

Impact of heavy smoking on the benefits from first-line EGFR-TKI therapy in patients with advanced lung adenocarcinoma

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Abstract

Smoking is a risk factor for nonsmall cell lung carcinoma (NSCLC) and is associated with a lower response to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI). The purpose of this study is to examine the impact of the smoking status on the benefits from first-line EGFR-TKI in NSCLC patients with EGFR mutation.

This was a retrospective study of 159 patients with advanced NSCLC treated at the Beijing Hospital between January 2011 and December 2016. The follow-up was censored on December 2017. EGFR mutation status, smoking (nonsmoker vs <30 packs/year (light smoker) vs ≥30 packs/year (heavy smoker)), treatment, treatment response, and progression-free survival (PFS) were collected from the charts.

Median follow-up was 10.0 (1.0–36.6) months. Response rate was lower in heavy smokers compared with nonheavy smokers (19.0% vs 71.7%, $P < .001$). There was no difference in PFS between nonsmokers (median, 10.5 months) and light smoker (median, 11.0 months), and these 2 groups were pooled together. PFS was longer in nonheavy smokers compared with heavy-smokers (median, 10.7 vs 6.0 months, $P < .001$). Smoking ≥30 packs/year (HR=2.48, 95% CI: 1.55–3.98, $P < .001$) was associated with PFS.

In patients with advanced NSCLC, the benefits and PFS of EGFR-TKI were better for nonheavy smokers than for heavy smokers.

Abbreviations: CR = complete remission, EGFR = epidermal growth factor receptor, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitors, NSCLC = nonsmall cell lung carcinoma, PFS = progression-free survival, PR = partial remission, RECIST = Response Evaluation Criteria In Solid Tumor, RR = response rate, TFS = tumor-free survival, TKI = tyrosine kinase inhibitor.

Keywords: chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibitors, nonsmall cell lung carcinoma, smoking, survival

1. Introduction

Lung cancer is one of the most frequent cancers worldwide, and is associated with high morbidity and mortality.^[1] Nonsmall cell lung carcinoma (NSCLC) represents 85% to 90% of the cases.^[2] NSCLC mostly affects adults aged ≥65 years^[2] and have a predominance toward males.^[3] Smoking is the most important cause of lung cancer.^[2] Clinical studies found that the pathogenesis, clinical manifestation, and prognosis of smokers and nonsmokers are different.^[4–6]

Genetic differences have been found in the tumors of nonsmokers versus smokers.^[7–9] Indeed, nonsmokers with lung cancer are more

likely to carry epidermal growth factor receptor (EGFR) mutations, mostly in exons 19 and 21,^[7,10] but other mutations are also known (such as in exons 18 and 20).^[11,12] About 10% of lung tumors in the United States harbor an EGFR mutations, compared with 35% in East Asians.^[13,14] The presence of EGFR mutations is a key predictor of the efficacy of EGFR-tyrosine kinase inhibitors (TKI).^[15,16] Nevertheless, EGFR-TKI drugs are not effective for all patients with EGRF gene sensitive mutation and NSCLC and a number of factors are associated with a better response to EGFR-TKI: East Asian ethnicity, female sex, never-smoking status, adenocarcinoma histology, EGFR mutations, and high EGFR protein expression.^[17,18]

Smoking is related to lower rates of EGFR mutations and poor outcomes.^[7,8] Igawa et al^[19] showed that among patients harboring activating EGFR mutations, the response to gefitinib was higher among nonsmokers compared to smokers. Meta-analyses revealed better survival with erlotinib or gefitinib in never smokers compared to smokers.^[20,21] Smoking status also affects the response to conventional chemotherapy, with nonsmokers achieving better response rates to pemetrexed than smokers.^[22] Nevertheless, the predictors of response to EGFR-TKI remain controversial.^[23] Therefore, improving the prediction of the efficacy of EGFR-TKI drugs is a current problem needing to be solved. In addition, previous studies suffer from heterogeneity in EGFR-TKI, disease stage, and line of treatment.

Therefore, the aim of the present study was to examine the impact of the smoking status on the benefits from first-line EGFR-TKI in NSCLC patients with EGFR mutation. The results could help selecting the patients who would benefit the most from treatments.

