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Serum carcinoembryonic antigen as a predictive marker for sensitivity to gefitinib in advanced non-small cell lung cancer

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Abstract

Gefitinib is an inhibitor of epidermal growth factor receptor tyrosine kinase, which has a tumour reducing effect in non-small cell lung cancer (NSCLC). In this study, we retrospectively reviewed the clinical data from 105 patients with advanced NSCLC treated with gefitinib at our department between May 2002 and April 2004. The overall response rate was 27.8% and the median survival time was 9.3 months. Pretreatment characteristics suggested that those with no history of smoking or an elevated serum carcinoembryonic antigen (CEA) level were more likely to be sensitive to gefitinib ($P = 0.009$). A multivariate analysis indicated good PS ($P < 0.0001$) and elevated serum CEA level ($P = 0.0027$) to be independent prognostic factors. These data show that the serum CEA level can be a predictive factor for the efficacy of gefitinib treatment while it is also a prognostic factor for advanced NSCLC patients undergoing this treatment.

Keywords: Gefitinib; CEA; NSCLC; EGFR; Tyrosine kinase inhibitor

1. Introduction

The majority of patients with non-small cell lung cancer (NSCLC) have such advanced disease that it can not be resected at initial treatment. Although chemotherapy can potentially prolong survival of patients with advanced cancer, the advantages are relatively small [1].

A molecular target drug, gefitinib (Iressa, AstraZeneca, London, UK), has recently been developed as a tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), which was found to be a potential anti-cancer agent [2]. Two large phase II studies conducted in pretreated non-small lung cancer patients have demonstrated a response rate of 18% and 11.8% with symptomatic improvement in 40% and 43% of patients [3,4]. Based on these results, gefitinib has been approved for treating patients with NSCLC upon the failure of other chemotherapies. Although gefitinib was developed as a specific molecular target drug for EGFR, the clinical target of the drug in human tumours is not fully understood. Both basic and clinical research has not been able to show that the expression level of EGFR correlates with sensitivity of NSCLC to gefitinib. Analysis of clinical data from phase II clinical trials have suggested that gefitinib shows greater activity in patients of Japanese origin, females and those who had adenocarcinoma. Another report showed that patients with bronchioloalveolar carcinoma and no history of smoking were associated with a higher sensitivity to the drug [5].

Recently, two studies from different groups have shown that mutations in the tyrosine kinase domain of EGFR are associated with sensitivity of NSCLC to gefitinib [6,7]. Small in-frame deletions and missense substi-

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tutions were detected within the adenosine triphosphate (ATP) binding pocket of the EGFR catalytic domain in 10–28% of NSCLC tumours. Clinical observations demonstrated that almost all tumours sensitive to gefitinib had one of these mutations, while the tumours showing no response did not have them. Moreover, a recent study showed that such downstream molecules as Akt and STAT3/5 played a crucial role in the anti-apoptotic pathway of the mutant EGFR protein in tumour cells [8]. Another group found that activated Akt was associated with higher efficacy of gefitinib when investigating clinical specimens by immunohistochemical approaches [9].

In spite of these remarkable observations, the true mechanism of the tumour response to gefitinib is still not fully understood. In addition, the detection of mutations in EGFR is still not generally established in practice. We therefore investigated the clinical data of consecutive patients treated by gefitinib monotherapy in our department to detect or confirm specific characteristics in gefitinib sensitive patients, in order to better understand the molecular targets of this drug. We were particularly interested in patient serum carcinoembryonic antigen (CEA) levels prior to cancer treatment, since NSCLC patients with high CEA levels often showed good clinical response to gefitinib therapy.

2. Patients and methods

Between May 2002 and April 2004, 105 patients with advanced NSCLC were treated at the Department of Thoracic Oncology at the National Kyushu Cancer Center, Japan. All patients had unresectable lesions and 90% of patients received one or more regimens of chemotherapy before receiving gefitinib treatment. Generally, gefitinib was administered orally at a dose of 250 mg/day until disease progression, the appearance of unacceptable toxicity or patients' withdrawal from the treatment. The pretreatment variables analysed were: age, gender, clinical stage, ECOG performance status (PS), cell type, smoking history, number of prior chemotherapy regimens and CEA serum concentration. Histological analysis of tumours were based on WHO classification for cell types [10]. The clinical stage of these patients was determined based on the TNM classification of the Union Internationale Contre le Cancer (UICC) [11]. For TNM staging, all patients underwent a computed tomography (CT) scan of the thorax and the upper part of abdomen, a bone scintigram, and a brain CT or magnetic resonance imaging (MRI). Serum CEA was measured by an enzyme immunoassay (SRL, Fukuoka, Japan) within six weeks before starting the gefitinib treatment. According to the manufacturer, the normal range of serum CEA level is below 5.0 ng/ml. The clinical responses to the drug were defined according to the response evaluation criteria of WHO for patients with measurable disease [12]. For patients whose tumour burden could not be quantified using these criteria, two physicians assessed each patient. Written informed consent was obtained from each patient before treatment start.

