Effect of gefitinib on serum EGFR and CYFRA21-1 in patients with advanced non-small cell lung cancer

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Abstract. Changes of epidermal growth factor receptor (EGFR) and cytokeratin fragment antigen 21-1 (CYFRA21-1) in patients with advanced non-small cell lung cancer (NSCLC) before and after gefitinib treatment were observed to explore the significance of such changes. A total of 175 patients with advanced NSCLC who were admitted to Hubei Cancer Hospital from July 2012 to October 2015 were collected and divided into two groups: the control group (85 patients who received conventional chemotherapy) and the experimental group (90 patients treated with gefitinib combined with chemotherapy). The serum expression levels of EGFR and CYFRA21-1 were detected by enzyme-linked immunosorbent assay (ELISA). The therapeutic efficacy and 3-year survival of the two groups were compared, and the factors affecting the survival of the patients were analyzed. The total effective rate and local effective rate of the experimental group were significantly higher than those of the control group ($P<0.05$). Before treatment, no significant difference was detected in the levels of EGFR and CYFRA21-1 between the two groups ($P>0.05$). After treatment, the expression levels of EGFR and CYFRA21-1 in the two groups were significantly lower than those before treatment ($P<0.05$). According to the 3-year survival rate, the experimental group was divided into the survival group and the non-survival group. Single factor analysis was performed on the general data, showing that the influencing factors of the survival include the KPS score, smoking history, number of lesions, pathological stage, EGFR, and CYFRA21-1. Gefitinib can bring significantly improved therapeutic efficacy, lower expression levels of EGFR and CYFRA21-1, and longer survival time for patients with advanced NSCLC. Indicators including confirmed smoking history, a KPS score less than or equal to 60 points, multiple lesions, pathological stage IV, high expression of EGFR and CYFRA21-1, are important factors affecting the survival of patient with advanced NSCLC.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). According to clinical statistical analysis of human cancer, non-small cell lung cancer (NSCLC), with an incidence rate of 85%, and small cell lung cancer, with an incidence rate of 15%, belong to different types (2), and the increasing incidence rate of NSCLC seriously jeopardizes human health (3,4). Most NSCLC patients do not get the correct diagnosis until reaching the advanced stage, thus losing the best time for treatment (5,6). Despite some progress in the treatment options of NSCLC in recent years, the prognosis for NSCLC is still very poor (7). Currently, radiotherapy, biological therapy, molecular targeted therapy, and chemotherapy are the main treatments for NSCLC (8,9). The clinical application of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), one of the molecular targeted drugs that are widely used to treat advanced NSCLC after chemotherapy, surgery, and radiotherapy, has made breakthroughs in the treatment of NSCLC (10,11).

Gefitinib, an oral molecular targeted drug, belongs to the class of aniline quinazolines. It is currently the first-line drug for patients with advanced NSCLC, with an anti-tumor effect mainly achieved through its competitive combination with EGFR (12,13). Chemotherapy, as the main measure for the treatment of advanced NSCLC, can improve the quality of life, inhibit the growth of tumor cells *in vivo*, and prolong the survival period, but it causes great damage to the body function of patients and has many side effects (14). However, further research is needed on the specific efficacy of targeted drugs combined with chemotherapy in the treatment of advanced NSCLC. EGFR, a member of the type I transmembrane receptor protein tyrosine kinase Erb B family (15), its main function of mediated signal transduction, is closely related to tumor cell proliferation and differentiation regulation (16). The cytokeratin fragment antigen 21-1 (CYFRA21-1) is a tumor marker for detecting NSCLC, especially lung squamous cell carcinoma, mainly found in the cytoplasm of monolayer and pseudostratified epithelial cells (17).

This study mainly observed the changes of serum EGFR and CYFRA21-1 levels before and after gefitinib treatment,

compared the clinical efficacy between the two groups, and explored the prognostic factors affecting the survival of patients with advanced NSCLC.

Patients and methods

General information. One hundred and seventy-five patients with advanced NSCLC, admitted to Hubei Cancer Hospital (Wuhan, China) from July 2012 to October 2015, were collected [85 patients receiving conventional chemotherapy enrolled in the control group (50 males and 35 females; a mean age of 60.17±8.78 years, a duration of disease of 1.33±0.76 years, including 53 cases of adenocarcinoma and 32 cases of squamous cell carcinoma), and 90 patients receiving gefitinib treatment combined with chemotherapy enrolled in the experimental group (54 males and 36 females; a mean age of 61.25±9.11 years, a duration of disease of 1.46±0.86 years, including 59 cases of adenocarcinoma and 31 cases of squamous cell carcinoma)].

