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Original Article

Monitoring of cyclooxygenase-2 levels can predict EGFR mutations and the efficacy of EGFR-TKI in patients with lung adenocarcinoma

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Abstract: Background: Epidermal growth factor receptor (EGFR) mutation detection has become a routine molecular test with significant implications for prognosis and therapeutic options of EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, acquiring sufficient amounts of tissue for analyzing EGFR mutations is not often feasible, and not all the patients with sensitive EGFR mutations have benefit from EGFR-TKI treatment. Method: EGFR mutations were detected by amplification refractory mutation system (ARMS) in 44 patients of newly diagnosed lung adenocarcinoma, and patients with EGFR-positive mutations received EGFR-TKI treatment. The serum cyclooxygenase-2 (COX-2) levels were tested before EGFR-TKI treatment and on the 30th days after EGFR-TKI treatment. Results: Twenty-nine cases were detected EGFR mutations. EGFR mutation rate of serum COX-2 high-level group was significantly higher than low-level group (92.9% vs. 53.3%, $P = 0.025$). Multivariate analysis showed that serum COX-2 level was independently associated with EGFR mutation ($P = 0.033$, OR = 12.385, 95%CI, 1.231-124.567). Analysis of the correlation between clinical characteristics and the response of EGFR-TKI showed that the serum COX-2 high-level group had a better efficacy than low-level group ($P = 0.000$), and multivariate logistic regression analysis showed that the serum COX-2 level was the independently influencing factor ($P = 0.004$). Kaplan-Meier analysis showed that patients of COX-2 high-level group have longer progression-free survival (PFS, $P = 0.013$), and the Cox regression analysis showed that the same result ($P = 0.003$; OR = 0.980, 95% CI, 0.967-0.993). Conclusion: The serum COX-2 level seems to be closely associated with EGFR mutations in patients with Lung adenocarcinoma. The serum COX-2 level could help us to predict the responses of EGFR-TKI and the PFS in patients harboring EGFR mutation.

Keywords: Cyclooxygenase-2, EGFR mutation, lung adenocarcinoma, prognosis

Introduction

Lung cancer is one of the leading causes of cancer-related mortality worldwide. Most diagnosed patients are advanced [1]. Currently, the 5-year survival rate for advanced non-small cell lung cancer (NSCLC) patients remains unsatisfied [2]. Studies purporting to improve the survival of NSCLC patients mainly focus on novel targeted molecular therapies against key signaling pathways, in particular, EGFR-targeted therapy.

The efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) has been proven in the treatment of patients harboring sensitive EGFR mutations [3-7]. Detection of EGFR mutations has become a routine molecular test guiding significant prognosis and therapeutic decision. However, sufficient amount of tissue is difficult to be acquired for EGFR mutations analysis. So it is crucial to search a simple and easy method.

EGFR mutations are frequently observed in patients with lung adenocarcinoma, who are likely to express cyclooxygenase-2 (COX-2) [8]. So we guess the COX-2 may be related to the EGFR mutations. But it is still not clear whether there is a correlation between EGFR mutation rate and serum COX-2 level or not, particularly whether the serum COX-2 level can be used to predict the efficacy of EGFR-TKI in patients with lung adenocarcinoma. Therefore, tissue and serum samples were collected to test the relationship between EGFR mutation and serum COX-2 level. Meanwhile, the correlation between

Table 1. The relationship between the clinical features and the status of EGFR mutation in patients with lung adenocarcinoma

Variable	Mutant EGFR (n = 29)	Wild-type EGFR (n = 15)	χ^2	*P*
Gender				
Male	14	12	2.908	0.088
Female	15	3		
Age, y				
< 60	12	6	0.008	0.930
≥ 60	17	9		
Smoking status				
Never-smoker	14	4	1.120	0.290
Current/former smoker	15	11		
Stage				
IIIB	8	5	0.157	0.692
IV	21	10		
ECOG score				
0~1	19	8	0.619	0.431
2~3	10	7		
Serum COX-2 level				
< 100 ng/mL	16	14	4.994	0.025
≥ 100 ng/mL	13	1		

Table 2. Multivariate logistic regression analysis of the predictive elements for incidence of EGFR mutation

Variable	Coefficient	SE	OR	95% CI	*P*
Gender	-1.855	1.328	0.156	0.012-2.112	0.162
Age, y	0.022	0.030	1.023	0.965-1.084	0.452
Stage	-0.189	0.853	0.828	0.156-4.411	0.825
Smoking status	-1.076	1.308	0.341	0.026-4.431	0.411
ECOG score	-1.292	0.842	0.275	0.053-1.432	0.125
Serum COX-2 level	2.516	1.178	12.385	1.231-124.567	0.033

