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ORIGINAL ARTICLE

Therapeutic effect of gefitinib in advanced non-small cell lung cancer and its effect on the EGFR level in peripheral blood

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Summary

Purpose: *This study was designed to investigate the therapeutic effect of gefitinib in advanced non-small cell lung cancer (NSCLC) and its effect on the level of epidermal growth factor receptor (EGFR) in peripheral blood.*

Methods: *A total of 58 patients with NSCLC were treated with gefinitib (iressa) (250 mg per day). EGFR levels in the peripheral blood were measured with ELISA assay before and after treatment. Statistical analyses of patient quality of life, survival and other clinical data were conducted including logistic regression analysis, x^2 test and t-test. Quality of life assessment was quantified based on the Chinese version of the QLQ-C30 and QLQ-LC13 questionnaires of the European Organization for Research and Treatment of Cancer.*

Results: *The overall response rate to iressa was 38% (22 patients), and the disease control rate (response+stable) was 74% (43 patients). The mean scores of assessment of physiological functions and comprehensive quality of life in QLQ-C30 questionnaire were significantly increased with an improvement rate of 91-100%. Similarly, the mean scores of assessment of disease symptoms in QLQ-LC12 questionnaire were significantly reduced with an overall improvement rate of 73-100%. Adverse drug effects were mainly grade I and II skin rashes and diarrhea. The EGFR levels in peripheral blood were significantly decreased after treatment ($p<0.05$).*

Conclusion: *Based on our results, gefitinib showed meaningful effects in treating advanced NSCLC, significantly improving clinical symptoms and ameliorating the patient quality of life.*

Key words: *comprehensive quality of life score, epidermal growth factor receptor, gefitinib, non-small cell lung cancer*

Introduction

The incidence of lung cancer has been increased significantly in the last years along with the improvements in economic development around the globe [1,2]. NSCLC accounts for about 75% of all the lung cancers. Epidemiological evidence shows that in China the average 5-year survival rate is merely 16% for all NSCLC, with the 5-year survival rate being 20% for non-advanced NSCLC patients, and 3% for metastatic cancer patients [3-5]. Gefitinib is a selective inhibitor of the EGFR, useful in the treatment of locally advanced lung cancer or NSCLC patients who had previously undergone chemotherapy or are not suitable for chemotherapy [6,7]. However, as of this time, there is no clear information about its therapeutic effect, its safety or the effects it may have in improving patients' quality of life. This study aimed at providing a theoretical basis for clinical application of gefitinib for the treatment of patients with advanced NSCLC, by examining the clinical efficacy and prognosis in several treated cases.

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Methods

Subjects

A total of 58 patients with advanced NSCLC were enrolled in this study. The patients were admitted to our hospital from January 2010 to January 2012, and their age ranged from 27-82 years (mean 58.3 ± 12.7). Detailed clinical data of all the participants are listed in Table 1.

Inclusion criteria: All eligible patients signed informed consent. All of them should have been diagnosed and pathologically confirmed with stage IIIB or IV NSCLC. They should be 18 years or older, and should be not responsive to or suitable for standard chemotherapy or radiotherapy. The patients should have an expected survival of at least 3 months, had at least one measurable or assessable tumor lesion, had normal bone marrow hematopoiesis and liver and kidney function tests, and should not be treated with any anti-tumor therapy in at least one month.

Exclusion criteria: Pregnant or lactating women, patients with active infections or other potentially serious diseases, and patients without clinical indicators other than brain or bone metastases.

