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The level of serum carcinoembryonic antigen is a surrogate marker for the efficacy of EGFR-TKIs but is not an indication of acquired resistance to EGFR-TKIs in NSCLC patients with EGFR mutations

JINGQUAN HAN[1*], YUZHANG LI[2*], SHOUQIANG CAO[1,3], QING DONG[1], GUIBIN ZHAO[1], XIANGYU ZHANG[1] and JIAN CUI[1]

[1]Department of Thoracic Surgery, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001; [2]Department of Thoracic Surgery, Heilongjiang Provincial Hospital, Harbin, Heilongjiang 150036; [3]Science and Technology Innovation Park, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, P.R. China

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Abstract. The aim of the present study was to define the relationship between carcinoembryonic antigen (CEA) and survival in non-small cell lung cancer (NSCLC) patients receiving epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and to investigate whether the level of serum CEA is related to the mechanism for acquisition of resistance to EGFR-TKIs. A total of 100 patients with advanced NSCLC (stage IIIB or stage IV) and harboring EGFR mutations were included. All patients received erlotinib or gefitinib treatment. The correlation between CEA serum level and clinical benefit from erlotinib or gefitinib treatment was analyzed. Patients were appraised by a review of data from a prospective re-biopsy protocol for lung cancer patients with an EGFR-mutated phenotype with acquired resistance to EGFR-TKI therapy. Of 100 patients, 49 and 21 patients carried high and low level of CEA, respectively; 30 carried normal CEA. Median progression-free survival was 6.4 and 4.5 months in patients with high and low level of CEA, respectively (P=0.027). Median PFS of patients in low-CEA group longer than that of those with normal level of tumors (3.0 months; P=0.002). The difference between groups L and N was not significant regarding objective response rate and overall survival. No significant difference was found in three groups of acquired resistance to EGFR-TKIs. The relative CEA level could predict benefit of EGFR-TKI therapy in advanced NSCLC, but could not predict acquired resistance to EGFR-TKIs.

Correspondence to: Dr Shouqiang Cao, Department of Thoracic Surgery, The Fourth Affiliated Hospital of Harbin Medical University, 37 Yi yuan Street, Harbin, Heilongjiang 150001, P.R. China
E-mail: csqrock@hotmail.com

*Contributed equally

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Introduction

Lung cancer has taken over from liver cancer as the leading cause of death in patients with malignant tumors in China (1). At least 30% of non-small cell lung cancer (NSCLC) patients missed the opportunity to have an operation when first visiting the doctor; therefore, their prognosis became worse, due to lack of effective therapy (2). EGFR-targeted therapy is a promising strategy for the treatment of NSCLC; some randomized trials have demonstrated a significantly higher tumor remission rate and longer progression free survival (PFS) in patients with EGFR mutation treated with first-line TKI (2-7). The frequency of the EGFR mutation in NSCLC in the Asian population is ~30%, while the white population is ~20% (8,9). In clinical subgroups, the frequency of mutation in Asian males and smokers is lower than that of Asian females and non-smokers (5,10).

Despite the initial success of these drugs in all patients, the median progression free survival was 12-16 months (4,7,11). Acquired resistance to EGFR-TKIs has been attributed to several molecular mechanisms, although the resistance of patients with unknown etiology is ~35% (12). The most common causes of resistance are the development of the T790M mutation (13), amplification of MET (14,15) and, in rare cases, transformation to small cell histology (16). Despite clinical evidence for progress in the treatment of EGFR-TKI, continued EGFR inhibition seems to provide sustained clinical benefit (17,18).

Carcinoembryonic antigen (CEA), recognized as a NSCLC marker, is also can be used for detecting adenocarcinoma with ~60% sensitivity and 50% specificity (19,20), whereas the

sensitivity and specificity is ~25 to 40% and 25%, respectively, for squamous cell carcinoma (21,22). According to previous reports, CEA was a significant predictor of sensitivity and survival in patients treated with gefitinib (23,24) However, the CEA level as a predictive marker of response to EGFR-TKIs has not been extensively evaluated. The authors assumed that the level of CEA could predict the extent of benefit from EGFR-TKIs, and tumor patients with high serum CEA level may benefit more from EGFR-TKIs than those with low serum CEA level.