Inclusion criteria: Patients confirmed with advanced NSCLC by cytology and histology; patients not receiving other recent anti-tumor treatments; patients with no serious vascular invasion according to the imaging examination; and patients with an expected survival time of more than 3 months.

Exclusion criteria: Patients who failed to complete the treatment plan due to a strong request for withdrawal or loss of follow-up or other reasons; patients with chemotherapy contraindications; patients with autoimmune system defects; pregnant or lactating female patients; patients with poor compliance during treatment; and patients stopping the treatment due to adverse reactions or intolerance.

With a detailed description of the experimental content, this study was approved by the Ethics Committee of Hubei Cancer Hospital. All the subjects signed a complete informed consent form and had complete clinical data.

Treatment plan. The control group received conventional chemotherapy: pemetrexed (Eli Lily and Company; medical product permitted by the China Food and Drug Administration, no. H20100060) at a dose of 500 mg/m^2 and cisplatin (Jiangsu Hansoh Pharmaceutical Group Co., Ltd.; medical product permitted by the China Food and Drug Administration, no. H20040812) at a dose of 75 mg/m^2 were given from the first day of chemotherapy, and the treatment lasted for continuous 4 to 6 courses, with 21 days marking a treatment course. On the basis of chemotherapy, patients in the experimental group were also treated with a molecular targeted drug: gefitinib [AstraZeneca (Wuxi) Trading Co., Ltd., medical product permitted by the China Food and Drug Administration, no. J20070047] was orally administered at a dose of 250 mg per day according to the condition with the same treatment duration as the control group, and the efficacy was evaluated after treatment. The patient's performance and adverse reactions were closely monitored, and the disease control and cancer cell size changes were recorded regularly. The drug administration was stopped as a result of disease progression or intolerance.

Serum specimen collection. Fasting elbow venous blood (4 ml) was taken from all experimental subjects in the morning at 24 h before treatment and 24 h after treatment, and then the blood was centrifuged at 2,600 x g for 15 min at 4˚C. The slurry in the test tube was carefully absorbed to collect the serum which was then stored in a freezer at -20˚C and tested by a designated person.

Detection of serum EGFR, CYFRA21-1 expression levels by enzyme-linked immunosorbent assay (ELISA). ELISA was performed to detect the serum EGFR, CYFRA21-1 expression levels. The EGFR kit and CYFRA21-1 kit were provided by Jiangsu Baolai Biotechnology Co., Ltd. (batch nos. MM-1698H1, MM-1113H2). The BS-1101 enzyme label analyzer was purchased from Beijing Linmao Technology Co., Ltd. The sample well, standard well and blank control well were separately set, and 50 μl of the sample was accurately added to the standard well on the enzyme label coated plate, 40 μl of the sample dilution and 10 μl of the sample were added to the sample well. Caution was taken during the operation to avoid touching the wall as far as possible, and the plate was jiggled. The plate was then sealed with a sealing film and incubated at 37˚C for 30 min. After that, the sealing film was carefully uncovered and the liquid was discarded, then the wells were dried with absorbent paper then filled with the washing solution. After standing for 30 sec, the discarding and refilling were repeated five times and the wells were finally patted dry. Each well, except for the blank wells, was added with 50 μl of the enzyme labeling reagent. Then, 50 μl of developer A and 50 μl of developer B were sequentially added to every well and mixed, away from light at 37˚C for 15 min. Next, 50 μl of the stop solution was added to each well to terminate the reaction, and yellow color appeared in the wells. Within 15 min, with the blank well as the zero reference value, the OD value of each well was measured at a wavelength of 450 nm. A standard curve was used to calculate the concentration of EGFR and CYFRA21-1 in the sample. All operations were in strict accordance with manufacturer's instructions.

