Impact of active smoking on survival of patients with metastatic lung adenocarcinoma harboring an epidermal growth factor receptor (*EGFR*) mutation

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ABSTRACT

Lung cancer in smokers and non-smokers demonstrates distinct genetic profiles, and cigarette smoking affects epidermal growth factor receptor (EGFR) function and causes secondary EGFR tyrosine kinase resistance. We evaluated the effect of active smoking in patients with metastatic lung adenocarcinoma. A total of 132 metastatic lung adenocarcinoma patients, diagnosed between 2008 and 2013, with known *EGFR* mutation status, were evaluated retrospectively. Among these patients, 40 had an activating *EGFR* mutation. Patients who continued smoking during the treatment were defined as active smokers. Former smokers and never smokers were together defined as non-smokers. The outcomes of the treatment in relation to the *EGFR* mutation and smoking status were evaluated. The median follow-up time was 10.5 months. The overall response rate for the first-line therapy was significantly higher among the *EGFR*-mutant patients ($p = 0.01$), however, smoking status had no impact on the response rate ($p = 0.1$). The *EGFR*-mutant active smokers progressed earlier than the non-smokers ($p < 0.01$). The overall survival (OS) of the non-smokers and patients treated with erlotinib was significantly longer ($p = 0.02$ and $p = 0.01$, respectively). Smoking status did not affect the OS in *EGFR* wild type tumors ($p = 0.49$) but *EGFR*-mutant non-smokers had a longer OS than the active smokers ($p = 0.01$). The active smokers treated with erlotinib had poorer survival than the non-smokers ($p = 0.03$). Multivariate analysis of *EGFR*-mutant patients showed that erlotinib treatment at any line and non-smoking were independent prognostic factors for the OS ($p = 0.04$ and $p = 0.01$, respectively). Smoking during treatment is a negative prognostic factor in metastatic lung adenocarcinoma with an *EGFR* mutation.

KEY WORDS: Lung adenocarcinoma; epidermal growth factor receptor; smoking
DOI: http://dx.doi.org/10.17305/bjbms.2016.1380 *Bosn J Basic Med Sci. 2016;16(4):280-285. © 2016 ABMSFBIH*

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common cause of cancer related deaths all over the world [1]. Smoking is the most important known risk factor for lung cancer. NSCLC may also develop in light smokers or never smokers. Ten percent of men and 20% of women who have NSCLC are never smokers and most of them have adenocarcinoma [2]. NSCLC in smokers has a different genetic profile and mutations are more frequent [3]. The cause and pathogenesis of NSCLC in non-smokers are still not clear.

The epidermal growth factor receptor (EGFR) pathway is one of the most important molecular pathways in NSCLC development and progression. The discovery of EGFR tyrosine kinase inhibitors (EGFR-TKIs) has changed NSCLC treatment algorithms. In previous studies, EGFR-TKIs, gefitinib and erlotinib, were found to be effective in Asian female non-smokers or former light smokers with adenocarcinoma [4,5]. It was realized that patients with these characteristics more frequently have activating *EGFR* mutations [6,7]. In accordance with this, tumors harboring activating *EGFR* mutations were more responsive to the EGFR-TKI treatment [8-10]. Smoker patients and males with lung adenocarcinoma may also

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Submitted: 10 May 2016/Accepted: 16 June 2016

harbor activating *EGFR* mutations. In a study on the frequencies of *EGFR* mutations in current smokers, former smokers, and males, the frequencies of the mutations were 6%, 15%, and 19% respectively [11].

Smoking is a negative prognostic factor for NSCLC. Kawaguchi et al [12] demonstrated in two separate analyses that never smokers had a longer overall survival (OS) and that never smoking was a good, independent prognostic factor for NSCLC. Smoking affects tumor biology and pharmacokinetics and pharmacodynamics properties of the drugs [13,14]. Therefore smoking may affect the response to treatment and survival outcomes of patients with metastatic lung adenocarcinoma.

We retrospectively reviewed our patients' data to define prognostic importance of smoking in metastatic lung adenocarcinoma patients according to the *EGFR* mutation status.