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Table 1**Characteristics of the patients.**

	Nonsmokers, n=120	<30 packs/y, n=18	≥30 packs/y, n=21	P (3 groups)	P (<30 vs ≥30 packs/y)
Age, y	63.5±11.7	61.7±13.8	67.1±7.5	.301	.157
Gender				<.001	<.001
Male	26 (21.7%)	17 (94.4%)	20 (95.2%)		
Female	94 (78.3%)	1 (5.6%)	1 (4.8%)		
EGFR mutation				.234	.145
Exon 19	68 (56.7%)	10 (55.6%)	8 (38.1%)		
Exon 21	49 (40.8%)	7 (38.9%)	11 (52.4%)		
Others	3 (2.5%)	1 (5.6%)	2 (9.5%)		
Metastasis at diagnosis					
Pleural	48 (40%)	6 (33.3%)	5 (23.8%)	.345	.176
Brain	25 (20.8%)	6 (33.3%)	2 (9.5%)	.201	.250
Bone	44 (36.7%)	8 (44.4%)	7 (33.3%)	.758	.701
Lymph node	15 (12.5%)	4 (22.2%)	4 (19%)	.347	.511
Response				<.001	<.001
PR	86 (71.7%)	12 (66.7%)	4 (19%)		
SD	32 (26.7%)	5 (27.8%)	13 (61.9%)		
PD	2 (1.7%)	1 (5.6%)	4 (19%)		

EGFR=epidermal growth factor receptor, PD=progressive disease, PR=partial response, SD=stable disease.

2. Methods

2.1. Study design and patients

This was a retrospective study of 159 patients with advanced NSCLC treated at the Beijing Hospital between January 2011 and December 2016. The inclusion criteria were: unresectable, locally advanced, and/or recurrence or metastasis of NSCLC; stage IIIB/IV NSCLC; known EGFR mutation status; first-line treatment (either erlotinib or gefitinib); complete baseline data; and complete follow-up data. NSCLC and EGFR mutation status were confirmed using specimens obtained by surgery, fiber-optic bronchoscopy, needle biopsy, pleural effusion analysis, or biopsy of metastatic lymph node or metastasis. The study was approved by the ethics committee of the Beijing Hospital. The need for individual consent was waived by the committee because of the retrospective nature of the study.

2.2. Data collection

Nonsmokers were defined as a lifetime smoking of <100 cigarettes. For smokers, 30 packs/year was used to discriminate between light and heavy smokers.^[24–26] The EGFR mutation status had been tested routinely and data were obtained from the medical charts.

All patients received EGFR-TKIs (either erlotinib or gefitinib) as first-line treatment until disease progression or occurrence of intolerable toxicity. Treatment benefits were evaluated according to the Response Evaluation Criteria In Solid Tumor (RECIST).^[27] The response rate (RR) represented the complete remission (CR) rate plus the partial remission (PR) rate. Progression-free survival (PFS) was determined as the time between start of treatment and any progression. The follow-up was censored on December 2017.

2.3. Statistical analysis

Continuous data were presented as mean±standard deviation and analyzed using ANOVA and the Tukey post hoc test. Categorical data were presented as proportions and analyzed using the Chi-square or Fisher exact test, as appropriate. All statistical analyses were performed with SPSS 17.0 (IBM,

Armonk, NY). The Kaplan–Meier method and the log-rank test were used to analyze the PFS. The Cox hazard model was used for the univariate analysis of risk factors for PFS. Two-sided *P* values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the patients

There were 120 nonsmokers, 18 light smokers, and 21 heavy smokers, all with an EGFR mutation. Table 1 presents the characteristics of the patients with an EGFR mutation. The age ranged from 29 to 89 years (median, 63 years). There were no differences in age, mutation, and metastases at NSCLC diagnosis among the 3 groups, but female gender was more frequent in the nonsmoker group (*P*<.001) and treatment response was better in the nonsmoker and <30 packs/year groups (*P*<.001). Smoking had no impact on the type of EGFR mutation (*P*=.145).

3.2. Comparison of first-line EGFR-TKI therapy benefits for nonsmokers and smokers

Median follow-up was 10.0 (1–36.6) months. Response rate was lower in heavy smokers compared with nonheavy smokers (19.0% (4/21) vs 71.7% (86/120), *P*<.001). There was no difference in PFS between nonsmokers (median, 10.5 months) and light smoker (median, 11.0 months), and these 2 groups were pooled together. PFS was longer in nonheavy smokers compared with heavy smokers (median, 10.7 vs 6.0 months, *P*<.001) (Fig. 1).

