus platinum-based doublets), third-line chemotherapy (present or absent), number of metastasis (<2 or ≥ 2).

Statistical Analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for windows). The differences of the clinical characteristics between the two groups were analyzed by chi-square test and student t test. OS was calculated from the start of the first cycle of chemotherapy to the date of death from any cause or the date of the last follow-up. PFS was defined as the time from the first day of chemotherapy till progression or death. PFS and OS were estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine statistical significant variables related to survival. Differences were assumed to be significant when P value of less than 0.05.

Results

Patient Characteristics

Between August 2002 to March 2012, 107 patients received a second-line treatment after failing a first-line cisplatin-based chemotherapy. The median age of patients was 54 years (range 28-76) with 81 (75.7%) males and 26 (24.3%) females. The number of patients with a PS score 0-1 was 74 (69.2%). Forty-eight (44.9%) were diagnosed as having stage IIIB and 59 patients (55.1%) had stage IV.

Table 3. Multivariate Analysis of Prognostic Factors

Factors	OR	%95 CI	P
PFS: PS	2.39	1.20-4.76	0.01
Response to second-line chemotherapy	0.43	0.22-0.82	0.01
OS: PS	2.94	1.34-6.43	0.007
Response to first-line chemotherapy	0.45	0.23-0.89	0.02
Response to second-line chemotherapy	0.45	0.22-0.91	0.02

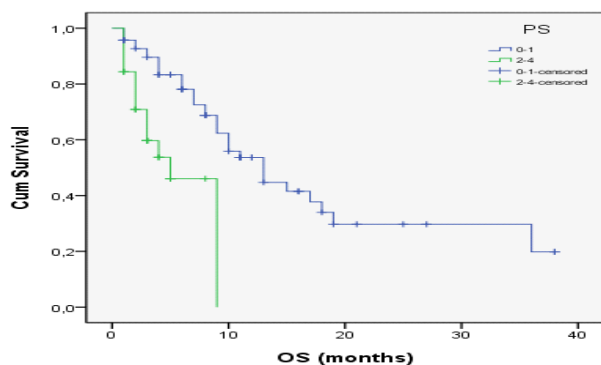


Figure 1. Survival of Patients According to Performance Status

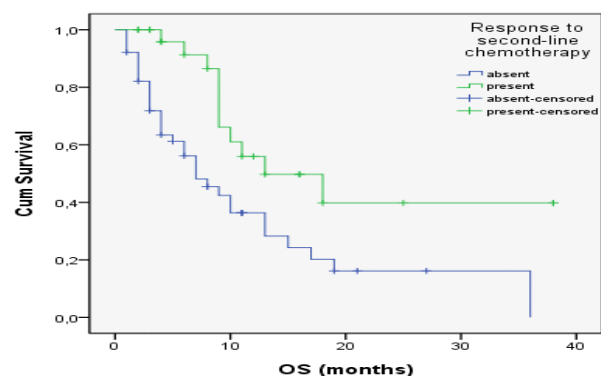


Figure 2. Survival of Patients According to Response to Second-line Chemotherapy

Adenocarcinoma was the most common histologic type (44.9% of patients). There was a significant association between sex and tumour histology: adenocarcinoma was more common than squamous cell carcinoma among women (73.1% and 7.7%, respectively).

Among patients receiving second-line therapy, median OS was 6 months and median PFS was 3 months. 23 patients (21.5%) received chemotherapy as a third-line therapy.

Prognostic Factor Analysis

The results of univariate analysis for OS are summarized in Table 2. Among the fourteen variables of univariate analysis, five variables were identified to have prognostic significance: PS ($p < 0.001$), stage ($p = 0.003$), response to first-line chemotherapy ($p = 0.001$), response to second-line chemotherapy ($p = 0.006$) and number of metastasis ($p < 0.001$).

The results of univariate analysis for PFS are summarized in Table 3. Among the fourteen variables of univariate analysis, four variables were identified to have prognostic significance: PS ($p = 0.001$), DM (p

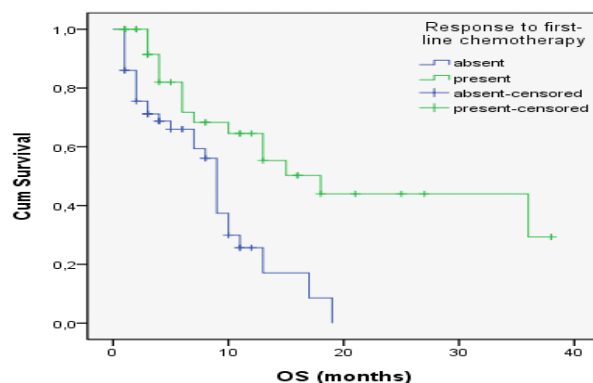


Figure 3. Survival of Patients According to Response to First-line Chemotherapy

$= 0.02$), response to first-line chemotherapy ($p = 0.001$) and response to second-line chemotherapy ($p < 0.001$).