MATERIALS AND METHODS

Patients

One hundred thirty-two patients diagnosed with metastatic lung adenocarcinoma between 2008 and 2013, with known *EGFR* gene mutation status, were reviewed retrospectively. Demographic and clinical information of the patient age at diagnosis, smoking status, gender, the Eastern Cooperative Oncology Group (ECOG) performance status, chemotherapy, metastatic sites, and responses to the treatment according to the Response Evaluation Criteria in Solid Tumor (RECIST) were obtained from the patient records. Disease control rate (DCR) was defined as proportion of patients with complete response (CR), partial response (PR), and stable disease (SD), and objective response rate (ORR) was defined as proportion of CR and PR with the best response to the first-line chemotherapy. Patients who continued smoking during the treatment were defined as active smokers. Patients who stopped smoking before the diagnosis, former smokers, patients who smoked less than 100 cigarettes in their life time, and never smokers were together defined as non-smokers. Progression-free survival (PFS) for the first-line treatment was calculated from the start of therapy to the date of clinical or radiologic progression, and the OS was calculated from the start of therapy to the date of death from the disease or last follow-up. This retrospective analysis was approved by the Institutional Review Board.

Molecular methods

DNA was isolated from the primary tumor tissues of all the patients with the QIAamp® DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). The therascreen® EGFR RGQ PCR Kit (Qiagen) was used for the *EGFR* analysis.

Statistical analysis

The relationship between non-parametric variables was studied by the Chi-square test. Parametric variables were compared with the independent-sample *t*-test. Survival estimates were calculated by using the Kaplan-Meier method. The log-rank test was used to compare survival estimates. A p value <0.05 was considered as statistically significant.

RESULTS

A total of 132 metastatic lung adenocarcinoma patients were included in the study. Thirty (22.7%) patients were male. Forty patients (30.3%) had an activating *EGFR* mutation. Among these 40 patients, 26 had a deletion in the exon 19 and 14 patients had a mutation in the exon 21. The median age of the patient population was 59 (28-80) years. Baseline characteristic features of the *EGFR*-mutant and wild type patients were similar except the sex and smoking status (Table 1). The *EGFR* mutations were significantly more frequent among the females and non-smokers ($p < 0.01$ and $p < 0.01$, respectively).

At the first-line therapy, 7 patients had been treated with erlotinib and the other 125 patients had been treated with platinum-based chemotherapy. Thirty patients, 7 at the first-line and 23 at the second-line therapy, with the tumor harboring an *EGFR* mutation, received erlotinib. One CR, 32 PRs, 59 SDs, and 40 progressive diseases were observed as the best responses to the first-line chemotherapy. The ORR in the tumor with an *EGFR* mutation and wild type tumor were 40.0% and 19.6% ($p = 0.01$) respectively, and the DCR was 80% and 65.2% ($p = 0.09$) respectively. When we excluded the patients who received erlotinib at the first-line therapy, the ORR was still significantly higher in the *EGFR*-mutant patients than in the *EGFR* wild type patients (39.4%, $p = 0.02$). Smoking status did not affect the ORR at the first-line therapy ($p = 0.10$). The active smokers and non-smokers had similar ORR among the patients with the tumor harboring an *EGFR* mutation and wild type tumor ($p = 0.20$ and $p = 0.94$, respectively).

The median follow-up time was 10.5 (2.2-38.5) months. At the time of data analysis, 105 disease progressions (34 mutant and 71 wild type) occurred and 85 patients died of lung cancer (27 mutant and 58 wild type). The median PFS was 6.6 (95% confidence interval [CI]; 5.73-7.5) months. The PFS was similar in the *EGFR*-mutant and wild type patients, 7.1 and 6 months respectively ($p = 0.24$). Although smoking status had no impact on the PFS in all patients ($p = 0.21$), the *EGFR*-mutant active smokers progressed significantly earlier than the non-smokers (4.6 months vs. 10 months, $p < 0.01$). Active smoking did not affect the PFS in the *EGFR* wild type patients (6.0 vs. 7.1, $p = 0.49$). The age, sex, and the presence of

metastasis in more than one organ, were not associated with the PFS (Table 2).