Efficacy evaluation criteria (18). The evaluation was accoding to the response evaluation criteria in solid tumors (RECIST). Complete remission (CR): all lesions disappear and the situation is maintained for 1 month; partial remission (PR): total lesion diameter is reduced by equal or >30% and the situation is maintained for 1 month; progressive disease (PD): total diameter of lesion increases by equal or >20% or new lesions appear; stable disease (SD): the reduction of total diameter of the lesion is smaller than PR or the increase of total diameter of the lesion is smaller than PD. Effective rate = (CR case number + PR case number)/total case number x100%. Local tumor control rate = (CR case number + PR case number + SD case number)/total case number.

Grouping according to the total effective rate: effective group = complete remission group + partial remission group; invalid group = stable disease group + progressive disease group.

Follow-up and observation indicators. Regular follow-up was conducted by subsequent consultation with doctors and by telephone interviews. The 3-year survival of the two groups of patients after treatment was recorded. The treatment effect was evaluated according to the World Health Organization (WHO) response evaluation criteria in solid tumors, and the overall efficacy was recorded. Disease mutation during the follow-up was promptly treated, and the examination was strengthened every time. The survival time was recorded from the first day

Table I. Comparison of the general information between the two groups (mean ± SD)/[n (%)].

Clinical factors	Experimental group (n=90)	Control group (n=85)	χ^2/t value	P-value
Sex			0.025	0.874
Male	54 (60.0)	50 (58.8)		
Female	36 (40.0)	35 (41.2)		
Average year	61.25±9.11	60.17±8.78		
Weight (kg)			0.286	0.593
<50	21 (23.3)	17 (20.0)		
≥50	69 (76.7)	68 (80.0)		
Smoking			0.001	0.979
Yes	39 (43.3)	37 (43.5)		
No	51 (56.7)	48 (56.5)		
Drinking			0.206	0.650
Yes	57 (63.3)	51 (60.0)		
No	33 (36.7)	34 (40.0)		
KPS score			0.078	0.780
≤60	50 (55.6)	49 (57.6)		
>60	40 (44.4)	36 (42.4)		
Duration of disease (year)	1.46±0.86	1.33±0.76	1.057	0.292
Tumor size (cm)			0.043	0.836
≤3	42 (46.7)	41 (48.2)		
>3	48 (53.3)	44 (51.8)		
Pathological type			0.195	0.659
Adenocarcinoma	59 (65.6)	53 (62.4)		
Squamous cell carcinoma	31 (34.4)	32 (37.6)		
Number of lesions			0.116	0.733
Single	34 (37.8)	30 (35.3)		
Multiple	56 (62.2)	55 (64.7)		
Pathological stage			0.049	0.825
IIIB	30 (33.3)	27 (31.8)		
IV	60 (66.7)	58 (68.2)		

of treatment to the death or the last day of follow-up. The last day of follow-up was October 5, 2018.

Statistical analysis. The experimental data were statistically analyzed using SPSS 17.0 statistical software (SPSS Inc.); n (%) indicates enumeration data, which was compared between the two groups using the Chi-square test; (mean ± SD) indicates measurement data, which was compared between the two groups using an independent sample t-test; and a paired t-test was used for comparison between the situation before and after treatment. Survival analysis of the two groups was performed using the Kaplan-Meier method and compared using the log-rank test, and Cox regression was used to analyze the independent prognostic factors of NSCLC patients. A statistical difference was recognized at P<0.05.

Results

Comparison of the general information between the two groups. According to the general information of the two groups shown in Table I, both the experimental and control groups were comparable since the two groups of patients were not significantly different in terms of sex, age, weight, smoking and drinking, KPS score, duration of disease, tumor size, pathological type, number of lesions, and pathological stage (P>0.05).

Comparison of clinical efficacy between the two groups. The experimental group had an effective rate of 66.7% and a local tumor control rate of 87.8%, including 24 cases of CR, 36 cases of PR, 19 cases of SD, and 11 cases of PD. The control group showed an effective rate of 34.1% and a local tumor control rate of 68.2%, with 10 cases of CR, 19 cases of PR, 29 cases of SD, and 27 cases of PD. The total effective rate and local effective rate of the experimental group were significantly higher than those of the control group (P<0.05) (Table II).

Changes in the concentration of EGFR and CYFRA21-1 before and after treatment in both groups (Figs. 1 and 2). Before treatment, the expression levels of EGFR and CYFRA21-1 in the

Table II. Comparison of clinical efficacy between the two groups [n (%)].