Statistical significance for the various clinicopathological factors among compared categories was evaluated using the χ^2 test, Fisher's exact probability test or the Mann–Whitney test. Overall survival was defined as the period from the starting date of the gefitinib treatment to the date of death. Patients alive at data cutoff were censored at the last date the patient was known to be alive, and the terminal event was death due to any cause. A survival analysis for each categorical variable regarding overall survival was estimated according to the Kaplan–Meier method. The statistical significance of the differences between the survival curves was evaluated by the log-rank test. A univariate analysis of several prognostic factors was carried out using the Cox proportional hazards model. In multivariate survival analysis, all variables investigated were further analysed in a stepwise manner. Statistical difference was considered to be significant if the P value was below 0.05.

3. Results

3.1. Clinical characteristics of patients treated by gefitinib

The clinical characteristics of the 105 patients are summarised in Table 1. Ninety-one percent of patients had stage IV diseases, 83.8% had adenocarcinoma and 90% had received one or more regimens of prior chemotherapy (mainly platina-based). The serum CEA level was positive (CEA $\geqslant$ 5 ng/ml) for 62.9% of the patients. A complete response (CR) and partial response (PR) were observed in 2 and 26 patients, respectively, and overall response rate was 27.8%. We compared the clinical characteristics of responders (CR + PR) with those with stable disease (SD) and progressive disease (PD) by the Mann–Whitney test (Table 2). Patients with no history of smoking and those with an elevated serum CEA level were more likely to be sensitive to gefitinib ($P = 0.009$). Thirty-five percent of the patients with elevated CEA levels experienced objective regressions compared to 16% of those with normal CEA levels. All responders with elevated CEA achieved a reduction in the serum CEA levels and 6 of 22 (27%) showed a reduction which reached normal levels.

3.2. Survival

The overall follow-up time ranged from 5.6 to 28.7 months with a median follow-up of 18.4 months. The one- and two-year overall survival rates were 44% and 23%, respectively, and the median survival time was

Table 1
Clinicopathological characteristics of the 105 patients treated by gefitinib

Category	*n*	%
Age		
Median (range)	61.9 (37–86)	
Gender		
Male	61	58.1
Female	44	41.9
Clinical stage		
IIIA	2	1.9
IIIB	7	6.7
IV	96	91.4
Performance status		
0	31	29.5
1	51	48.6
2	18	17.1
3–4	5	4.8
Histologic type		
Adenocarcinoma	88	83.8
Squamous	6	5.7
Large	3	2.9
Adenosquamous	3	2.9
Undefined	5	4.8
Smoking history		
None	62	59.0
Current + former	43	41.0
Serum CEA level		
<5 ng/ml	39	37.1
⩾5 ng/ml	66	62.9
No. of prior chemotherapy regimens		
0	11	10.5
1	38	36.2
2	26	24.8
3 or more	30	28.6
Response to gefitinib		
Complete response	2	1.9
Partial response	26	24.8
Stable disease	36	34.2
Progressive disease	36	34.3
Not evaluable	5	4.8

9.3 months. We analysed the effect of pretreatment serum CEA level on the survival of patients treated by gefitinib. Table 3 shows a comparison of the pretreatment clinicopathological characteristics between the patients with an elevated CEA level and normal CEA level. Although the adenocarcinoma patients tended to have a more elevated CEA level than other cell types, there was no significant difference between the two groups with respect to the analysed categories. The survival curve of the two levels of serum CEA showed that survival of patients with higher pretreatment CEA level to be significantly better (Fig. 1). A univariate analysis of several prognostic factors using Cox proportional hazards model indicated that younger age, presence of adenocarcinoma, good PS and elevated serum CEA levels to be positive prognostic factors for gefitinib treatment (Table 4). A multivariate analysis using a stepwise method also confirmed that a good PS and elevated serum CEA levels to be independent prognostic factors (Table 5).

Table 2
Comparison of pretreatment clinicopathological characteristics among patients with response, stable disease and progressive disease by gefitinib treatment

Category	CR + PR (*n* = 28)	SD (*n* = 36)	PD (*n* = 36)	*P* value
	n	*n*	*n*	
Age				
<65	17	22	16	0.17
⩾65	11	14	20	
Gender				
Male	13	19	24	0.10
Female	15	17	12	
Histologic type				
Adenocarcinoma	26	30	28	0.11
Non-adenocarcinoma	2	6	8	
Clinical stage				
III	1	2	4	0.23
IV	27	34	32	
Performance status				
⩽1	24	29	26	0.18
⩾2	4	7	10	
Smoking history				
None	18	14	11	0.0092
Current + former	10	22	25	
No. of prior regimens				
⩽1	14	11	21	0.39
⩾2	14	25	15	
Serum CEA level				
<5 ng/ml	6	12	19	0.009
⩾5 ng/ml	22	24	17	
Total (%)	28 (28%)	36 (36%)	36 (36%)	