3.3. Cox hazard analysis

Table 2 presents the Cox hazard analysis. Smoking ≥30 packs/year (HR=2.48, 95% CI: 1.55–3.98, *P*<.001) was associated with PFS. Since no other factor was associated with PFS on univariate analysis, no multivariate analysis could be performed.

4. Discussion

Smoking is a risk factor for NSCLC^[2] and is associated to a lower response to EGFR-TKI.^[20,21] Nevertheless, the predictors of

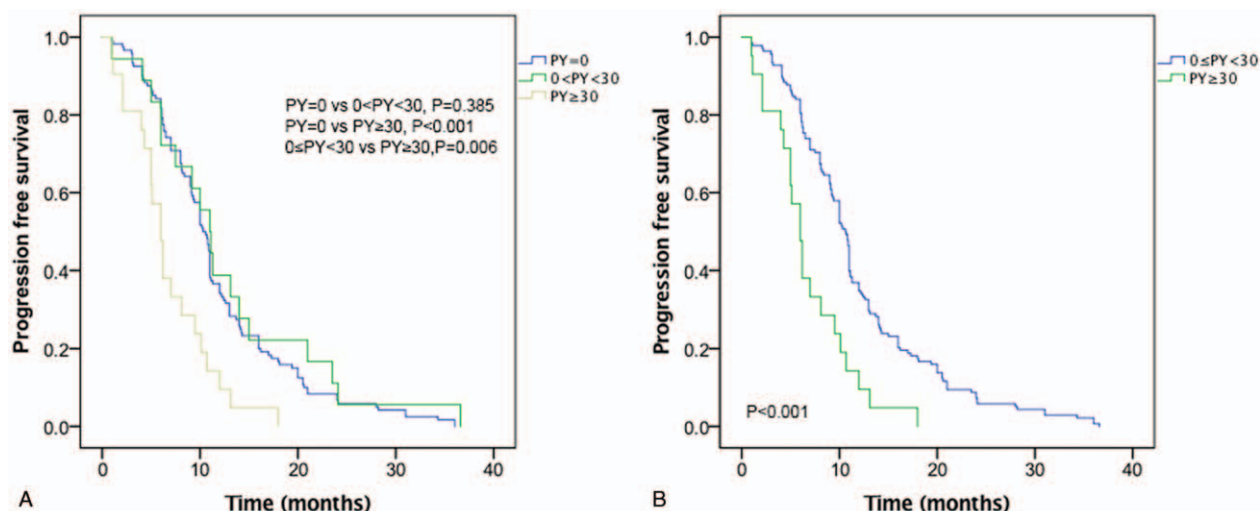


Figure 1. Progression-free survival. (A) Nonsmokers versus <30 packs/year versus ≥30 packs/year ($P < .001$). (B) <30 packs/year versus ≥30 packs/year ($P < .001$).

response to EGFR-TKI remain controversial.^[23] Therefore, improving the prediction of the benefits from EGFR-TKI drugs is a current problem needing to be solved. In addition, previous studies suffer from heterogeneity in the EGFR-TKI, disease stage, and line of treatment. Therefore, the present study aimed to examine the impact of the smoking status on the benefits from first-line EGFR-TKI in NSCLC patients with EGFR mutation. The results showed that in patients with advanced NSCLC, the benefits and PFS of EGFR-TKI were better for nonheavy smokers than for heavy smokers, which is supported by a Korean study.^[26]

Smoking is the main risk factor for lung cancer.^[2] The pathological type found among nonsmokers is mostly adenocarcinoma, while squamous cell carcinoma and small cell lung cancer are very rare.^[2] Furthermore, there are significant differences in the gene mutation patterns between smoking and nonsmoking lung cancer patients.^[7-9] The frequency of EGFR gene mutation is higher for nonsmokers with lung adenocarcinoma than for smokers.^[7,10] In lung cancer, KRAS mutations are present in 15% to 25% of patients with lung cancer,^[28] but they are rare in lung squamous carcinoma,^[28] tumors harboring mutations in EGFR or ALK, and in East

Asians.^[29,30] In addition, KRAS mutations are even rarer in never-smoker lung cancer patients versus former/current smokers.^[7,9,29-32] The exact prognostic impact of KRAS mutations is poorly known, but KRAS mutations are negative predictors of radiologic response to EGFR tyrosine kinase inhibitors.^[33,34] In addition, some studies have reported that PD-L1 expression is different between smoking and nonsmoking lung cancer patients.^[35] Lung cancer PD-L1 expression is significantly higher in smokers,^[36,37] but this is controversial.^[38,39] Nevertheless, a recent meta-analysis showed that PD-L1 expression was associated with poor survival of patients with lung cancer.^[40] Taken together, KRAS mutations and PD-L1 expression could be involved in the impact of smoking on lung cancer survival, but additional studies are necessary to examine these factors in relation to heavy smoking.

