Prognostic and predictive value of CEA and CYFRA 21-1 levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib

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Abstract. The prognostic and predictive value of pre-treatment serum levels of carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1) were assessed in advanced non-small cell lung cancer (NSCLC) patients treated with gefitinib or erlotinib. Pre-treatment CEA and CYFRA 21-1 levels were measured in 123 advanced NSCLC patients receiving gefitinib or erlotinib. High CEA levels (h-CEA) were significantly associated with females, patients with adenocarcinoma and non-smokers. Low CYFRA 21-1 levels (l-CYFRA 21-1) were significantly associated with a good performance status (ECOG PS 0-1). The overall response rate (RR) was 27.6%, and a higher RR was associated with adenocarcinoma, h-CEA, and epidermal growth factor receptor (EGFR) mutation. Patients with h-CEA had significantly longer progression-free survival (PFS) (P=0.021). Patients with l-CYFRA 21-1 had significantly longer PFS and overall survival (OS) (P=0.006 and P<0.001, respectively). Notably, h-CEA and l-CYFRA 21-1 levels were associated with good prognosis in patients with unknown EGFR mutation status or patients with squamous cell carcinoma (P=0.021 and P=015, respectively). A good ECOG PS (HR=0.45, P=0.017), h-CEA (HR=0.41, P=0.007), l-CYFRA 21-1 (HR=0.52, P=0.025), and an EGFR mutation (HR=0.22, P<0.001) were independently predictive of a longer PFS. A good ECOG PS (HR=0.52, P=0.018), l-CYFRA 21-1 (HR=0.36, P=0.004), and EGFR mutation (HR=0.53, P=0.051) were independently predictive of longer OS. h-CEA and l-CYFRA 21-1 may be prognostic and predictive serum markers for higher response and longer survival in patients with advanced NSCLC receiving gefitinib or erlotinib, particularly in patients with unknown EGFR mutation status or patients with squamous cell carcinoma.

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the world. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases (1). The oral small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, promote responses in 10-18% of patients who had a failed response to prior chemotherapy. Erlotinib was found to have a 2-month median survival advantage over a placebo (2), and gefitinib did not exhibit an inferior efficacy when compared with docetaxel (3).

Treatment with an EGFR TKI is effective in women, Asians, non-smokers, and patients with adenocarcinoma. An EGFR mutation was found to be the most important predictive factor for patient response to an EGFR TKI (4). However, acquiring adequate tissue for an EGFR mutational analysis is often not feasible, particularly in patients with advanced disease (2-4). Therefore, the identification of clinical parameters that can serve as surrogates markers for an EGFR mutation may prove useful when mutational analysis is not feasible. A recent study reported that the molecular analysis of circulating tumor cells from the peripheral blood of patients with lung cancer was useful in monitoring changes in epithelial tumor genotypes during the course of treatment (5). However, this molecular analysis may prove to be difficult as a specific microfluidic-based device, the CTC chip, is required.

Therefore, a marker that is easily analyzed and predicts the responses to EGFR TKI treatment is needed. Several serum markers have been considered potentially prognostic and

Table I. Comparison of pre-treatment clinicopathological characteristics according to CEA and CYFRA 21-1 levels.

		CEA, n (%)			CYFRA 21-1, n (%)		
Patient characteristics	n (%)	<5 ng/ml	≥5 ng/ml	P-value	<3.3 ng/ml	≥3.3 ng/ml	P-value
Total	123 (100)	53 (43.1)	70 (56.9)		59 (48)	64 (52)	
Age (years)							
Median (range)	55 (34-88)			0.265			0.451
<65	81 (65.9)	32 (39.5)	49 (60.5)		41 (50.6)	40 (49.4)	
≥65	42 (34.1)	21 (50.0)	21 (50.0)		18 (42.9)	24 (57.1)	
Gender				<0.001			0.192
Male	70 (56.9)	40 (57.2)	30 (42.9)		30 (42.9)	40 (57.1)	
Female	53 (43.1)	13 (24.5)	40 (75.5)		29 (54.7)	24 (45.3)	
Histologic type				0.043			0.995
Adenocarcinoma	73 (59.3)	26 (35.6)	47 (64.4)		35 (47.9)	38 (52.1)	
Non-adenocarcinoma	50 (40.7)	27 (54.0)	23 (46.0)		24 (48.0)	52 (52.0)	
Clinical stage				0.439			0.628
IIIB	35 (18.5)	17 (48.6)	18 (51.4)		18 (51.4)	17 (48.6)	
IV	88 (71.5)	36 (40.9)	52 (59.1)		41 (46.6)	47 (53.4)	
Performance status				0.100			0.017
0-1	83 (67.5)	40 (48.2)	43 (51.8)		46 (55.4)	37 (44.6)	
2	40 (32.5)	13 (32.5)	27 (67.5)		13 (32.5)	27 (67.5)	
Smoking history				0.036			0.072
None	59 (47.5)	19 (32.8)	39 (67.2)		33 (56.9)	25 (43.1)	
Current + former	64 (52.5)	33 (51.6)	31 (48.2)		26 (40.6)	38 (59.4)	
No. of prior regimens				0.631			0.485
≤1	40 (32.5)	16 (40.0)	24 (60.0)		21 (52.5)	19 (47.5)	
≥2	83 (67.5)	37 (44.6)	46 (55.4)		38 (45.8)	45 (54.2)	
TKI				0.669			0.203
Gefitinib	72 (58.5)	29 (40.3)	43 (61.4)		37 (51.4)	35 (48.6)	
Erlotinib	51 (41.5)	24 (47.1)	27 (52.9)		22 (43.1)	29 (56.9)	
EGFR mutation (n=84)				0.418			0.789
Negative	47 (38.2)	19 (40.4)	28 (59.6)		23 (48.9)	24 (51.1)	
Positive	37 (30.1)	14 (37.8)	23 (62.2)		19 (51.4)	18 (48.6)	
Unknown	39 (31.7)	20 (51.3)	19 (48.7)		17 (43.6)	22 (56.4)	

CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin-19 fragments; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor

predictive in NSCLC. Among these NSCLC markers, carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1) have been considered sensitive and valuable tumor markers for diagnosis, prognosis, and the monitoring of therapy (6-10). According to recent reports, CEA and CYFRA 21-1 were significant predictors of sensitivity and survival in patients treated with gefitinib (11-13). Therefore, we investigated the clinical significance of the pre-treatment serum levels of CEA and CYFRA 21-1 in advanced NSCLC patients who were treated with gefitinib or erlotinib.

Materials and methods

We retrospectively collected clinical data on 123 NSCLC patients whose pre-treatment levels of CEA and CYFRA 21-1 had been measured and who received gefitinib or erlotinib treatment at Severance Hospital, Yonsei University Health System, Seoul, Korea, from January 2006 to December 2008. Variables used in the pre-treatment analysis were age, gender, clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histological type, smoking history, number of prior chemotherapy regimens, and EGFR mutation if possible. Serum CEA (normal range, 0-5 ng/ml) and CYFRA 21-1 (normal range, 0-3.3 ng/ml) were measured using a chemiluminescence enzyme immunoassay kit (Beckman Coulter, MN, USA) and an electrochemiluminescence immunoassay on an automatic analyzer (Elecsys 200; Roche Diagnostics Mannheim, Basel, Switzerland), respectively, before TKI treatment. Histological analysis of the tumors was based on the WHO classification of cell types