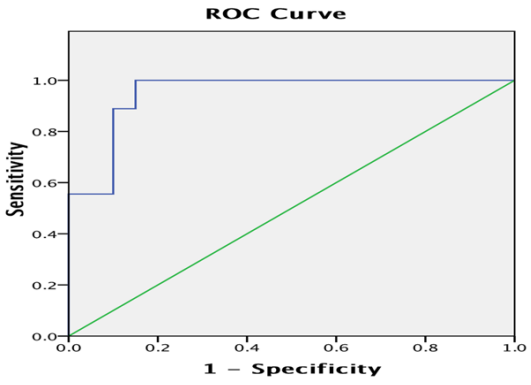

Figure 1. ROC curves for the serum COX-2 levels in respect of the response of EGFR-TKI.

serum COX-2 level and the efficacy of EGFR-TKI was also investigated.

Materials and methods

Patients

From January 2013 to June 2014, totally 44 primary lung adenocarcinoma patients were enrolled in this study. There are respectively 26 males and 18 females, aging 31~85 (median age 65.5). There were 26 smokers (smoking index ≥ 100) and 18 non-smokers in this study. All patients were required to have stage IIIb or IV with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0~3. What's more, all patients were required to have enough tumor tissue for EGFR testing. The study was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University School of Medicine, and each patient of participating in this study signed informed consent.

Study design

EGFR mutation status of patients' tissues was detected by amplified refractory mutation system (ARMS). Patients who had EGFR-positive mutation received EGFR-TKI treatment (gefitinib 250 mg/day or erlotinib 150 mg/day orally). The COX-2 levels were measured before and after two months EGFR-TKI treatment, respectively. The response of EGFR-TKI and the progression-free survival (PFS) were observed by Response Evaluation Criteria in Solid Tumors (RECIST). The PFS was evaluated from the date of enrollment to the first time of disease progression or death from any cause. The treatment was stopped when the disease progressed or presented a serious adverse event. Tumor response was valued every two months until disease progression.

Serum COX-2 measurement

Serum was obtained from peripheral venous blood acquired from patients at baseline and 8 weeks after the initiation treatment. Serum

Table 3. The characteristics of the patients and the efficacy of EGFR-TKI

Features	n	PR	SD	PD	x^2	*P*
Gender						
Female	15	6	6	3		
Male	14	3	5	6	2.013	0.343
Age (years)						
< 60	12	5	4	3		
≥ 60	17	4	7	6	1.093	0.579
Stage						
IIIB	8	3	4	1		
IV	21	6	7	8	0.364	0.834
Smoke						
No	14	6	5	3		
Yes	15	3	6	6	3.460	0.177
ECOG score						
0~1	19	5	8	6		
2~3	10	4	3	3	1.376	0.503
serum COX-2 level (pre-treatment)						
< 100 ng/mL	16	0	8	8		
≥ 100 ng/mL	13	9	3	1	24.640	0.000

was collected to clot for 2 hours at room temperature. Then the serum samples were centrifuged at 3500 rpm for 15 minutes. The resulting serum was stocked at -80°C until use. The serum COX-2 level was measured in triplicate by enzyme linked immunosorbent assay Kit for COX-2 (Uscn Life Science Inc, Wuhan, China) following the manufacturer's instructions.

EGFR mutation analysis

Forty-four tumor tissue samples were collected from the primary site. All samples were examined histologically to confirm the diagnosis of adenocarcinoma. Tumor tissue samples were fixed in formalin and embedded in paraffin wax. The EGFR mutation status of tissue derived from all 44 patients was assessed using the EGFR 29 Mutations Detection Kit (Amoy Diagnostics, Xiamen, China).

Statistical analysis

All analyses were performed with SPSS 17.0 statistical software. The method of χ^2 test or Fisher's exact test was used to evaluate the association between EGFR mutations and clinical parameters, and the overall response rates in different groups. Multivariate logistic regression was used to confirm the correlation between the individual factors and the status of EGFR mutation or the efficiency of EGFR-TKI. Serum COX-2 levels were compared between two time points (0 versus 8 weeks) with the paired *t* test. The one-way analysis of variance models was used to compare the baseline level of COX-2 among the three response groups. The Kaplan-Meier method was used to analyze the PFS and the multivariate Cox proportional hazards regression model was used to evaluate assess independent predictive factors associated with PFS. Differences were considered statistically significant at *P* values less than 0.05.

Results

EGFR gene mutations

Mutations at EGFR gene were found in 29 of the 44 patients. In 29 cases (65.91%) were observed EGFR gene mutations, including 12 cases of L858R mutation, 15 cases of exon 19 mutation, and 2 cases of exon 18 mutation.

