

## RESEARCH ARTICLE

# Serum CEA Level Change and Its Significance Before and after Gefitinib Therapy on Patients with Advanced Non-small Cell Lung Cancer

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### Abstract

**Objective:** The aim of this study was to explore change and significance of serum carcino-embryonic antigen (CEA) before and after gefitinib therapy in patients with advanced non-small-cell lung cancer (NSCLC). **Methods:** Forty patients with advanced NSCLCs in III~IV stages were selected as study objects given gefitinib therapy combined with routine local radiotherapy until tumor progression or intolerable toxicity. After treatment, all patients were divided into control and non-control groups according to the results of evaluation based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors in 2009). Peripheral fasting blood from all patients was collected in the early morning and serum CEA was assessed by electro-chemiluminescence immunoassay (ECLIA) before and after treatment. Before treatment, patients were divided into high CEA group (CEA level > 50 ng/mL) and low CEA group (CEA level ≤ 50 ng/mL). Adverse reactions were noted and progression-free survival (PFS) in both groups was recorded after long-term follow-up that ended in December, 2012. **Results:** There was no difference between control and non-control groups in CEA level before treatment ( $P > 0.05$ ), whereas serum CEA decreased more markedly lower in the control group after treatment ( $P < 0.01$ ). All patients were divided into high CEA group (26) and low CEA group (14) according to serum CEA level. There was no statistically significant difference between two groups in adverse reactions ( $P > 0.05$ ) but the rate in former group was lower. Additionally, survival rates at 9 and 12 months in high CEA group were clearly higher than in the low CEA group ( $P < 0.01$ ). **Conclusions:** Serum CEA level can serve as a biochemical index to evaluate the prognosis with gefitinib treatment for NSCLC.

**Keywords:** Non-small-cell lung cancer - advanced - gefitinib - carcino-embryonic antigen

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### Introduction

Lung cancer is one of the worst malignant tumors in the world, in which NSCLC is commonly treated by conventional systematic chemotherapy (Liu et al., 2013; Lu et al., 2013). Though the chemotherapy can prolong patients' survival to some degree, but it has poor effect on middle and advanced NSCLC. Studies in recent years have showed that molecular targeted therapy is favorable in treating NSCLC (Maftouh et al., 2013; Sechler et al., 2013). As one of the molecular targeted therapeutic drugs and as the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), gefitinib has great anti-tumor function in progressive and recurrent NSCLC (Lee et al., 2013; Morabito et al., 2013; Sudo et al., 2013). The purpose of this study was to explore the serum CEA level change and its significance before and after gefitinib treatment in patients with advanced NSCLC.

### Materials and Methods

#### General Data

Of the 40 patients with NSCLC in III~IV stage admitted in our hospital from April, 2009 to April, 2011, 20 were males and the others were female aging from 35 to 75 with average age being  $62.3 \pm 5.9$ , in which 29 patients were with adeno-carcinoma and 11 with non- adeno-carcinoma, according to WHO classification criteria in histology, while 3 were classified in IIIA stage, 4 in IIIB stage and 34 in IV stage in clinic based on International Classification for Lung Cancer established by International Union Against Cancer (IUAC) in 2009. Patients received operations, radiotherapy and chemotherapy over 1 week or those with sever abnormality in electrocardiogram, routine blood and hepato-renal function were excluded from the research, then those enrolled were examined by transbronchial lung biopsy to diagnose pathology, and

**Table 1. General Data of Two Groups**

Programs	Control group	Non-control group
Cases	25	15
Ages	61.5±6.1	63.0±5.2
Genders (male/female)	13/12	7/8
Pathological types		
Adenocarcinoma/cases	18	11
Non-adenocarcinoma/cases	7	4
TNM stages		
IIIA stage/cases	2	1
IIIB stage/cases	2	1
IV stage/cases	21	13
Smoking situation		
Smoker	10	8
Non-smoker	15	7

**Table 2. Comparison of Serum CEA Level Before and after Treatment Between Two Groups ( $\bar{x}\pm s$ )**

Groups	Cases	CEA/ng·mL <sup>-1</sup>
Control group	25	
Before treatment		67.25±1.90
After treatment		42.66±1.64***#
Non-control group	15	
Before treatment		66.35±1.86
After treatment		56.45±2.63**

Compared with treatment before, \*\*P<0.01; Compared with non-control group, #P<0.01

were given routine head, chest and abdomen CT scan and whole body bone scan.