TABLE 1. Comparison of clinical features in *EGFR*-mutant and wild type patients

	EGFR-mutant n (40)	*EGFR* wild type n (92)	*p* value
Age (median)	57.5 (35-78)	59.5 (28-80)	0.25
65<	27 (67.5%)	66 (71.7%)	0.68
65≥	13 (32.5%)	26 (28.3%)	
Gender			
Male	19 (47.5%)	83 (90.2%)	<0.001
Female	21 (52.5%)	9 (9.8%)	
ECOG PS			
Good (ECOG 0-1)	33 (82.5%)	81 (88.0%)	0.39
Poor (ECOG 2)	7 (17.5)	11 (12.0%)	
Erlotinib at any line			
Yes	30 (75.0%)		
No	10 (25.0%)		
Site of metastasis			
Single	23 (57.5%)	66 (71.7%)	0.11
Multiple	17 (42.5%)	26 (28.3%)	
Brain metastasis			
Yes	6 (15.0%)	13 (14.1%)	0.89
No	34 (85.0%)	79 (85.9%)	
Liver metastasis			
Yes	5 (12.5%)	13 (14.1%)	0.80
No	35 (87.5%)	79 (85.9%)	
Smoking status			
Active smoker	12 (30.0%)	62 (67.4%)	<0.001
Non-smoker	28 (70.0%)	30 (32.6%)	

ECOG PS: The Eastern Cooperative Oncology Group performance scale

In the multivariate analysis of all patients, none of the factors appeared as an independent prognostic factor for the PFS (data not shown). However, in the multivariate analysis of *EGFR*-mutant patients active smoking was associated with a worse PFS (hazard ratio [HR]: 0.33; 95% CI; 0.13-0.79, $p = 0.01$).

The median OS was 13.1 (95% CI; 11.71-14.57) months. The OS was similar in the *EGFR*-mutant and wild type patients, 15.2 and 12.7 months respectively ($p = 0.13$) (Figure 1A). The OS was significantly longer in the non-smokers than in the active smokers ($p = 0.02$) (Figure 1B). The patients treated with erlotinib at any line also lived significantly longer than the patients who were not treated with erlotinib ($p = 0.01$) (Table 2). In the multivariate analysis of all patients, the treatment with erlotinib at any line was associated with longer survival (HR: 0.50; 95% CI 0.30-0.85, $p = 0.01$).

The smoking status did not affect the OS in the *EGFR* wild type tumors (7.1 months vs. 6.0 months, $p = 0.49$). The active smokers and non-smokers had similar OS outcomes in *EGFR* wild type tumors (12.7 months vs. 13.3 months, $p = 0.87$). The OS of *EGFR*-mutant non-smokers was significantly longer than in the active smokers (22.3 months vs. 7.0 months, $p = 0.01$) (Figure 2A). The OS of active smokers was also worse than in the former smokers (7 months vs. 15.2 months, $p = 0.02$).There was no significant survival difference between the former smokers and never smokers (15.2 months vs. 22.3 months, $p = 0.94$)

TABLE 2. Progression-free survival (PFS) and overall survival (OS) of all patients according to prognostic factors