Patients and methods

Patients. Patients with the clinic diagnosis of NSCLC treated at the Department of Thoracic Surgery of the Fourth Affiliated Hospital, Harbin Medical University (Harbin, China) were recruited between February 2012 and May 2015. Inclusion criteria comprised: Patients with stages IIIB to IV NSCLC who had received palliative surgical resection were confirmed for EGFR mutations (either exon 19 deletions or L858R in exon 21) and received either erlotinib 150 mg/day or gefitinib 250 mg/day orally (clinical stage was determined by the 7th edition of tumor, node, metastasis classification) (25). The patients were enrolled for palliative care with EGFR-TKIs if they had an Eastern Cooperative Oncology Group performance status of 0-2 and life expectancy >3 months. Patients were appraised by a review of data from a prospective re-biopsy protocol of patients with acquired resistance to EGFR tyrosine kinase inhibitors. Patients with a previous history of malignancy were excluded. The study was approved by the institutional review boards of the Fourth Affiliated Hospital of Harbin Medical University (Harbin, China). Informed consent was acquired from each patient prior to the commencement of treatment.

Methods. Serum CEA was measured by an enzyme immunoassay within one week before starting the erlotinib or gefitinib treatment. Measurement was performed at the Clinical Laboratory of the Fourth Affiliated Hospital of Harbin Medical University using a sequential chemiluminescence immunoassay (Immulite 2000 Immunoassay System; Siemens Healthineers, Erlangen, Germany). The total included 100 patients were categorized into three groups according to their serum CEA level: High-CEA group (H), CEA baseline levels >10 ng/ml, normal-CEA group (N), CEA baseline levels <5.0 ng/ml and low-CEA group (L), CEA baseline levels between 5 ng/ml and 10 ng/ml. The authors analyzed the correlation between serum CEA level and clinical benefits in the patients receiving EGFR-TKI treatment.

Statistical analyses. The primary endpoint, progression-free survival was calculated from the first day of treatment to the date of the first disease progression or, under the condition without disease progression, the last follow-up or death. The overall survival (OS) rate was calculated from the first day of treatment to the date of mortality due to any cause or the date of the last follow-up. The secondary endpoints contained objective response rate (ORR), OS and safety. The PFS and OS rates were estimated using the Kaplan-Meier life-table method and the survival curves were compared using the log-rank test. Comparison of ORRs in different groups was performed using χ^2 tests. Independent predictive factors associated with PFS were evaluated in multivariate analysis using a Cox regression model. All P-values were based on two-sided testing and statistical analyses were carried out using SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. Between February 2012 and May 2015, a total of 320 patients with the diagnosis of advanced NSCLC were screened for EGFR mutations before the start of EGFR-TKIs. A total of 100 patients were completely consistent with the inclusion criteria. Of the 100 patients, 54 were female and 46 men, with a mean age of 55 years (range, 23-84). In the 100 patients, 80 were non-smokers and 20 past or current smokers; 93 had adenocarcinoma, 6 squamous cell carcinoma and one adenosquamous carcinoma; according to TNM classification, 13 were in stage IIIB and 87 in stage IV. A total of 49 patients (49%) with a baseline CEA level (>10 ng/ml) were recruited with median CEA of 222.8 ng/ml (group H) (range, 10-6,840 ng/ml). A total of 21 patients with a baseline CEA level between 5 and 10 ng/ml were recruited with median CEA of 6.8 ng/ml (group L). A total of 30 patients with a baseline CEA level (<5.0 ng/ml) were in the normal group (group N). The characteristics of all patients are shown in Table I. Sex and smoking status were well balanced among these groups.