Table 1. Clinicopathological data of enrolled patients

Clinicopathological data	*Patients, n*	%
Gender		
Male	33	56.9
Female	25	43.1
Tumor histology		
Adenocarcinoma	29	50
Bronchial alveolar carcinoma	14	24.14
Squamous cell carcinoma	10	17.24
Large cell and undifferentiated carcinoma	5	8.62
Age (years)		
< 70	50	86.21
≥ 70	8	13.79
TNM stage		
IIIB	9	15.52
IV	49	84.48
ECOG PS score before treatment (points)		
0-1	37	63.79
2	12	20.69
3	9	15.52
Past treatment history		
Never treated	15	25.86
First-line (NP,GP,TP)	23	39.66
Above second-line (TXT)	20	34.48

ECOG: performance status score, NP: navelbine+cisplatin, GP:gemcitabine+cisplatin, TP: taxotere+cisplatin, TXT: taxotere

Procedures

All patients received Iressa 250 mg per day orally, stopping the treatment either because of disease progression or serious adverse reactions. Patients were reviewer-examined every 3-4 weeks. Every 6 months a chemotherapy cycle was completed. Cycles continued in the absence of significant adverse reactions or signs of drug resistance.

Evaluation of objective response and adverse reactions

A pre-treatment baseline was obtained by performing computed tomography scan of the chest and brain, ultrasound of the abdomen, radionuclide scan of bone, and laboratory tests including blood, liver and kidney function tests. After each chemotherapy cycle, the measurable lesions were re-assessed. The above checks were repeated every 3 months during treatment. The tumor response assessment was conducted according to the World Health Organization response criteria published in 1981, which included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The response rate (RR) was calculated from the sum of the percentage of CR + PR. The response had to be maintained for more than one week to be considered positive. Adverse reactions were evaluated using 0-IV degrees in accordance with the FG8 toxicity of anticancer drugs [3].

Quality of life assessment

The core questionnaire of the European Organization for Research and Treatment of Cancer (EORTC), QLQ-C30, and the lung cancer-specific questionnaire (QLQ-LC13) were used for quality of life evaluation before treatment and at the end of each chemotherapy cycle. Improvement of patients' symptoms and quality of life were analyzed after three consecutive treatment cycles.

Measurement of EGFR level in peripheral blood by enzyme-linked immunosorbent assay (ELISA)

An ELISA kit was used to measure the expression of EGFR in peripheral blood. The kit was purchased from Nanjing Jiancheng Co., Nanjing, China. Peripheral blood (4 mL) was collected from the patient's arm, and EDTA was added to the sample for anticoagulation. The ELISA kit user instructions were followed for running the assay.

Statistics

The SPSS 21.0 software (SPSS Inc., IL, US) was used in this study to perform the statistical analysis of the data obtained. Logistic regression analysis was applied to determine the impact of the patient's pre-treatment condition on the treatment response and prognosis. The median time to progression (TTP) and the median overall survival (OS) were assessed by the Kaplan-Meier method. The log-rank or the Wilcoxon tests were applied to the hierarchical analysis. The paired t-test was used to compare the symptoms and quality of life scores of patients before and after 2 cycles of treatment. The x^2 test was used to compare the symptoms and quality of life improvement of patients, with and without an objective response after treatment.

Results

Objective response

Among the cases studied, there were 22 responding patients, giving a response rate of 38% (PR only). There were 21 SD cases (36%), and the disease control rate (PR+SD) was of 74% (43 cases). The logistic regression analysis showed the response was correlated with gender and tumor histology ($p<0.01$), but not with the age of the patient, TNM staging or past chemotherapy regimen ($p>0.05$). Further analysis demonstrated that female patients had better response than male patients (Wald (x^2) test, OR=3.062, 95%CI=1.502-6.225, $p<0.01$). Bronchial alveolar carcinoma resulted in a better patient response than other type of lung cancers (exact x^2 test, OR=3.013, 95% CI=1.793-5.632, $p<0.01$). The results are shown in Tables 2 and 3.

Survival analysis

The mean follow-up time for all the patients was of 278 days (range 42-568), and the mean TTP was 252 days (95% CI=177.04-328.92). Patients with adenocarcinoma had a TTP of 287 days (95% CI=205.44-372.56), which was significantly longer than the 93 days (95% CI=88.44-92.56) for patients with other cancer types (log-rank test, $p<0.01$). At the end of treatment there were 40 patients with adenocarcinoma who had survived, with an OS longer than 429 days. In contrast, patients with other cancer types had a significantly shorter OS of only 158 days (95% CI=53.88-214.32; log-rank test $p<0.01$).