	Median PFS[a] (months) (CI 95%)	*p* value[b]	Median OS[a] (months) (CI 95%)	*p* value[b]
Overall	6.6 (5.73-7.5)		13.1 (11.71-14.57)	
Age				
65<	6.6 (5.43-7.84)	0.75	14 (9.93-18.25)	0.79
65≥	6.8 (5.00-8.66)		12.7 (10.20-15.22)	
Gender				
Male	6 (4.70-7.29)	0.31	12.6 (10.86-14.37)	0.06
Female	7.1 (4.64-9.68)		14 (7.47-20.71)	
EGFR				
Mutant	7.1 (5.35-8.96)	0.24	15.2 (10.25-20.23)	0.13
Wild type	6 (5.73-7.22)		12.7 (11.12-14.30)	
Site of metastasis				
Single	6.9 (5.85-8.07)	0.4	13.3 (12.03-14.70)	0.87
Multiple	5.9 (4.02-7.87)		13.1 (9.22-17.05)	
Brain metastasis				
Yes	4.6 (2.68-6.51)	0.23	8.1 (5.52-19.59)	0.33
No	6.9 (5.90-8.02)		13.14 (11.80-14.47)	
Liver metastasis				
Yes	5.9 (4.61-7.84)	0.10	15.9 (9.54-22.26	0.76
No	6.4 (5.35-7.52)		13.1 (11.63-14.52)	
ECOG PS				
Good (ECOG 0-1)	6.6 (5.51-7.75)	0.93	13.3 (11.66-15.08)	0.96
Poor (ECOG 2)	6 (4-67-7.32)		13.14 (10.08-16.20)	
Smoking status				
Active smoker	5.9 (4.88-7.01)	0.21	12.3 (10.98-13.78)	0.02
Non-smoker	7.1 (6.28-8.03)		15.2 (9.55-20.93)	
First-linetherapy				
Chemotherapy	6.3 (5.09-7.58)	0.03		
Erlotinib	23.4 (not reached)			
Erlotinib at anyline				
No			12.3 (10.25-14.51)	0.01
Yes			15.9 (10.11-21.69)	

CI: Confidence interval, [a]Kaplan-Meier method, [b]Log-rank test

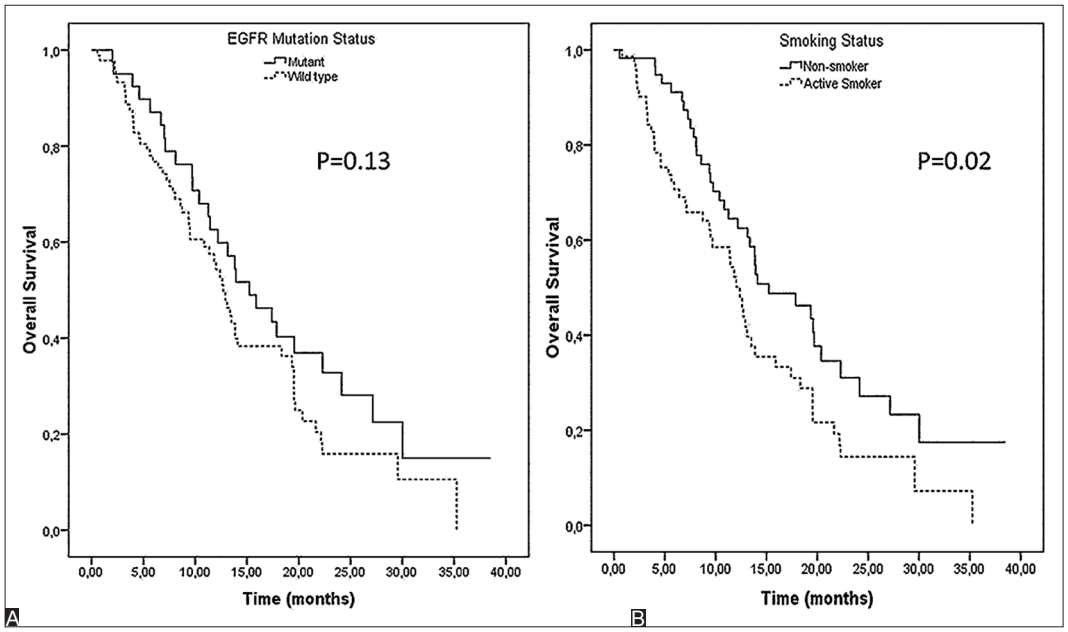

FIGURE 1. (A) Survival outcomes of all patients according to *EGFR* mutation status (wild and mutant types) (B) Survival outcomes of all patients according to smoking status (non-smokers and active smokers).