4. Discussion

Gefitinib is a tyrosine kinase inhibitor of EGFR, which has the potential to reduce tumour volume in NSCLC patients. Two large phase II studies conducted in pretreated non-small lung cancer patients have demonstrated a response rate of 18% and 11% [3,4]. In the analysis of the former trial, Japanese patients observed higher response rate than non-Japanese patients (27.5% *vs.* 10.4%, odds ratio = 3.27; $P = 0.0023$). In a multivariate analysis employed at 10% significance level, a good PS, female, adenocarcinoma and a history of receiving prior immuno/hormonal treatment were all found to be independent predictable factors for response. Also a retrospective study demonstrated that patients with adenocarcinoma of the bronchioloalveolar subtype and no history of smoking were more likely to

Table 3
Comparison of pretreatment clinicopathological characteristics between patients with elevated serum CEA level and those without

Category	CEA < 5 ng/ml	CEA ⩾ 5 ng/ml	*P* value
	n	*n*	
Age (<65, ⩾65)	20, 19	37, 29	0.78
Gender (Male, female)	23, 16	38, 28	>0.99
Histologic type (Adeno, non-adeno)	29, 10	59, 7	0.080
Clinical stage (III, IV)	6, 33	3, 63	0.12
Performance status (⩽1, ⩾2)	33, 6	49, 17	0.32
Smoking history (None, current + former)	14, 25	29, 37	0.54
No. of prior regimens (⩽1, ⩾2)	18, 21	31, 35	>0.99
Total (%)	39 (37.1%)	66 (62.9%)	

Table 4
Analysis of various pretreatment prognostic factors influencing survival of patients treated with gefitinib (Cox proportional hazards model)

Variables	Hazard ratio	95% CI	*P* value
Age (<65 *vs.* ⩾65)	1.72	1.02–2.90	0.042
Gender (Male *vs.* female)	0.69	0.40–1.17	0.17
Histologic type (Adeno *vs.* non-adeno)	1.88	1.01–3.51	0.046
Clinical stage (III *vs.* IV)	0.78	0.33–1.83	0.57
Performance status (⩽1 *vs.* ⩾2)	5.41	3.07–9.62	<0.0001
Smoking history (None *vs.* current + former)	1.56	0.90–2.68	0.11
No. of prior regimens (⩽1 *vs.* ⩾2)	1.35	0.79–2.29	0.28
CEA (<5 *vs.* ⩾5 ng/ml)	0.53	0.32–0.90	0.018

Table 5
Multivariate analysis of various pretreatment prognostic factors influencing survival of patients treated with gefitinib

Variable	Category	Hazard ratio	*P* value
Performance status	(⩽1 *vs.* ⩾2)	6.10	<0.0001
CEA	(<5 *vs.* ⩾5 ng/ml)	0.44	0.0027

have an objective response to gefitinib treatment (odds ratio = 13.5 and 4.2) [5]. However, no report has so far investigated the relationship between the serum CEA concentration and responses to. In this study, a similar overall response rate (26.7% of all patients treated) as that reported in the former study of Japanese patients and association of smoking history to gefitinib sensitivity was also observed. We also demonstrate for the first time, that patients with a serum CEA concentration of over 5 ng/ml were more sensitive to gefitinib treatment than those with a concentration of below 5 ng/ml. Moreover, those with an elevated serum CEA level showed a significantly better prognosis for gefitinib treatment than those with no such increased levels based on both univariate and the multivariate analyses. These data were very surprising since an elevated serum CEA level is generally considered to be a negative prognostic factor for NSCLC [13].

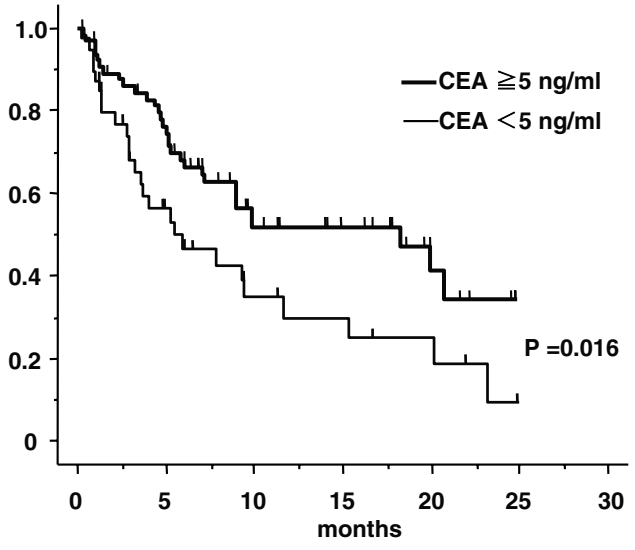

Fig. 1. The survival curves of gefitinib treated patients with elevated serum CEA (⩾5 ng/ml) and normal CEA levels (<5 ng/ml).