*Therapeutic methods*

All study objects were given gefitinib, 1 tablet/d combined with routine local radiotherapy until tumor progression or being intolerable. Head and chest CT scan and abdominal CT were conducted every month to record the scope and size of metastatic tumors, and long-term follow-up was carried out until December, 2012.

*Serum CEA detection*

Peripheral fasting blood of all patients were collected in early morning before and 2 courses after gefitinib therapy to detect serum CEA level while tumor-associated antigen quantitative assay kit and ELECYS 2010 full-automatic ECLIA analyzer from German Roche were adopted for CEA collection and detection.

*Efficacy evaluation*

Therapeutic efficacy was divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD), according to the results of head CT scan and nuclear magnetic resonance, chest and abdomen CT scan as well as bone scan, and efficacy of gefitinib was evaluated based on RECIST 1.1 Criteria in 2009. Patients with CR, PR and SD were divided into control group while those with PD served as non-control group.

*Observational index*

Before treatment, all patients were divided into

**Table 3. Adverse Reactions in Two Groups [n (%)]**

Adverse reactions	High CEA group (n=26)	Low CEA group (n=14)
Pruritus	7(26.9)	6(42.9)
Rash	8(30.8)	5(35.7)
Diarrhea	5(19.2)	4(28.6)
Nausea	1(3.8)	1(7.1)
Constipation	1(3.8)	1(7.1)
Fever	2(7.7)	2(14.3)

**Table 4. Comparison of PFS Progression in Two Groups [n(%)]**

PFS	High CEA group (n=26)	Low CEA group (n=14)
3 month	25(96.2)	12(85.7)
6 month	22(84.6)	9(64.3)
9 month	16(61.5)*	4(28.6)
12 month	13(50.0)*	2(14.3)
Over 12 month	4(15.4)	1(7.1)

Compared with low CEA group, \*P<0.05

high CEA group (CEA level > 50 ng/mL) and low CEA group (CEA level ≤ 50 ng/mL) with 50 ng/mL being the boundary of CEA level. Adverse reactions and PFS were observed.

*Statistical data analysis*

SPSS13.0 software was applied and T test was used to compare the means of two groups with enumeration data being presented as mean ± standard deviation ( $\bar{x}\pm s$ ). P<0.05 was regarded as statistically significant.

**Results**

*Clinical features before treatment*

After treatment, CR had 0 out of 40 patients, PR 20, SD 5 and PD 15, in which 25 were in control group and 15 in non-control group. General data of two groups are shown in Table 1.

*Comparison of serum CEA level before and after treatment between two groups*

As shown in Table 2, serum CEA level had no difference between two groups before treatment (P>0.05), but it decreased evidently and was lower in control group than in non-control group after treatment (P<0.01).

*Adverse reactions*

All patients were divided into high CEA group (26) and low CEA group (14) according to serum CEA level before treatment. As shown in Table 3, the adverse reactions mainly include pruritus, rash, diarrhea, nausea, constipation and fever, etc. The rate of adverse reactions in high CEA group was higher than in low CEA group, but there was no statistically significant difference (P>0.05).

*PFS analysis*

As shown in Table 4, PFS in 9 and 12 months were significantly higher in high CEA group than in low CEA group (P<0.05).