Multivariate analysis included the prognostic significance factors in univariate analysis. The results of multivariate analysis are shown in Table 4. Multivariate analysis by Cox proportional hazard model showed that PS, response to first-line chemotherapy and response to second-line chemotherapy were considered independent prognostic factors for OS ($p = 0.007$, $p = 0.02$ and $p = 0.02$, respectively). Furthermore, PS and response to second-line chemotherapy were considered independent prognostic factors for PFS ($p = 0.01$ and $p = 0.01$, respectively).

Discussion

Platinum-based chemotherapy in advanced NSCLC is still considered the first choice, which presents a modest survival advantage (Schiller et al., 2002; Azzoli et al., 2009). However, these patients with advanced NSCLC eventually experience disease progression and require second-line therapy. While there are reliable predictors to identify patients receiving first-line chemotherapy, very little knowledge is available about the prognostic factors in patients who receive second-line treatments. In spite of the clinical benefit of second-line treatments is often to observe toxic side effects. Prognostic factors are not sufficiently predictive of second-line treatment efficacy, while it may be concluded help that the choice of a treatment should be based according to prognostic factors. The aim of this study was to investigate the prognostic factors for survival in the patients receiving second-line treatment.

The effects of response to first- and second-line treatment have not been clearly or consistently identified as a prognostic value for PFS and OS in patients receiving second-line treatment. The few prior studies (Wataya et al., 2009; Scartozzi et al., 2010; Zieteman et al., 2011) did not show any significant interaction between the response to previous treatment and OS. Contrary to this, based on the data of nine randomized trials (Maio et al., 2010) and two prospective study (Weiss et al., 2007; Maio et al., 2012) found that response to previous chemotherapy had a predictive value for survival in advanced NSCLC. We found that two characteristics of treatment were independently associated with OS: patients obtaining objective response during first- and second-line

treatment. More interestingly, patients obtaining objective response during second-line treatment were shown to be an independent prognostic factor of PFS. However, Zietemann et al. (2011) found that response of second-line treatment had no impact on PFS, but response to previous chemotherapy had a predictive value with regard to PFS.

A poor PS is usually accepted a negative prognostic factor for all cancer patients (Mitry et al., 2004; Krishnan et al., 2006; Kim et al., 2008). The importance of PS was also confirmed in advanced NSCLC patients who received second-line treatment (Weiss et al., 2007; Wataya et al., 2009; Scartozzi et al., 2010; Maio et al., 2012). The current study demonstrated that PS not only negative affected OS, but also affected PFS negatively.

Many patients who maintain a poor PS and no tolerate therapy due to significant toxicities will not receive third-line treatment. Life expectancy of patients with poor PS was substantially shorter than patients of a good PS.

It remains ambiguous whether stage at diagnosis in patients receiving second-line treatment will ensure prognostic knowledge for survival. The previously by many authors (Weiss et al., 2007; Di Maio et al., 2010; Scartozzi et al., 2010) had shown that stage at diagnosis had significant effect for survival, while Zietemann et al. (2011) and Maio et al. (2012) no observed a prognostic value of stage. In our study, stage at diagnosis was identified to have prognostic significance for OS in univariate analysis, but the trend did not reach statistical significance in multivariate analysis by Cox proportional hazard model. This result might be due to the small number of patients and difference of treatment choice

The present study has got some limitations. Firstly, its retrospective study. Secondly, we did not evaluate molecular characteristics of the tumor. Thirdly, there was the small number of patients.

In conclusion, PS, response to first and second-line chemotherapy were identified as important prognostic factors for OS in advanced NSCLC patients who were undergoing second-line palliative treatment. Furthermore, PS and response to second-line chemotherapy were considered independent prognostic factors for PFS. It may be concluded that these findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for the correct choice of treatment. Therefore, prospective and larger clinical trials are needed.

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