Groups	no.	CR	PR	SD	PD	Effective rate	Local tumor control rate
Experimental group	90	24 (26.7)	36 (40.0)	19 (21.1)	11 (12.2)	66.7%	87.8%
Control group	85	10 (11.8)	19 (22.3)	29 (34.1)	27 (31.8)	34.1%	68.2%
χ^2 value						21.78	11.66
P-value						<0.001	0.0006

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table III. The serum levels of tumor markers in the subgroups of the experimental group before and after treatment.

		EGFR(ng/l)		CYFRA21-1(ng/ml)	
Groups	Case no.	Before treatment	After treatment	Before treatment	After treatment
Effective group	60	24.35±5.77	11.89±3.65[a]	10.87±2.98	3.09±0.08[a]
Ineffective group	30	24.01±5.91	25.27±7.97	10.78±2.77	9.92±2.09
t value		0.269	10.60	0.181	13.71
P-value		0.788	<0.001	0.857	<0.001

[a]P<0.05, when compared with the data before treatment.

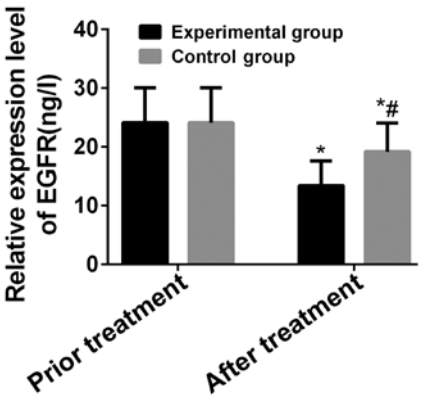

Figure 1. Changes in the concentration of EGFR before and after treatment. Before treatment, no significant difference was detected in the concentration of EGFR between the experimental and control groups (P>0.05). After treatment, the expression levels of EGFR both in the experimental and control groups were significantly lower than those in the two groups before treatment (P<0.05), with much lower expression level of EGFR in the experimental group than in the control group, and the differences were statistically significant (P<0.05). *P<0.05, when compared with the data before treatment; #P<0.05, when compared with the data of the experimental group after treatment.

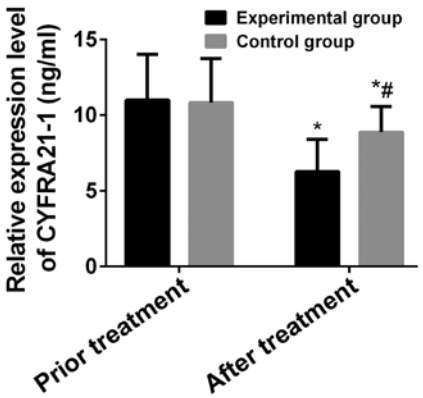

Figure 2. Changes in the concentration of CYFRA21-1 before and after treatment. Before treatment, no significant difference was detected in the concentration of CYFRA21-1 between the experimental and control groups (P>0.05). After treatment, the expression levels of CYFRA21-1 both in the experimental and control groups were significantly lower than those in the two groups before treatment (P<0.05), with much lower expression level of CYFRA21-1 in the experimental group than in the control group, and the differences were statistically significant (P<0.05). *P<0.05, when compared with the data before treatment. #P<0.05, when compared with the data of the experimental group after treatment.

experimental group were 24.13±5.87 ng/l and 10.98±3.02 ng/ml, the expression levels of EGFR and CYFRA21-1 in the control group were 24.09±5.91 ng/l and 10.82±2.91 ng/ml, with no significant difference being detected between the experimental and control groups (P>0.05). After treatment, the expression levels of EGFR and CYFRA21-1 in the experimental group were 13.37±4.21 ng/l and 6.27±2.12 ng/ml, statistically lower than those of the control group (expression level of EGFR at 19.14±4.87 ng/l and expression level of CYFRA21-1 at 8.87±1.68 ng/ml) (P<0.05), and both groups had much lower expression levels of EGFR and CYFRA21-1 after treatment than those before treatment (P<0.05).

The serum levels of EGFR and CYFRA21-1 in the subgroups of the experimental group before and after treatment. Before

Table IV. Comparison of general information between the survival and non-survival groups of the experimental group [n (%)].