Adverse reaction analysis

The incidence of rash was 50.0 %, and of diarrhea 27.6% taking into account all the subjects treated with gefitinib. Other adverse reactions were mild, and no one had to discontinue the administration of the drug due to a severe adverse reaction. The detailed adverse reaction analysis is shown in Table 4.

Quality of life assessment

Among the 58 patients in this study, 46 were assessed for quality of life before and after treatment. The scores of the EORTC QLQ-C30 after

Table 2. Multivariate analysis of the relationship between overall survival and prognostic factors

Prognostic factors	*Patients, n*	*OS (months)*	*p value*
Gender			0.007
Male	33	48.4±5.5	
Female	25	61.3±6.1	
Tumor histology			0.017
Adenocarcinoma	29	55.4±7.2	
Bronchial alveolar carcinoma	14	64.2±7.3	
Squamous cell carcinoma	10	42.3±3.2	
Large cell and undifferentiated carcinoma	5	32.5±8.4	
Age, years			0.748
< 70	50	47.8±5.1	
≥ 70	8	54.3±9.2	
TNM Stage			0.386
IIIB	9	57.6±10.2	
IV	49	45.9±5.1	
ECOG score before treatment (points)			0.398
0-1	37	57.7±7.1	
2	12	43.6±7.2	
3	9	44.9±8.1	
Past treatment history			0.323
Never treated	15	47.3±7.5	
First-line (NP, GP, TP)	23	49.7±5.3	
Above second-Line (TXT)	20	48.3±3.3	

OS: overall survival. For other abbreviations see footnote of Table 1

Table 3. Multivariate analysis of risk factors

Variable	*B*	*SE*	*WALD*	*df*	*Sig*	*OR*	*95% CI for Exp (B)*	
							Lower	Upper
Gender	0.268	0.216	3.062	1	0.056	3.062	1.502	6.225
Tumor histology	0.484	0.227	3.321	1	0.026	3.013	1.793	5.632

treatment had significantly improved, and therefore the scores of the EORTC QLQ-LC13 were significantly lower (Table 5). The improvement rates in the general health status, physical condition, role capacity, and social behavior in the EORTC QLQ-C30 questionnaire correlated with the response after treatment ($p<0.01$). Similarly, the improvement rates for fatigue, anorexia, suffocation, cough and others in the EORTC QLQ-LC13 questionnaire correlated with response after treatment as well ($p<0.01$).

EGFR expression in peripheral blood

The expression of EGFR in the peripheral blood of the patients was significantly lower than that before treatment ($p<0.05$; Table 6).

Discussion

EGFR is a big transmembrane glycoprotein with a molecular weight of about 180 kDa and possesses ligand-induced tyrosine kinase activity. EGFR is a member of the ErbB family of receptors [8]. ErbB receptors have in common an extracellular ligand-binding domain, a single transmembrane segment, and a cytoplasmic protein tyrosine kinase domain [9]. About one- to two-thirds of patients with NSCLC have high EGFR expression [8]. It has been found that the activation of overexpressed EGFR initiates uncontrolled cell division through signal transduction cascades, which may lead to cell proliferation and angiogenesis. NSCLC, in cases with EGFR overexpression, tends to be highly aggressive and prone to metastasis, and displays poor response to chemotherapy, short recurrence time, high recurrence rate and short survival [9]. EGFR tyrosine kinase (EGFR-TK) is an important target for tumor chemotherapy, due to its role in signal transduction of the EGFR signal pathway [9]. Selective tyrosine kinase inhibitors can inhibit activation of EGFR, thus inhibiting cell cycle progression. Inhibiting cell division and angiogenesis results in cell apoptosis. In theory, tumor cell infiltration and metastasis would get suppressed, which in turn provides tumor cells with enhanced sensitivity to radiotherapy and chemotherapy [10,11]. EGFR has tyrosine kinase activity, and once bound with epidermal growth