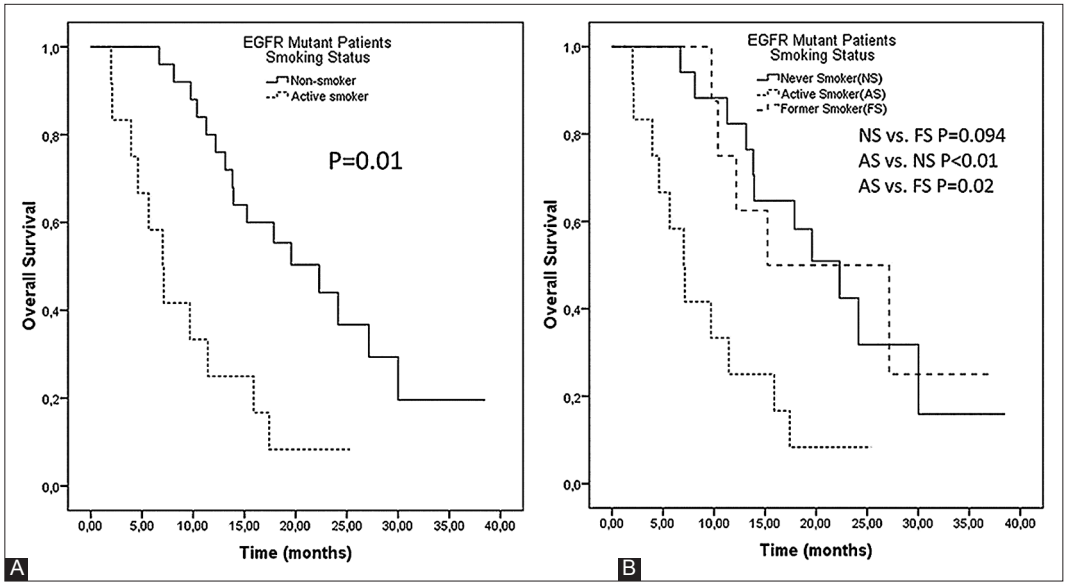

FIGURE 2. (A) Survival outcomes of *EGFR*-mutant patients according to smoking status (non-smokers and active smokers) (B) Survival outcomes of *EGFR*-mutant patients according to smoking status (never, active, and former smokers).

(Figure 2B). Using erlotinib at any line provided significant OS benefit in all *EGFR*-mutant patients (17.8 months vs. 6.7 months, $p < 0.01$). However, in the *EGFR*-mutant patients who were treated with erlotinib, active smoking was related to poor OS (9.6 months vs. 22.3 months, $p = 0.03$). In the multivariate analysis of *EGFR*-mutant patients, the treatment with erlotinib (HR: 0.38; 95% CI; 0.15-0.95, $p = 0.04$) and non-smoking (HR: 0.33; 95% CI; 0.14-0.78, $p = 0.01$) were associated with longer OS.

DISCUSSION

In this study, we showed that active smoking has a negative impact on the survival of metastatic lung adenocarcinoma patients who have an activating *EGFR* mutation. We could not find any impact of active smoking on the survival of the patients with the *EGFR* wild type tumor.

Lung adenocarcinoma in smokers and never smokers has different genetic properties. Govindan et al. [3] performed a whole-genome analysis of 17 NSCLC (16 adenocarcinoma, 1 large cell carcinoma) tissue samples. They reported that smokers had significantly more mutations and that the mutation spectrum in smokers and never smokers was different. *EGFR* mutations, anaplastic lymphoma kinase (*ALK*) fusions, and proto-oncogene tyrosine-protein kinase (*ROS1*) were detected in non-smokers and smokers, while tumor protein p53 (*TP53*), V-Ki-ras2 Kirsten rat sarcoma viral oncogene

homolog (*KRAS*), proto-oncogene B-Raf (*BRAF*), Janus kinase 2 (*JAK2*), *JAK3*, and mismatch repair gene mutations were detected in smokers.

The amount of smoked cigarettes is associated with *EGFR* mutation incidence. In a study from Korea, *EGFR* mutation incidence was significantly lower in patients smoking more than 25 pack-years. The *EGFR* mutation in the exon 20 was more common in smokers, whereas the exon 19 or 21 mutations were related to low exposure to cigarette smoke [15].

The response rates of the tumors with *EGFR* mutations to chemotherapy are high [16,17]. Consistent with the current literature, in our study the ORR was significantly higher in the *EGFR*-mutant patients. However, active smoking did not affect the ORR in both *EGFR*-mutant and wild type patients.