Correlation between clinical characteristics and EGFR mutations

We analyzed the relationship between clinical characteristics and EGFR mutations and found that the serum COX-2 level before treatment of EGFR-TKI was the only correlative factor (**Table 1**). The rate of EGFR mutation was significantly higher in serum COX-2 high-level group than low-level group (92.9% vs. 53.3%, $P = 0.025$). Multivariate logistic analysis also showed that serum COX-2 high-level was independently associated with EGFR mutation (**Table 2**). We also tried to elevate the efficacy of high serum COX-2 level to predict EGFR mutation. The sensitivity, specificity, positive predictive value, and negative predictive value of high serum COX-2 level (≥ 100 ng/ml) to predict EGFR mutation were 44.8%, 93.3%, 92.9% and 46.7%, respectively.

Relationship between serum COX-2 levels and the efficacy of EGFR-TKI

Twenty-nine patients received the targeted therapy of EGFR-TKI. Then we assessed the efficacy of EGFR-TKI and followed up the

Table 4. Multivariate logistic regression analysis of the predictive characteristics for the efficacy of EGFR-TKI

Variable	Coefficient	SE	OR	95% CI	*P*
Gender	-1.666	1.361	0.189	0.013-2.732	0.221
Age, y	-0.018	0.033	0.982	0.920-1.048	0.585
Stage	-1.037	0.922	0.354	0.058-2.161	0.261
Smoking status	0.773	1.371	2.167	0.148-31.834	0.573
ECOG score	-0.633	0.814	0.531	0.108-2.616	0.436
Serum COX-2 level (pre-treatment)	0.038	0.013	1.039	1.012-1.067	0.004

Table 5. Association of short-term responses to EGFR-TKI therapy with the expression levels of serum COX-2

Short-term responses	n	COX-2 (ng/mL) ($\bar{x}$ ± s)
PR		
Pre-treatment	9	139.42 ± 2.14
Post-treatment	9	75.91 ± 1.60[a]
SD		
Pre-treatment	11	74.68 ± 3.16*
Post-treatment	11	61.02 ± 1.54
PD		
Pre-treatment	9	51.87 ± 3.97*
Post-treatment	9	89.07 ± 4.28[b]

[a]*P* = 0.000, decrease at week 8 in patients with PR, [b]*P* = 0.000, increase at week 8 in patients with PD, **P* = 0.000, baseline value in patients withSD or PD compared with patients with PR.

patients' PFS. The total ORR is 31.0%; DCR is 69.0%. Relationship between the serum COX-2 level before treatment and the response of EGFR-TKI was evaluated by ROC curve analysis (**Figure 1**). The area under curve value was 0.950 (95% CI, 0.000-1.000, *P* = 0.000). Analysis of the correlation between clinical characteristics and the response of EGFR-TKI showed that the serum COX-2 high-level group had a better efficacy than low-level group (*P* = 0.000; **Table 3**). Multivariate logistic regression analysis showed that the serum COX-2 level was the independently influencing factor (*P* = 0.004; **Table 4**). We measured serum COX-2 level at baseline and at weeks 8 of study treatment. Baseline levels of serum COX-2 were higher in PR group than SD or PD group (*P* = 0.000; **Table 5**). The serum COX-2 levels at week 8 were significantly decreased in patients who achieved a PR and increased in patients who achieved a PD (*P* = 0.000; **Table 5**). The Kaplan-Meier analysis showed that patients with high COX-2 level had longer PFS (*P* = 0.013; **Figure 2**). Multivariate Cox regression analysisshowedthesameresult (*P* = 0.003; OR = 0.980, 95% CI, 0.967 -0.993).

Discussion

The EGFR signal transduction pathway has been highlighted in cancer research, especially in lung cancer. With respect to NSCLC, EGFR-TKIs have been rapidly developed including reports of efficacy [9-12]. However, the efficacy of EGFR-TKIs mostly occurs in patients possessing sensitive EGFR mutations [3-7]. EGFR mutations have been considered to be associated with better prognosis in patients treated with EGFR-TKIs [13]. EGFR mutations are frequently observed in patients with lung adenocarcinoma [14]. Tumor tissue is usually the source of samples for detecting EGFR mutations; however, insufficient amount of tissue specimens is a limiting factor in detection for most advanced NSCLC. A previous study has shown that the expression of COX-2 was increased in human lung cancers, specifically in adenocarcinomas [8]. In the present study, we investigated the relationship between EGFR mutation status and serum COX-2 level. Meanwhile, our research was the first to debate the correlation between serum COX-2 level and EGFR-TKI treatment. In our study, the results showed that among 29 NSCLC patients with EGFR-positive mutation, the EGFR mutations mainly occurred in exons 21 and 19, the mutation rates were 41.38% and 51.72%, respectively. This is similar to the former reports [16]. However, EGFR mutations were not associated with smoking status and gender in our study. This was different from previous studies [15].