Table 4. Adverse reaction analysis

Adverse reactions	*Grade I-II*	*Grade IIIB-IV*	*Total*
Rash	25	4	29
Diarrhea	14	2	16
Ulcer	4	0	4
Anorexia	3	0	3
Elevated glutamine transferase	0	1	1
Glossitis	1	0	1

Table 5. Quality of life assessment

Items	*Before treatment*	*After treatment*	*p value*
EORTC QLQ-C30			
General Health Status	36.4±25.3	55.2±18.2	0.001
Physical Functioning	47.3±21.3	65.8±20.3	0.004
Role Functioning	42.3±35.4	56.2±25.8	0.005
Emotional Functioning	67.8±28.3	85.3±19.4	0.003
Cognitive Functioning	66.8±28.3	76.4±18.3	0.002
Social Functioning	42.3±32.5	61.2±28.3	0.008
EORTC QLQ-LC13			
Fatigue	63.3±25.4	45.3±22.4	0.001
Loss of appetite	41.2±37.2	20.5±24.9	0.002
Short of breath	60.4±28.3	39.5±23.5	0.009
Cough	58.4±36.5	28.9±30.4	0.008
Chest pain	35.6±32.3	17.5±19.5	0.562

Table 6. EGFR expression in peripheral blood of the patients before and after treatment

Case number	*Before treatment*	*After treatment*	*T value*	*p value*
58	38.4 ± 12.9	21.8 ± 10.2	21.8	0.002

factor (EGF) it can stimulate relevant genes within the nucleus, thereby promoting cell division and proliferation. Gastric, breast, bladder cancers and squamous cell carcinoma of the head and neck all display an overexpressed EGFR [12-15].

Gefitinib is a selective inhibitor of EGFR-TK that is normally expressed in epithelial-derived solid tumors [18,19]. Inhibition of EGFR-TK activity can suppress tumor growth, metastasis and angiogenesis, leading to tumor cell apoptosis. *In vivo* gefitinib broadly inhibits tumor growth in xenografts of human tumor cell lines in nude mice, and enhances the antitumor activity of chemotherapeutic agents, radio-and hormone therapies [20]. In clinical trials gefitinib was shown to stimulate an antitumor response to locally-advanced or metastatic NSCLC and to improve disease-related symptoms [21]. In terms of its pharmacokinetic properties, after intravenous administration gefitinib was rapidly cleared and widely distributed with an average clearance half-life of 48 hrs [21].

In two large-scale phase II clinical trials (IDEAL1, IDEAL2) conducted in Europe and the United States, 526 patients with advanced NSCLC, who experienced disease progression after treatment with a platinum-based and/or taxotere (TXT) chemotherapy regimen, were randomized to take gefitinib 250 mg per day or 500 mg per day [21]. Both studies showed that gefitinib was effective in the treatment of patients with NSCLC who failed previous treatment with platinum-based and/or TXT chemotherapy regimen with a similar response in the low- and high-dose groups, but with a significant reduction in adverse events. In this study the overall response rate of gefinitib was 38% (22 patients), and the disease control rate (PR+stable) was 74% (43 patients). The average scores of assessment of physiological functions and comprehensive quality of life in QLQ-C30 questionnaires were significantly increased with an improvement rate of 91-100%. Accordingly, the average scores of assessment of disease symptoms in QLQ-LC12 questionnaires were significantly reduced with an overall improvement rate of 73-100%. Adverse drug effects were mainly grade I and II skin rashes and diarrhea. The EGFR levels in peripheral blood were significantly decreased after treatment, and the differences were statistically significant ($p<0.05$). Our results showed that gefitinib treatment can effectively improve EGFR expression levels in the patients' peripheral blood, and can significantly improve the patient quality of life. On the basis of previous studies, clinical safety and applications of gefitinib were further explored in this study. In conclusion, gefitinib treatment of advanced NSCLC has a definite beneficial therapeutic effect, and can significantly improve the clinical symptoms and the patient quality of life and therefore it should always be considered as a therapeutic agent in these cases.

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Conflict of interests

The authors declare no conflict of interests.

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