Efficacy and toxicities. Between February 2012 and May 2015, 100 patients commenced erlotinib or gefitinib treatment (Table II). The last follow-up was carried out on June 30, 2016, and median follow-up duration was 20.5 months (range, 2.5-48.0). Disease progression occurred in 93 patients. The median PFS indicated statistical significance among the three groups (P<0.001; Fig. 1). The median PFS was significantly longer in group H (6.4 months) than in group L (4.5 months; P=0.027). Furthermore, the median PFS was also statistically longer in group L than in group N (3.0 months; P=0.002). From the results of PFS, the authors could suggest that the patients with high serum CEA level were able to benefit more from gefitinib therapy than those with low serum CEA. In a multivariate Cox equilibrium regression model, patients were grouped by CEA level, gender, smoking status and pathology as concomitant variables, and results displayed that group H was an independent positive predictive factor for PFS [hazard ratio (HR), 1.25; 95% confidence interval (CI), 1.09-1.39].

The ORRs were 65.3, 38 and 33.3%, respectively, in groups H, L and N. ORR were significantly higher in group H than in groups N and L (P=0.006 and 0.035, respectively), while no statistical difference was observed between groups L and N (P=0.726). A total of 80 patients had not died at the last follow-up date. The median OS of patients were 11.9, 9.4 and 7.8 months, respectively, in groups H, L and N. Similar with ORR, the median overall survivals (OS) was significantly longer in group H than in groups N and L (P<0.001 and P=0.022, respectively; Fig. 2), while no statistical difference was observed between groups L and N (P=0.115). These results suggest that the patients with pre-therapeutic high serum CEA

Table I. Patient demographics and clinical characteristics.

Characteristic	Group H	Group L	Group N	P-value
Age (years)				0.823
Median	54.5	51.5	56	
Range	27-84	37-69	23-75	0.927
Gender				
Women	29	12	13	
Men	20	9	17	
Smoking history				0.752
Non-smoker	42	18	20	
Smoker	7	3	10	
ECOG				0.798
0	18	9	6	
1	28	10	18	
2	3	2	6	
Clinical stage				0.893
IIIB	6	3	4	
IV	43	18	26	
Histology				0.532
Non-adenocarcinoma	2	1	3	
Adenocarcinoma	47	20	27	
Site of metastatic disease				0.634
Lung	22	17	19	
Brain	5	2	3	
Bone	13	9	10	
Lymph node	23	17	22	
Visceral (liver, spleen)	4	2	3	
Baseline CEA				0.000
Median	222.8	6.8	3.7	
Range	10-6,840	5-10	0.8-5	
Oral medicine				0.758
Gefitinib (250 mg/day)	22	25	19	
Erlotinib (150 mg/day)	12	11	11	
EGFR mutation type				0.354
Exon 19 deletion	25	22	23	
Exon 21 L858R	9	11	10	
Resistance mechanism				1.000
T790M	13	12	10	
MET amplification	2	1	3	
Small cell histology	1	1	1	
Unknown	7	4	5	

ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor.

level have better response to gefitinib or erlotinib and longer OS than those with low or normal serum CEA level.

The most common adverse events were skin rash and anorexia (75 and 51% in the current study, respectively), and there were no significant differences in their incidences among the three groups. Most patients showed only grade 1/2 adverse events. Grade 3 rash was observed in nine patients, and no dose reduction or discontinuation was performed in any patients due to intolerable toxicities. No interstitial lung disease occurred.

Acquired resistance to EGFR-TKIs. Of 100 samples, 76 developed acquired resistance to EGFR-TKIs. A total of 60 patients were identified that received re-biopsy at the

Table II. Efficacy of erlotinib or gefitinib treatment.