EGFR mutation can abnormal activate the downstream of EGFR signal pathways, and in turn prevent the cell apoptosis and proliferation [16, 17]. Cyclooxygenase (COX) is a rate-limiting enzyme converting arachidonic acid to prostaglandin (PG) [18], which has 2 isozymes of COX, namely, COX-1 and COX-2. COX-1 enzyme is constitutively expressed in many normal tissue types. COX-2 is an inducible enzyme and is over-expressed in inflammatory and many neo-

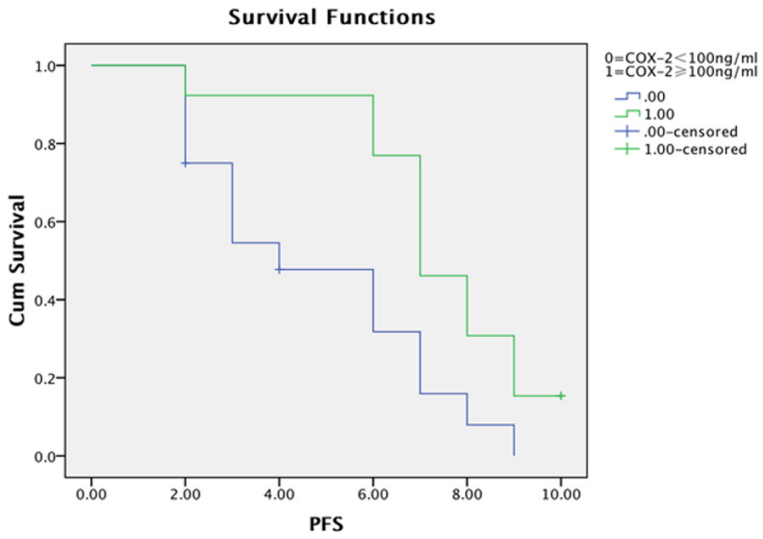

Figure 2. Kaplan-Meier survival curves of serum cyclooxygenase-2.

plastic tissues [19-25]. COX-2 appears to contribute to various aspects of carcinogenesis, primarily through the synthesis of PG [26-29]. And COX-2 can be induced by many stimuli, including oncogenes, tumor promoters, and growth factors [30]. In a recent review, Dannenberg suggested the potential interaction of EGFR and COX-2 in cell signal transduction [31]. And other studies also indicated that EGFR activation might lead to COX-2 expression and the EGFR signal transduction pathway may participate in COX-2 stimulation [32-34]. So there seems a relation between serum COX-2 level and EGFR gene mutations. In our study, the results showed that the serum COX-2 level before treatment of EGFR-TKI was the only correlative factor and the rate of EGFR mutation was significantly higher in serum COX-2 high-level group than low-level group (92.9% vs. 53.3%, $P = 0.025$; **Table 1**). Multivariate logistic analysis also showed that serum COX-2 high-level was independently associated with EGFR mutation ($P = 0.033$; **Table 2**). The incidence rate of EGFR mutations was significantly increased as the elevation of serum COX-2 levels. We also tried to use high serum COX-2 level to predict EGFR mutation, and the specificity of high serum COX-2 level (≥ 100 ng/ml) to predict EGFR mutation was 93.3%. But the sensitivity was not satisfied (44.8%). The patients who were detected EGFR mutation were all received the targeted therapy of EGFR-TKI. Then we assessed the efficacy of EGFR-TKI and followed up the patients' PFS. The total ORR is 31.0%; DCR is 69.0%. The ROC curve results showed the serum COX-2 level can predict efficacy of EGFR-TKI ($P = 0.000$; **Figure 1**). Our results showed that the serum COX-2 the serum COX-2 level has a close relationship with the efficacy of EGFR-TKI ($P = 0.000$; **Table 3**), and was the independently influencing factor ($P = 0.004$; **Table 4**). We measured serum COX-2 level at baseline and at weeks 8 of study treatment. Baseline levels of serum COX-2 were higher in PR group than SD or PD group ($P = 0.000$; **Table 5**). The serum COX-2 levels at week 8 were significantly decreased in patients who achieved a PR and increased in patients who achieved a PD ($P = 0.000$; **Table 5**). The Kaplan-Meier analysis showed that patients with high COX-2 level had longer PFS ($P = 0.013$; **Figure 2**). Multivariate Cox regression analysis showed the same result ($P = 0.003$; OR = 0.980, 95% CI, 0.967-0.993).

In conclusion, a positive relationship between serum COX-2 level and EGFR mutations is observed. The incidence rate of EGFR mutations was significantly increased as the elevation of serum COX-2 levels. If the patients' tissue samples are insufficient for EGFR mutation detecting, or cannot be obtained at all, to test serum COX-2 expression is an easy and simple method to predict EGFR mutation. What's more, we can use the serum COX-2 level to predict the responses of EGFR-TKI and the PFS in patients harboring EGFR mutation.

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Disclosure of conflict of interest

None.

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