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ORIGINAL ARTICLE

Smokers having Activating EGFR Mutant Non-Small Cell Lung Cancer Might Benefit from EGFR-TKI Treatment – Single-Center Experience

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OBJECTIVE

This study aims to evaluate the predictive impacts of cigarette smoking on treatment outcomes of EGFR tyrosine kinase inhibitors (TKIs) in Non-Small Cell Lung Cancer (NSCLC) patients with activating EGFR mutations.

METHODS

We retrospectively evaluated the data of 46 patients with metastatic NSCLC (adenocarcinoma) and EGFR mutation (exon 19 deletion, exon 21 mutation, and exon 18 activating mutation) treated with EGFR-TKI between 2012 and 2017.

RESULTS

Median age was 61 (range 30-80), and 56.5% (26/46) was female. Median follow-up was 39 months. The rate of smoking was 41.3% (19/46). The EGFR mutations were present in the patients, exon 19 deletion in 29 patients (64%), exon 21 mutation in 13 patients (28%) and exon 18 activating mutations in four patients (8%). Progression-free survival (PFS) was 21 months in smokers, whereas it was 25 months in non-smokers (p=0.330). Median PFS was 21 months for patients using EGFR TKI in the first-line (35 patients), and 13 months in the second-line setting (11 patients).

CONCLUSION

There were no statistically significant PFS differences between the smoker and non-smoker groups. Smokers should be tested for EGFR mutations, as some patients may benefit from EGFR TKI treatment for longer than reported in the literature.

Keywords: Epidermal growth factor receptor; smoking; tyrosine kinase inhibitors.

Introduction

Lung cancer is among the most common cancers worldwide. Although smoking is proven to be one of the major risk factors for lung cancer, approximately 25% of lung cancer cases worldwide are not attributable to smoking.[1-3]

EGFR mutations are more prevalent in certain subpopulations of patients with NSCLC, such as women, patients in East Asia, patients with adenocarcinoma

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histologic types, and non-smokers.[4-5] The frequency of activating EGFR mutations, including exon 19 in-frame deletions and exon 21 L858R substitution, has been reported to be 40% to 60% in non-smoking patients compared to 10% to 20% in tobacco-associated patients for NSCLC.[6-9]

Treating NSCLC patients having activating EGFR mutations with tyrosine kinase inhibitor (TKI) significantly prolongs progression-free survival compared to standard chemotherapy and is more tolerable.[10-14] Various genetic alterations have been reported as resistance mechanisms to EGFR-TKI treatment, including T790M mutation, MET amplification and KRAS mutation,[15-17] but mechanisms and clinical factors that react differently to EGFR-TKI in EGFR mutated NSCLC are still largely unknown.[17]

Preclinical studies in recent years have shown that cigarette smoking abnormally activates the EGFR pathway and that active EGFR cells are resistant to smoking and EGFR-TKIs.[18,19] In addition, there were more somatic mutation incidence and genetic complexity in NSCLC patients with smoking history than non-smoking patients.[20]

Few studies directly focus on the relationship between EGFR-TKI's response and cigarette smoking history in NSCLC EGFR-mutant patients. In this study, we aimed to evaluate the effects of smoking cessation on anti-EGFR treatment in the Turkish patient population.

Materials and Methods

Between 2012-2017, EGFR activating mutations were present in 46 of 344 patients with stage 4 non-squamous NSCLC (13%). Forty-one of the patients were diagnosed in the metastatic stage and five in the non-metastatic stage. We retrospectively evaluated the data of 46 patients with metastatic NSCLC (adenocarcinoma) having activating EGFR mutations (exon 19 deletion in 29 patients, exon 21 mutation in 13 patients, exon 18 activating mutation in four patients) and treated with EGFR TKI (erlotinib) (first line 35 patients, second line 11 patients). We grouped the patients as smokers (n=16) and non-smokers (n=30) and compared the clinicopathologic features (ECOG performance status, mutation status, stage of diagnosis, EGFR TKI first line or second line usage, weight loss, gender, CEA and LDH level) of both groups. In descriptive statistics of data, we used mean, standard deviation, median lowest value, median highest value, frequency and rates. In the analysis of survival, we used Kaplan-Meier and Cox-regression analysis and in the analysis of qualitative data, we used the Chi-Square test.