Efficacy	Group H	Group L	Group N	P-value
PFS (median, months)	6.4	4.5	3.0	0.000
OS (median, months)	11.9	9.4	7.8	0.000
Tumor response				0.010
CR	2	1	1	
PR	30	7	9	
SD	14	8	12	
PD	3	5	8	

Group H, high-CEA group, CEA baseline levels >10 ng/ml; group L, low-CEA group, CEA baseline levels 5-10 ng/ml; group N, normal-CEA group, CEA baseline levels <5.0 ng/ml. Patients were enrolled in each group on the basis of tumor imaging changes. CEA, carcinoembryonic antigen; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

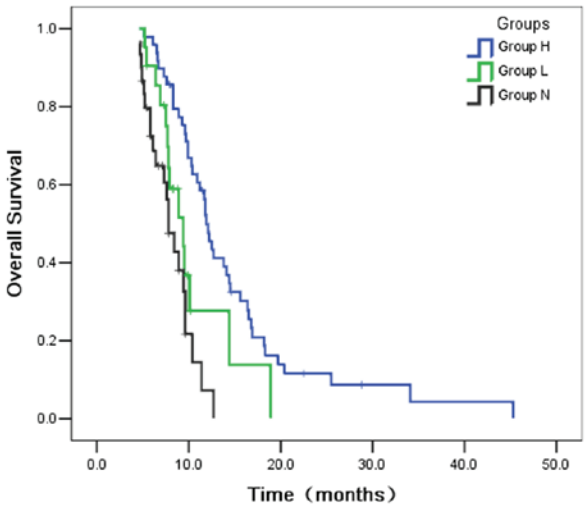

Figure 1. Overall survival of patients in the three groups. High-CEA group (H), CEA baseline levels >10 ng/ml; normal-CEA group (N), CEA baseline levels <5.0 ng/ml; and low-CEA group (L), CEA baseline levels between 5 and 10 ng/ml. CEA, carcinoembryonic antigen.

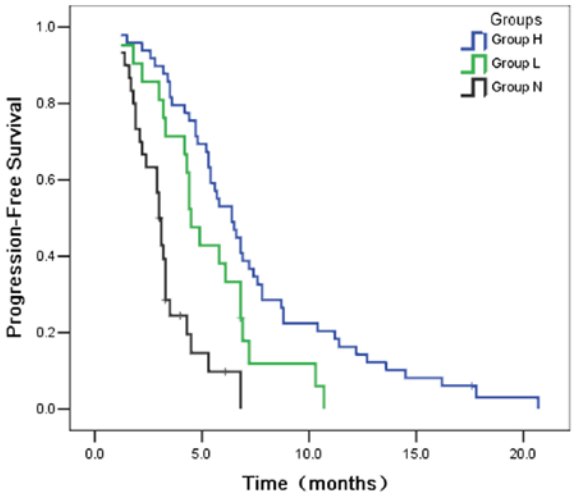

Figure 2. Progression-free survival of patients in the three groups. High-CEA group (H), CEA baseline levels >10 ng/ml; normal-CEA group (N), CEA baseline levels <5.0 ng/ml; and low-CEA group (L), CEA baseline levels between 5 and 10 ng/ml. CEA, carcinoembryonic antigen.

time of development of acquired resistance successfully. The resistance mechanism was similar in three groups, with the acquired T790M mutation being most common, followed by MET amplification and small cell histologic transformation.

Discussion

The role of CEA as a prognostic factor has been well established in colon cancer and is now part of the routine follow-up evaluation recommended by the current NCCN guidelines (26-29). In NSCLC, a number of studies evaluating CEA and prognosis have been written with contrasting results in the perioperative setting, some showing its role as a prognostic value (30,31) and others not confirming it (22,32,33). To the best of the authors' knowledge, no serum marker for EGFR-mutated NSCLC has been reported to predict the efficacy of EGFR-TKIs; the present study may be the first to demonstrate that the pre-therapeutic serum CEA level may predict the extent of benefits from EGFR-TKIs in advanced NSCLC patients carrying the EGFR mutation. The research results revealed significantly different median PFS between these groups (P<0.001), suggesting that patients with high serum CEA level may benefit more than those with low serum CEA in spite of partial overlap of 95% CIs.

EGFR mutations occur most frequently in female, non-smoking, East Asian and adenocarcinoma patients (34). Therefore, tumor patients carrying EGFR activating mutations demonstrated a better response to EGFR-TKI treatment than those without EGFR mutations (9). However, the effectiveness of TKIs treatment is not the same in the patients carrying EGFR mutations. Some patients had dramatic response to EGFR-TKIs treatment, while others did not exhibit any response.