Clinical factors	Survival group (n=27)	Non-survival group (n=63)	t value	P-value
Sex			0.141	0.707
Male	17 (63.0)	37 (58.7)		
Female	10 (37.0)	26 (41.3)		
Age (year)			0.729	0.393
<50	12 (44.4)	22 (34.9)		
≥50	15 (55.6)	41 (65.1)		
Weight (kg)			0.027	0.870
<50	6 (22.2)	15 (23.9)		
≥50	21 (77.8)	48 (76.2)		
Duration of disease (year)			2.168	0.141
≤2	17 (63.0)	29 (46.0)		
>2	10 (37.0)	34 (54.0)		
Smoking			16.31	<0.001
Yes	3 (11.1)	36 (57.1)		
No	24 (88.9)	27 (42.9)		
Drinking			2.190	0.139
Yes	14 (51.9)	43 (68.3)		
No	13 (48.1)	20 (31.7)		
KPS score			17.36	<0.001
≤60	6 (22.2)	44 (69.8)		
>60	21 (77.8)	19 (30.2)		
Tumor size (cm)			0.077	0.782
≤3	12 (44.4)	30 (47.6)		
>3	15 (55.6)	33 (52.4)		
Pathological type			0.677	0.411
Adenocarcinoma	16 (59.3)	43 (68.3)		
Squamous cell carcinoma	11 (40.7)	20 (31.7)		
Number of lesions			13.69	0.0002
Single	18 (66.7)	16 (25.4)		
Multiple	9 (33.3)	47 (74.6)		
Pathological stage			11.67	0.0006
IIIB	16 (59.3)	14 (22.2)		
IV	11 (40.7)	49 (77.8)		
EGFR (ng/l)			10.41	0.001
High expression	10 (37.0)	46 (73.0)		
Low expression	17 (63.0)	17 (27.0)		
CYFRA21-1 (ng/ml)			13.69	0.0002
High expression	9 (33.3)	47 (74.6)		
Low expression	18 (66.7)	16 (25.4)		

EGFR, epidermal growth factor receptor; CYFRA21-1, cytokeratin fragment antigen 21-1.

treatment, no significant difference was detected in the levels of EGFR and CYFRA21-1 between the effective and ineffective groups (P>0.05). The serum expression levels of EGFR and CYFRA21-1 in the effective group after treatment were significantly lower than those before treatment (P<0.05). The serum expression levels of EGFR and CYFRA21-1 in the ineffective group were not significantly different from those before treatment. After treatment, the levels of EGFR and CYFRA21-1 in the effective group were significantly lower than those in the ineffective group (P<0.05) (Table III).

Comparison of survival analysis between the experimental and control groups. The follow-up and the comparison of survival between the two groups as shown in Fig. 3, the

Table V. Variable name and assignment.

Factors	Assignment
KPS score	≤60:1, >60:2
Smoking	Yes: 1, no: 2
Number of lesions	Single: 1, multiple: 2
Pathological stage	IIIB: 1, IV: 2
EGFR (ng/l)	High expression (≥13.37 ng/l): 1, low expression (<13.37 ng/l): 2
CYFRA21-1 (ng/ml)	High expression (≥6.27 ng/ml): 1, low expression (<6.27 ng/ml): 2

EGFR, epidermal growth factor receptor; CYFRA21-1, cytokeratin fragment antigen 21-1.

Table VI. Multivariate analysis of factors affecting the prognosis in patients with advanced NSCLC.

Factors	β	SD	χ^2 value	P-value	HR (95% CI)
KPS score	-1.847	0.875	4.458	0.035	0.158 (0.028-0.876)
Smoking	-3.065	1.072	8.171	0.004	0.047 (0.006-0.382)
Number of lesions	2.470	0.967	6.525	0.011	11.820 (1.777-78.636)
Pathological stage	2.467	0.928	7.064	0.008	11.782 (1.911-72.638)
EGFR (ng/l)	-2.221	0.906	6.007	0.014	0.109 (0.018-0.641)
CYFRA21-1 (ng/ml)	-2.535	0.933	7.391	0.007	0.079 (0.013-0.493)

EGFR, epidermal growth factor receptor; CYFRA21-1, cytokeratin fragment antigen 21-1; NSCLC, non-small cell lung cancer.