CEA was first described as a specific antigen that was present in both the fetal colon and colon adenocarcinoma [14]. It is a member of the immunoglobulin supergene family, which is a cell surface adhesion protein, and it is thought to play a role in cell-to-cell adhesion [15]. The overexpression of CEA has been found in many other types of carcinomas and is thought to play a role in tumourigenesis [16]. Screaton and colleagues have recently discovered that CEA has a dominant effect in blocking differentiation and it also cooperates with Myc and Bcl-2 in cellular transformation [17]. In addition, it can also inhibit cell death induced by a loss of anchorage to the extra cellular matrix (anoikis) [18]. Our data reported here suggests that NSCLC cells which produce an abundant amount of CEA protein tend to be more sensitive to the EGFR tyrosine kinase inhibitor gefitinib, and indicates that CEA proteins may play an important role in EGFR signaling in cancer cells. If this is true, then the serum CEA may be an important surrogate marker of the gefitinib treatment. In clinical practice, in the course of treating patients with gefitinib, we believe that a change in serum CEA levels seem to closely represent the burden of a CEA positive tumour.

Recently, mutations in the tyrosine kinase domain of EGFR have been found to be strongly associated with the sensitivity of NSCLC to gefitinib [6,7]. Mutations were detected within an ATP binding pocket of the catalytic domain, and the EGFR mutants also had an enhanced tyrosine kinase activity in response to the ligand. Moreover, current studies have shown that such down stream molecules as Akt and STAT3/5 play a crucial role in the anti-apoptotic pathways of the mutant EGFR in tumour cells [8,9]. Since CEA protein has been demonstrated to have an anti-apoptotic effect in cancer cells, it is possible that an anti-apoptotic signal of the mutant EGFR may elevate the expression level of CEA protein.

In conclusion, this study indicates that the serum CEA level may be a useful predictive factor for the efficacy of gefitinib treatment, while also being a prognostic factor for advanced NSCLC patients undergoing this treatment. Further basic research and clinical studies are needed to elucidate the relationship between sensitivity to gefitinib and the CEA protein.

Conflict of interest statement

None declared.

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References

1. The Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995, **311**, 899–909.
2. Wakeling AE, Guy SP, Woodburn JR, *et al*. ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. *Cancer Res* 2002, **62**, 5749–5754.
3. Fukuoka M, Yano S, Giaccone G, *et al*. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003, **21**, 2237–2246.
4. Kris MG, Natale RB, Herbst RS, *et al*. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003, **290**, 2149–2158.
5. Miller VA, Kris MG, Shah N, *et al*. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 2004, **22**, 1103–1109.
6. Lynch TJ, Bell DW, Sordella R, *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004, **350**, 2129–2139.
7. Paez JG, Janne PA, Lee JC, *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004, **304**, 1497–1500.
8. Sordella R, Bell DW, Haber DA, *et al*. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* 2004, **305**, 1163–1167.
9. Cappuzzo F, Magrini E, Ceresoli GL, *et al*. Akt phosphorylation and gefitinib efficacy in patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2004, **96**, 1133–1141.
10. Travis WD, Colby TV, Corrin B, *et al*. Histological typing of lung and pleural tumors. *World Health Organization international histological classification of tumors*. 3rd ed. Berlin, Springer, 1999.
11. International-Union-against-cancer. TNM classification of malignant tumors. 5th ed. New York, Wiley; 1997.
12. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Invest New Drugs* 1992, **10**, 239–253.
13. Concannon JP, Dalbow MH, Hodgson SE, *et al*. Prognostic value of preoperative carcinoembryonic antigen (CEA) plasma levels in patients with bronchogenic carcinoma. *Cancer* 1978, **42**, 1477–1483.
14. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J Exp Med* 1965, **121**, 439–462.
15. Benchimol S, Fuks A, Jothy S, *et al*. Carcinoembryonic antigen, a human tumor marker, functions as an intercellular adhesion molecule. *Cell* 1989, **57**, 327–334.
16. Hammarstrom S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. *Semin Cancer Biol* 1999, **9**, 67–81.
17. Screaton RA, Penn LZ, Stanners CP. Carcinoembryonic antigen, a human tumor marker, cooperates with Myc and Bcl-2 in cellular transformation. *J Cell Biol* 1997, **137**, 939–952.
18. Ordonez C, Screaton RA, Ilantzis C, *et al*. Human carcinoembryonic antigen functions as a general inhibitor of anoikis. *Cancer Res* 2000, **60**, 3419–3424.