An analysis of 26,957 NSCLC patients with all stages of the disease, showed that smoking status was an independent prognostic factor for OS [12]. In our study, the active smokers had a significantly worse OS (p = 0.02). The active smokers and non-smokers with the wild type tumor had similar survival outcomes (p = 0.87).This finding suggests that despite distinctive genetic profiles, platinum based chemotherapies may have a similar effect on both active smokers and non-smokers with *EGFR* wild type lung adenocarcinoma. Ferketich et al. [18] analyzed 4200 NSCLC patients. They found that in NSCLC stages I, II, and III, current smokers had worse survival than young never smokers (<55 years) with stage IV NSCLC. In addition, the current smokers had worse survival than patients who stop smoking more than 12 months before the diagnosis. Although the authors did not evaluate the tumor biology, they proposed that the tumor biology may cause this survival difference. In our study, we stratified the patients according to the *EGFR* mutation status and we found that the non-smokers with the tumor harboring an *EGFR* mutation had significantly longer OS than the active smokers (p = 0.01).

The EGFR-TKI therapy does not provide OS benefit, but it provides PFS benefit in *EGFR*-mutant patients [17]. In our study, we found that the non-smokers with the tumor harboring an *EGFR* mutation live longer than the active smokers. In the multivariate analysis of the *EGFR*-mutant patients, the smoking status and EGFR-TKI treatment were associated with significant improvement of the OS. The active smokers who received EGFR-TKIs had a worse OS outcome than the non-smokers.

Oxidative stress created by cigarette smoke in lung epithelial cells causes an aberrant activation of EGFR and impairs the receptor degradation. This subsequently leads to uncontrolled cell growth and oncogenesis. Moreover, the aberrant activation of EGFR by cigarette smoke cannot be inhibited with EGFR-TKIs [19,20]. In addition to this resistance mechanism, active smoking also decreases the exposure to erlotinib by increasing the clearance of erlotinib [21]. In a clinical pharmacokinetic study, the clearance of erlotinib was 24% faster in active smokers than in never and former smokers [22]. In our study, the active smokers had a worse survival than the non-smokers.

All patients, especially patients who were treated with EGFR-TKIs, must be informed about negative effects of smoking on survival outcomes. Active smokers should be encouraged to stop smoking.

In a recent study, Kim et al. [23] showed that smoking more than 30 pack-years has a negative impact on the survival results of patients with lung adenocarcinoma harboring an activating *EGFR* mutation treated with an EGFR-TKI. Smoking history has been taken into account in nearly all studies that evaluated the efficacy of EGFR-TKIs in NSCLC [24]. A meta-analysis of 9 studies showed that after TKI treatment, PFS of non-smokers was longer than in ever smokers among advanced NSCLC patients with an *EGFR* mutation [25]. However, there is not a standard definition of smoking history. In most trials, patients who had not been considered as current and former smokers were defined as never smokers. In some of the studies, current smokers and former smokers had been included in an ever smoker group. This may create a confusion in evaluating the effect of smoking status on the response and survival outcomes [24]. Generally, in these studies former smokers and active smokers have been compared to never smokers [26-28]. This approach may obscure the acute effects of smoking on the treatment. In the present study, we demonstrated the impact of active smoking on the survival. Separate analyses of active smokers and former smokers may give more reliable results.

The main limitation of the study was its retrospective design. Smoking history is subjective data obtained from patients. Occasionally, patients may not give the exact data about past smoking or may misinform physicians about active smoking habits and passive smoking. Incorporation of objective measures, such as cotinine levels, may give reliable smoking data in studies evaluating the effects of active smoking on the treatment [29]. Other smoking-related comorbidities, such as cardiovascular diseases and decreased lung capacity, may also interfere with the treatment efficacy. However, we could not evaluate these factors because of the retrospective nature of the study.

In conclusion, we found that active smoking is related to shorter OS in patients with metastatic lung adenocarcinoma harboring an *EGFR* mutation. Smoking status may not have an impact on objective chemotherapy response rates. These patients, especially patients treated with EGFR-TKIs, should be strongly encouraged to stop smoking.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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