The predictive and prognostic value of CEA level have been assessed in advanced NSCLC patients fully treated with gefitinib and erlotinib, due to conflicting results have been

reported higher levels of CEA and the response is directly related to EGFR-TKI, but its effectiveness has not yet been established (35). On the other hand, Okamoto *et al* (24) and Jung *et al* (23) reported that patients treated with EGFR-TKI with higher CEA levels had a longer survival and a better response than those with low CEA levels. Shoji *et al* (36) reported that the rate of EGFR gene mutation is significantly increased as the levels of CEA increases (for the levels of CEA of <5, ≥5 but <20 and ≥20 the rate of EGFR gene mutation was 35, 55 and 87.5%, respectively; P=0.040). Their study presented a significant association between EGFR gene mutations and the levels of CEA in patients with lung adenocarcinomas. To the best of the authors' knowledge, little is known about the function of CEA. Wirth *et al* (37) reported that CEA can inhibit the apoptosis and has prometastatic roles in colon cancer cells, and Ordonez *et al* (38) also reported that the overexpression of CEA can protect tumor cells from apoptosis and inhibit cell death. EGFR mutations were detected within an ATP binding pocket with catalytic domain, and the mutants also had an enhanced tyrosine kinase activity in response to the ligand. In addition, the present studies have demonstrated that such downstream molecules as Akt and STAT3 serve a crucial role in the antiapoptotic pathways of EGFR mutations in tumor cells (39). Moreover, the mutated EGFRs are autophosphorylated in the absence of interleukin-3 without EGF stimulation, and their expression leads to the STAT5 activation and the upregulation of the extracellular signal-regulated kinase 1 or 2 (Erk1 or 2), Erk5 and Akt (40). It is hypothesized that this continuous signal of the mutant EGFR can stimulate antiapoptotic activity in a ligand-independent manner. Thus, overexpression of the CEA protein as antiapoptotic may be observed in patients with EGFR mutants.

In the present study, the median OS of patients were 11.9, 9.4 and 7.8 months, respectively, in groups H, L and N. Similar to the ORR, the difference in the median OS between groups H and N and between groups H and L were significant (P<0.001 and P=0.022, respectively), whereas these between groups L and N were not (P=0.115). In addition, the multivariate analysis revealed that group H was an independent positive predictive factor for PFS (HR, 1.25; 95% CI, 1.09-1.39). Considering histologic heterogeneity in NSCLC, the authors hypothesized that the serum CEA level in patients with pretreated lung cancer partly represents the extent of the mutant EGFR component in the lung cancer. This hypothesis may partially explain why the effect durations were not as long as expected in some patients with EGFR mutations. By determining the serum CEA level, one could select the patients with high serum CEA levels for EGFR-TKIs treatment to guarantee the best therapy effect. Importantly, more attention should be paid to patients with low serum CEA levels while making therapeutic strategies, it is necessary for them to give combined strategies, rather than single administration of EGFR-TKIs.

With regard to the potential benefit of learning about a small cell histologic transformation, as well as the prognostic value of EGFR T790M mutation, the authors biopsy patients at the time of development of acquired resistance as part of routine consideration. These data demonstrate that there were no differences between the patients with low serum CEA and the patients who had high serum CEA. It is presumed that the level of CEA could not predict acquired resistance to EGFR-TKIs.

In summary, the present study suggests that the relative pre-therapeutic CEA level can predict the extent of benefits from EGFR-TKIs, but can not predict the acquired drug resistance to EGFR-TKIs therapy in patients with EGFR mutations. However, the current study is believed to possess some limitations. Firstly, the current study was the limited sample size of 100 patient cases. Secondly, it is uncertain whether the serum CEA level actually represents a rich mutant EGFR component in each patient. Further basic research is needed to clarify the possible molecular mechanisms behind this association.

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