Results

Median age was 61 (30-80), and 56.5% (26/46) was female. Median follow-up was 39 months. The rate of smoking was 41.3% (19/46). Fifteen of the 19 smokers had over 30 pack-year smoking history. Female gender (20/27) was higher in non-smoker patients and male sex (13/19) was higher in smokers (p=0.04). In all patients, PFS time was 21 months, where PFS was 21 months in smokers and 25 months in non-smokers (p=0.330) (Fig. 1). Overall survival was 26 months in the smoker group and 47 months in the non-smoker group (p=0.475) (Table 1).

We compared the clinicopathologic features (age, gender, 1st or 2nd line usage, LDH or CEA levels, ECOG PS, smoking, weight loss, mutation status) of smokers and non-smokers, and there was no significant difference. LDH elevation was found in 63% and CEA elevation was found in 50% of the patients. Sixty four percent (n=29) of the patients had exon 19 deletion, 28% (n=13) had exon 21 mutation, and 8% (n=4) had activating exon 18 mutations (Table 2).

Median PFS was 21 months (2-35) for patients using Erlotinib in the first-line (35 patients) and 13 months (5-30) in the second-line setting (11 patients). There were

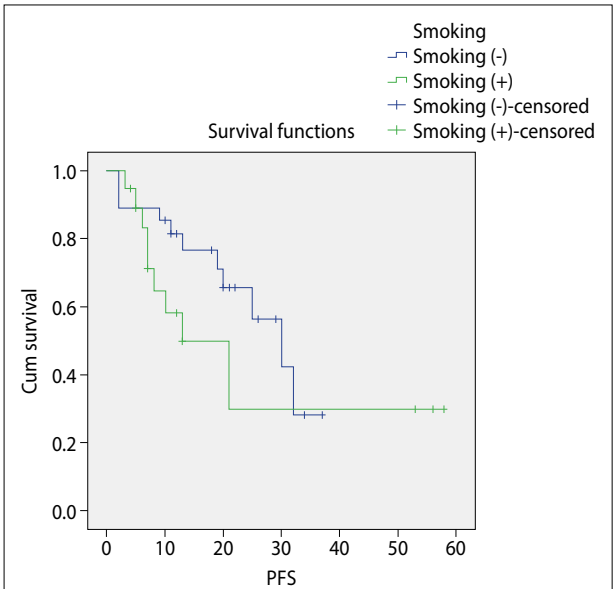

Fig. 1. Progression free survival (Pfs) in patients with or without smoking.

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Table 1 Survival data (Kaplan-Meier)

	Min.	-	Max.	Median	n	%	p
Follow-up duration (Months)	4	-	65	39		3.8	
Status							
Died					21	45.3	
Alive					25	54.3	
Progression-free survival (PFS)	2	-	58	21		370.0	
Progression							
No					23	50.0	
Yes					23	50.0	
Overall survival time							
Smoking (+)				26			0.408
Smoking (-)				47			
PFS time							
Smoking (+)				25			0.33
Smoking (-)				21			

Table 2 Clinicopathologic data (Chi-Square)

	Smoking (+)		Smoking (-)		All		
	n=19	41.3%	n=27	58.7%	n=46	100%	
Age							
≤65	12	63.2	13	48.1	25	54	0.314
>65	7	36.8	14	51.9	21	46	
EGFR-TKI 1st or 2nd line usage							
1st line	12	63.2	23	85.2	35	76	0.085
2nd line	7	36.8	4	14.8	11	24	
Stage of diagnosis stage							
Metastatic	18	94.7	23	85.2	41	89	0.305
Non-metastatic	1	5.3	4	14.8	5	11	
Mutation status							
Exon 19 deletion	13	68.4	16	59.3	29	64	0.135
Exon 21 mutation	5	26.3	8	21.6	13	28	
Exon 18 mutation	1	5.3	3	11.1	4	8	
ECOG PS							
< 1	18	100	23	85.2	41	89	0.189
≥2	1	0	4	14.8	5	11	
Gender							
Female	6	31.6	20	74.1	26	56.5	0.004
Male	13	68.4	7	25.9	20	46.5	
Weight loss							
Yes	3	17.6	2	13.3	5	15.6	0.598
No	14	82.4	13	86.7	27	84.4	
CEA							
Normal	6	50	8	50	14	50	0.647
High	6	50	8	50	14	50	
LDH							
Normal	5	29.4	7	36.8	12	36.8	0.637
High	12	70.6	12	63.2	24	63.2	

EGFR-TKI: Epidermal growth factor receptor-tyrosine kinase inhibitor; ECOG-PS: Eastern cooperative oncology group performance status; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase

Table 3 Cox-regression model of overall survival (OS) in EGFR mutant lung cancer

	OS								PFS							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
	95% CI				95% CI				95% CI				95% CI			
	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower	p	HR	Upper	Lower	p
Age (≤65, >65)	1.88	0.77	4.57	0.160					1.17	0.52	2.62	0.69				
Gender (Female/male)	1.08	0.44	2.65	0.850					1.16	0.51	2.65	0.71				
Smoking (-/+)	0.62	0.25	1.51	0.298					0.72	0.32	1.65	0.44				
LDH (Normal/high)	1.47	0.41	5.21	0.545					1.8	0.6	5.37	0.29				
CEA (Normal/high)	0.46	0.14	1.48	0.194					0.74	0.27	1.99	0.55				
ECOG (0-1, >2)	4.11	1.33	12.65	0.014	5.61	1.66	19.00	0.006	2.09	0.62	7.13	0.23				
Lose weight (No/yes)	0.29	0.09	0.89	0.031					2.09	0.61	7.13	0.23				
Type of mutation				0.421								0.122				
Stage of diagnosis (Non-metastatic/metastatic)	3.81	2.69	5.41	0.401					0.96	0.32	2.86	0.94				

LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; ECOG-PS: Eastern cooperative oncology group performance status

27 patients with PFS 12 months or more and 19 patients with less than 12 months. No statistically significant difference was found for PFS when clinicopathologic features (age, gender, 1st or 2nd line usage, LDH or CEA levels, ECOG PS, smoking, weight loss, mutation status) of these patients were compared (Table 3).

Median overall survival time (mOS) for metastatic disease was 39 months (range 4-65). The negative effects of ECOG-PS and weight loss on OS were shown by univariate analysis and the negative effects of ECOG-PS in multivariate analysis (Table 3).

Skin toxicity was observed in 18 patients (43%), which resulted in treatment interruption, and the dose was reduced in six patients (14%) due to side effects.

Discussion

NSCLC in never-smokers differs from NSCLC in smokers in many respects. EGFR mutations appear to be more common in never-smokers than in smokers.[21] Mutations in KRAS are more common in smokers than in never smokers.[22-24] Evidence suggests that these differences in molecular markers may have important implications for treatment choice.[23,24] There is also evidence that no smokers are independently more likely to survive than smokers, regardless of treatment.[25-27] Activating mutation in EGFR is the most important marker that predicts response to EGFR-TKIs in NSCLC.[28-30] The association between smoking history and efficacy of EGFR-TKIs therapy remains unclear. Few studies directly focus on the relationship between EGFR-TKI's efficacy and smoking history in NSCLC EGFR-mutant patients. A retrospective study showed that over 30 pack-years of cigarette smoking was an independent negative predictive factor of EGFR-TKI treatment outcome in lung adenocarcinoma patients with activating EGFR mutations.[31]

In a meta-analysis of Zhang et al. in 2015, for advanced NSCLC patients with EGFR mutations, non-smoking is associated with longer PFS than ever smoking after EGFR-TKIs treatment. However, there was no difference in objective response rates (ORR) and disease control rate (DCR). Smoking-related lung cancer is linked to multiple carcinogenic mechanisms. EGFR mutation may be one of the carcinogenic pathways of NSCLC in smokers, but not a single activated signaling pathway. EGFR-TKI may be effective for patients with EGFR mutation at the onset of treatment but cannot block other carcinogenic pathways induced by cigarette smoking, which may be due to that ORR and DCR are not different, although there are short PFSs in smokers.[32]

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A meta-analysis conducted by Mitchell et al. concluded that smoking and its effect on the EGFR-TKI response were still not determined because no data were available on smoking history and relationship to treatment response.[33] In our study, the frequency of patients who had a cigarette smoking history was 34.8%, and this was comparable to the results of the previous studies.[31,34,35]

There were no statistically significant PFS and OS differences between the smoker and non-smoker groups in our study. PFS was 21 months in smokers whereas it was 25 months in non-smokers. Overall survival was 26 months in the smoker group and 47 months in the non-smoker group (p=0.475). In our study, the overall median PFS time was 21 months, whereas median PFS is 21 months in patients using erlotinib in the first-line and 13 months in the second-line setting. Our PFS time results are much longer than the literature.

Our study had some limitations. This study was performed retrospectively with a limited sample. In addition, smoking history was only collected at the first diagnosis and smoking status during treatment was not followed up.

Conclusion

Smokers should be tested for EGFR mutations, as some patients may benefit from EGFR-TKI treatment for longer than reported in the literature. EGFR mutation status should also be considered in smokers. Smoking is known to be associated with poor prognosis in lung cancer, but these patients may benefit from EGFR-TKI treatments.

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