## Discussion

Lung cancer is one of the worst malignant tumors commonly seen in middle and elderly people. There are hardly any favorable therapies for patients with middle and advanced NSCLC due to its increasing morbidity and mortality (Wu, 2012; Han et al., 2013; Liang et al., 2013). Genetic markers, tumor vessels and T cell receptors are frequently used as the targets of molecular targeted therapy for lung cancer, in which epidermal growth factor receptor (EGFR) is the major one at present (Aydiner et al., 2013; Tomonaga et al., 2013; Wheler et al., 2013). With the development of human immunology and molecular biology, people have gained profound recognition of tumor markers and targeted molecules with marvelous achievements. The so called tumor markers are abnormal products of the reactions of human bodies to tumors or those secreted by synthesis of tumor cells, which can be used to diagnose and evaluate the efficacy and prognosis of drugs. Many studies have confirmed that the development of targeted drugs and therapies are beneficial to the clinical treatment of patients with NSCLC (Acunzo et al., 2013; Sakai et al., 2013; Tanaka et al., 2013). EGFR is one of the trans-membrane tyrosine kinase receptors, and its signal transduction pathway is closely associated with multiplication, invasion, metastasis, angiogenesis and vascular apoptosis of tumor cells. Previous reports have showed that EGFR is important in ErbB, including 3 structures named GHRI, GHRE and trans-membrane region. Once it binds with ligand, EGFR will produce a homodimer or heterodimer on cell surface, inhabiting the occurrence and development of lung cancer. Studies of some researchers have revealed that proper expression of EGFR in epithelium-derived tumor cells (breast cancer or NSCLC, etc.) not only regulate cell proliferation, but also has critical impact on the development of tumors, formation of vessels as well as metastasis and spreading of tumor cells, whereas over-expression of EGFR is insensitive to chemotherapy and radiotherapy, which can easily bring about distant metastasis and poor prognosis (Al et al., 2013; Karachaliou et al., 2013; Lopez-Rios et al., 2013). Results of other studies have indicated that EGFR is over expressed in 40~80% of NSCLC patients with poor prognosis but it can be activated by selective inhibition of targeted therapy on the activity of tyrosine kinase (TK) to inhibit proliferation, invasion and metastasis of tumor cells and strengthen chemotherapeutic effect (Al, 2012; Chen et al., 2013).

Gefitinib is the first targeted drug being registered and approved by U.S. FDA (Food and Drug Administration) in treating NSCLC presently, and is commonly used in clinic with reliable and favorable effects. Its main mechanism is to promote the apoptosis of tumor cells through competitive combination with triphosphadenine to inhibit phosphorylation of EGFR and downstream signals (Lee et al., 2012; Shrestha et al., 2012). CEA is one of the tumor markers widely used in clinic that can be directly produced by tumor cells and is in close association with recurrence and metastasis of tumors. It can also be secreted by the expression of tumor cell genes to early diagnose lung cancer, evaluate therapeutic effect

and observe the progression of disease. Remission rate of gefitinib on advanced lung cancer reaches to 10%~19%, demonstrating that it is effective in treating NSCLC and can improve patients' life quality synchronously. Some researchers found that serum CEA level could serve as the predictive index for EGFR-TKI in treating advanced NSCLC, for its detection was simple in method, mature in technology, efficient, quantitative and repeatable, and could be used to evaluate therapeutic effect by observing CEA level change during treatment. One research has indicated that serum CEA level can reflect the therapeutic effect and the higher the CEA level is before treatment, the better the effect will be, showing that serum CEA level before treatment can foretell the effect of gefitinib to some degree, but the mechanism is still unclear.

The results of this study showed that CEA level in peripheral blood was evidently lower after treatment of patients with advanced NSCLC than treatment before, and patients in control group had lower CEA level than those in non-control group, which was consistent with other researches, demonstrating that as the targeted drug for lung cancer, gefitinib could remarkably reduce the expressive level of CEA in peripheral blood of patients with advanced NSCLC, and the CEA level changed more obviously in patients with favorable outcomes. It was also found in this research that patients with high CEA expression had significant difference in PFS than those with low CEA expression, therefore it was believed that patients with high expression of CEA treated by gefitinib had better prognosis. As to adverse reactions, pruritus, diarrhea, nausea and rash were frequently seen in clinic with good tolerance, which had no influence on therapeutic effects.

This study also showed that PFS and survival time in advanced NSCLC patients with high CEA expression treated with gefitinib increased significantly, suggesting that as an important index for evaluating the therapeutic effect and prognosis of advanced lung cancer, CEA level could accurately predict, reflect and evaluate the clinical therapeutic effect of gefitinib on patients with advanced NSCLC.

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