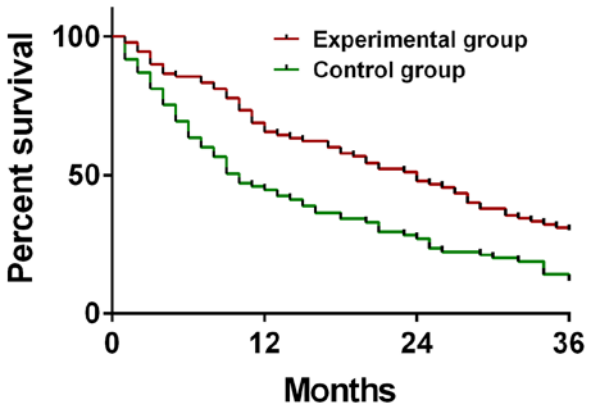

Figure 3. Comparison of the survival analysis between the experimental and control groups. The follow-up and the comparison of survival between the two groups showed the 3-year survival rate of the experimental group after treatment was 30.0%, much higher than the survival rate of 11.8% in the control group, and the difference was statistically significant (P<0.05).

3-year survival rate of the experimental group after treatment was 30.0%, much higher than the survival rate of 11.8% in the control group, and the difference was statistically significant (P<0.05).

Logistic regression analysis of survival and non-survival in the experimental group. According to the 3-year survival rate, the experimental group was divided into the survival group and the non-survival group. The single factor analysis was performed on the general data, showing that the influencing factors of the survival include the KPS score, smoking history, number of lesions, pathological stage, EGFR, and CYFRA21-1. Subsequently, the multivariate Cox regression analysis of different indicators showed that confirmed smoking history, a KPS score less than or equal to 60 points, multiple lesions, pathological stage IV, high expression of EGFR and CYFRA21-1 were important factors affecting the survival of advanced NSCLC (Tables IV-VI).

Discussion

The faster pace of life and environmental pollution have led to an increasing case number of sub-health, which, in the long run, may easily cause a variety of diseases, such as lung cancer, one of the most common malignant tumors worldwide, that attracts the focus of clinical attention due to its difficult diagnosis in early stage (19). Most patients with NSCLC do not get the correct diagnosis until reaching the locally advanced stage when distant metastasis or invasion of important surrounding organs occurs, making surgical treatment impossible (20). Advanced NSCLC is mainly treated by targeted therapy (21). Gefitinib, the most effective targeted drug for NSCLC, achieves its inhibition on tumor cell proliferation and division mainly by the contribution of EGFR-TKI to block the signal transduction of cellular proliferation (22).

EGFR is mainly present in the monomeric form on the cell membrane, and needs to be activated by its ligand and other ErbB family members, such as transforming growth factor-α, epidermal growth factor and amphiregulin, since its monomer is not active (23). With the conformation changes achieved by the binding of its ligands to receptors, EGFR can mediate

the proliferation, differentiation, metastasis, invasion, and the inhibition of apoptosis of tumor cells. The receptors can form heterodimers with other members of the EGFR family or form homodimers by themselves, which activates the tyrosine kinase domain to trigger autophosphorylation and transphosphorylation to form pEGFR to activate a cascade of downstream enzymatic signaling pathways that transmit signals to the nucleus (24-26). CYFRA21-1, an intermediate fiber between tumor cytoskeletal proteins and normal cells that exists in the cytoplasm of epithelial cells, releases cytokeratin into the blood when the cells become cancerous (27), resulting in higher expression of CYFRA21-1 in serum. Involved with tumor TNM stage, duration of disease, and prognosis, the serum level of CYFRA21-1 can be used as a reference index for disease judgement (28).