Studies showed that nonsmoking Asian females have more benefits from EGFR-TKI compared with the other groups.^[17,18] The IPASS study showed that smoking history and pathological types are independent factors affecting gene mutation,^[41] as confirmed by the PIONEER study.^[10] The present study examined the impact of smoking status and gender on EGFR mutations and found that there was no significant difference in

Table 2
Univariate analysis of PFS among patients with EGFR-mutated NSCLC treated with an EGFR-TKI.

Risk factors	HR	95% CI		P
		Lower	Upper	
Age ≥63 (based on the median)	1.009	0.995	1.023	.212
≥30 packs/y	2.482	1.548	3.977	<.001
Male	0.777	0.564	1.071	.124
Metastasis at diagnosis				
Pleural	0.924	0.668	1.278	.633
Brain	1.303	0.885	1.918	.180
Bone	1.124	0.814	1.553	.478
Lymph node	1.279	0.819	1.997	.280
Type of mutation	1.252	0.957	1.639	.101

CI=confidence interval, HR=hazard ratio.

the EGFR mutations within the same smoking status, regardless of gender. The results by Girard et al.^[42] also suggested that the most important predictor of EGFR mutation is the smoking index, while gender was not an independent predictor, as in the present study.

In the IPASS study,^[41] the objective response rate of gefitinib in patients with EGFR mutation was up to 71.2%, while for EGFR patients without mutations, it was only 1.1%. EGFR mutation is a strong predictor of tumor response. Nevertheless, EGFR-TKIs are not equally effective for all NSCLC patients with EGFR gene sensitive mutation.^[17,18] Nonsmoking lung cancer patients have higher EGFR mutation rate.^[7,10] Although many EGFR mutations are found in nonsmokers with adenocarcinoma, a significant proportion of patients with smoking history have mutated EGFR. In the present study, the effective rate of EGFR-TKI for different smoking statuses was analyzed, and the results showed that the effective rates of nonheavy smokers and heavy smokers with EGFR sensitive mutation were 71.8% and 18.8% respectively, showing a significant difference. The median PFS for nonheavy smokers and heavy smokers were 10.8 and 6.2 months, respectively, and the difference was statistically significant. Therefore, EGFR-TKIs have different efficiency in nonheavy smokers and heavy smokers. Compared with heavy smokers, nonheavy smokers with EGFR mutation had a higher effective rate and longer PFS after first-line TKI therapy.^[26] A previous study of 153 NSCLC patients with EGFR mutation showed that the overall response rate and tumor-free survival (TFS) for smokers and non-smokers were 66.7% and 9 months, and 10.7% and 5.4 months, respectively ($P=.0002$),^[19] but this is controversial. Indeed, Zeng et al.^[23] reported that the median PFS of patients receiving first-line EGFR-TKI was similar, regardless of smoking status (nonsmokers vs smokers: 9.9 vs 9.1 months, $P=.570$). The present study showed that smoking alone had no impact of PFS, but that the dose of cigarettes (>30 packs/year) is an independent factor associated with PFS. Therefore, it is possible that not only the smoking status is associated with EGFR-TKI response, but also the amount of cigarette smoke, as supported by Kim et al.^[26] In addition, Jain et al.^[43] showed that the mutation patterns were different between light and heavy smokers. Nevertheless, these results will have to be confirmed in future studies.

The present study is not without limitations. The sample size was small and from a single center. In addition, the retrospective nature of the study limited the data that could be analyzed. Among others, data about smoke exposure in nonsmokers (from cooking, heating, work, etc.) were not available. Additional studies are necessary to understand the risk factors for lung cancer and the factors associated with a better response to EGFR-TKI.

In conclusion, in patients with advanced NSCLC, the benefits and PFS of EGFR-TKI were better for nonheavy smokers than for heavy smokers.

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