The two groups of patients were comparable since they were not different in general information. According to this study, the total effective rate and local effective rate of the experimental group were significantly higher than those of the control group. In the study of Lemjabbar-Alaoui *et al* (29) that used gefitinib combined with GP regimen in the treatment of advanced NSCLC, the efficacy was greatly improved, the adverse reactions caused by chemotherapy drugs were reduced, along with a significantly improved patient prognosis. Jiang and Zhou (30) considered that gefitinib had better efficacy and tolerance than the traditional chemotherapy for patients with advanced NSCLC. Such previous studies, together with the result of this study, prove the good value of gefitinib for advanced NSCLC. One previous report suggests that serum tumor markers can reflect the process of malignant tumor cell transformation, and the detection of tumor marker expression has a good effect on tumor diagnosis, efficacy and prognosis evaluation (31). The study by Clifford *et al* (32) showed that EGFR, an expression product of proto-oncogene c-erbB1 activation that is highly expressed in various tumors such as lung cancer, and is closely related to tumor cell proliferation, invasion and metastasis. One study also found that CYFRA21-1 had a high sensitivity to the diagnosis of NSCLC, with an increase of serum concentration as the disease progressed (33). According to this study, after treatment, the expression levels of EGFR and CYFRA21-1 in the experimental and control groups were significantly lower than those in the two groups before treatment, with much lower expression levels of EGFR and CYFRA21-1 in the experimental group than in the control group, indicating the strong inhibition by gefitinib on the expression of EGFR and CYFRA21-1. The subgroups by efficacy showed the serum expression levels of EGFR and CYFRA21-1 in the effective group after treatment were significantly lower than those before treatment. The serum expression levels of EGFR and CYFRA21-1 in the ineffective group were not significantly different from those before treatment. After treatment, the levels of EGFR and CYFRA21-1 in the effective group were significantly lower than those in the ineffective group, suggesting that the detection of serum levels of EGFR and CYFRA21-1 can make certain prediction of the treatment efficacy. Boulmier *et al* (34) reported in their study that patients with advanced NSCLC who enjoyed good efficacy from targeted therapy had much decreased serum concentration of CYFRA21-1, while patients receiving poor efficacy from targeted therapy had greatly increased serum concentration of CYFRA21-1. A previous report pointed out that, considering the much reduced EGFR expression after the targeted therapy, the peripheral blood EGFR protein expression was capable of being a molecular biological indicator for predicting and evaluating the efficacy and prognosis gefitinib had for patients with advanced NSCLC (35). Based on the follow-up and the comparison of patient survival between the two groups, the 3-year survival rate in the experimental group was significantly higher than that in the control group, suggesting a longer survival time due to gefitinib combined with chemotherapy. Studies have reported that targeted drug treatment for EGFR mutation-positive NSCLC patients can significantly improve the patient's objective response rate and prolong the survival time (36). According to the 3-year survival rate, the experimental group was divided into the survival and non-survival groups. The single factor analysis was performed on the general data, showing that the influencing factors of the survival include the KPS score, smoking history, number of lesions, pathological stage, EGFR, and CYFRA21-1. Subsequently, the multivariate Cox regression analysis of different indicators confirmed that smoking history, a KPS score less than or equal to 60 points, multiple lesions, pathological stage IV, high expression of EGFR and CYFRA21-1 were important factors affecting the survival of advanced NSCLC. Studies have also demonstrated that the independent factors influencing the overall survival of patients include age, pathological type, number of previous chemotherapy regimens, and number of the chemotherapeutic cycles (37). Smoking history, a KSP score equal to or more than 70 points are factors affecting the prognosis of patients with locally advanced NSCLC that is not suitable for surgery (38). Further validation is needed to explore the specific risk factors that affect patients with advanced NSCLC. Some studies also stated that a decreased range equal to or >30% in the EGFR and CYFRA21-1 levels can be used as an independent prognostic factor for patients with advanced NSCLC (35,39).

This study made an exploration of the effect of gefitinib on serum EGFR and CYFRA21-1 in patients with advanced NSCLC. However, there are some limitations due to the lack of analysis of the drug tolerance in patients orally administered gefitinib and the possible bias of the experimental design of retrospective analysis.

In conclusion, gefitinib can bring significantly improved therapeutic efficacy, lower expression levels of EGFR and CYFRA21-1, and longer survival time for patients with advanced NSCLC. Indicators including confirmed smoking history, a KPS score less than or equal to 60 points, multiple lesions, pathological stage IV, high expression of EGFR and CYFRA21-1, are important factors affecting the survival of patients with advanced NSCLC.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HR wrote the manuscript. YangH and TX were responsible for ELISA. CJ and YanpingH analyzed and interpreted the patients' data. BY helped with statistical analysis. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hubei Cancer Hospital (Wuhan, China). Patients who participated in this research, signed the informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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