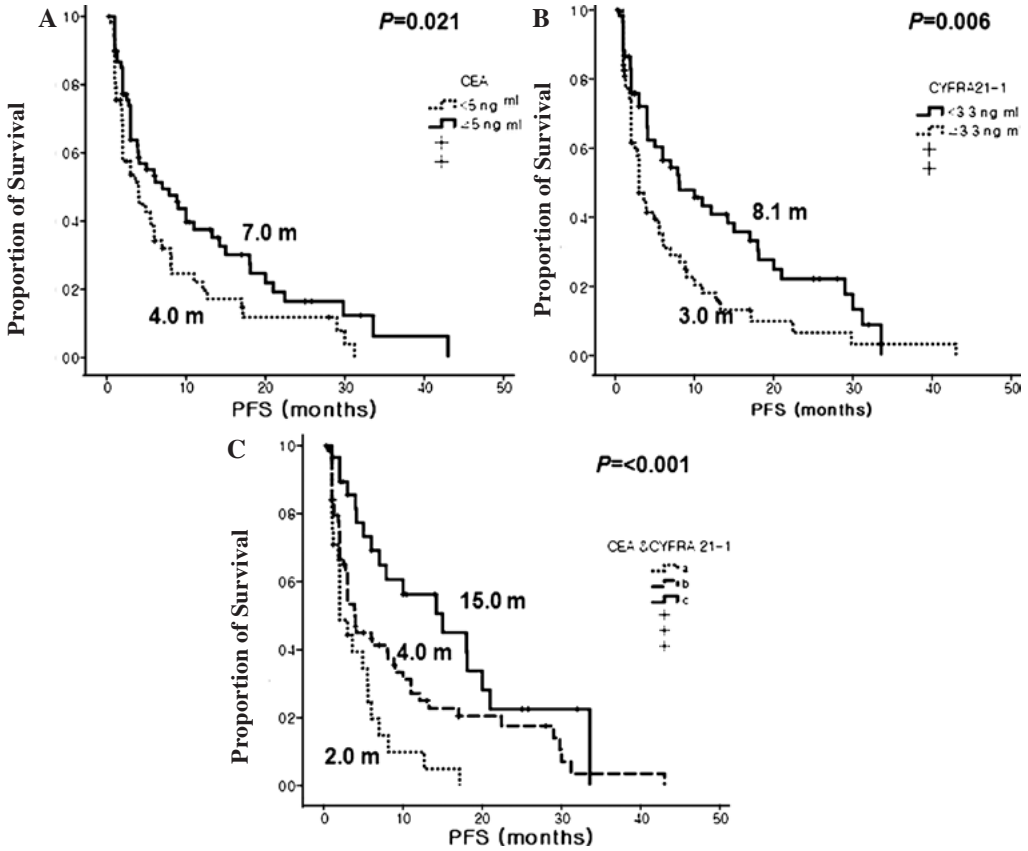

Figure 1. Progression-free survival (PFS) curves according to pre-treatment serum levels of carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1). (A) CEA. (B) CYFRA 21-1. (C) Combinations of CEA and CYFRA 21-1 by group: (a) patients with l-CEA and h-CYFRA 21-1, (b) patients with l-CEA and l-CEA or h-CEA and h-CYFRA 21-1 and (c) patients with a h-CEA and l-CYFRA 21-1.

(14). The clinical response to the drug was defined according to the response evaluation criteria of RECIST 1.0 for patients with measurable disease (15). Nucleotide sequencing of the kinase domain of EGFR (exons 18 to 21) was performed using nested polymerase chain reaction (PCR) amplification of individual exons. The details of sequencing have been described previously (16). This study was approved by the Institutional Review Board of the Yonsei University Health System (approval no. 4-2009-0700).

Statistical methods. The association between pre-treatment levels of CEA and CYFRA 21-1 and other categorical clinical variables were compared using the Pearson's Chi-square test. Progression-free survival (PFS) was defined as the time from the start day of TKI treatment until the date of tumor progression or death. Overall survival (OS) was measured from the date of diagnosis to the date of death or final follow-up. The survival data were estimated using a Kaplan-Meier curve and compared using the log-rank test. Multivariate analyses were performed to find prognostic markers using Cox's proportional hazards model. A P-value <0.05 was considered statistically significant.

Results

Patient characteristics. The clinicopathological characteristics of the 123 patients are summarized in Table I. Notably, a a high serum CEA (h-CEA) level (≥5 ng/ml) was observed in 70 (56.9%) patients, and was significantly more frequent in females, patients with adenocarcinoma and patients without a history of smoking. On the other hand, 64 (52%) patients had an elevated serum CYFRA 21-1 (h-CYFRA 21-1) level (≥3.3 ng/ml), which was significantly more frequent in patients with a poor ECOG PS (P=0.017) and in those with a history of smoking (P=0.072). There was no difference in either CEA or CYFRA 21-1 levels in terms of EGFR mutation status.

Association of serum markers with responses to EGFR TKIs. The median follow-up duration was 9.0 months (range, 0.2-43 months). The median PFS was 5.0 months (95% CI, 3.3-6.7 months), and the median OS was 16.0 months (95% CI, 8.7-23.3 months). Responses were not assessable in 7 patients; 4 patients died and 3 patients refused treatment before response evaluation. Thirty-two of the evaluable 116 (27.6%) patients showed partial responses. The response rate to EGFR TKIs was significantly higher in patients with adenocarcinoma, an EGFR mutation, and a h-CEA (≥5 ng/ml) serum level. The disease control rate in the patients with h-CEA levels was significantly higher than those with low CEA (l-CEA) levels (75 vs. 51.9%, P=0.034). There were no differences in the response rates according to gender, smoking history, or the number of prior chemotherapy regimens. There was a trend towards a better response rate in patients with

Table II. Comparison of pretreatment clinicopathological characteristics according to EGFR TKI responses.

Patient characteristics	PR, n (%)	SD, n (%)	PD, n (%)	P-value
Total (n=116)	32 (27.6)	43 (37.1)	41 (35.3)	
Age (years)				
<65	20 (25.6)	31 (39.8)	27 (34.6)	0.663
≥65	12 (31.6)	12 (31.6)	14 (36.8)	
Gender				
Male	16 (24.2)	28 (42.4)	22 (33.4)	0.371
Female	16 (32.0)	15 (30.0)	19 (38.0)	
Histologic type				
Adenocarcinoma	25 (35.2)	19 (26.8)	27 (38.0)	0.009
Non-adenocarcinoma	7 (15.6)	24 (53.3)	14 (31.1)	
Performance status				
0-1	26 (32.9)	30 (38.0)	23 (29.1)	0.07
2	6 (16.2)	13 (35.2)	18 (48.6)	
Smoking history				
None	17 (30.9)	18 (32.7)	20 (36.4)	0.673
Current + former	15 (25.0)	24 (40.0)	21 (35.0)	
No. of prior regimens				
≤1	13 (35.1)	13 (35.1)	11 (29.8)	0.436
≥2	19 (24.1)	30 (38.0)	30 (38.0)	
Serum CEA level (ng/ml)				
<5	11 (21.1)	16 (30.8)	25 (48.1)	0.034
≥5	21 (32.8)	27 (42.2)	16 (25.0)	
Serum CYFRA 21-1 level (ng/ml)				
<3.3	18 (32.7)	23 (41.8)	14 (25.5)	0.104
≥3.3	14 (23.0)	20 (32.8)	27 (44.2)	
Combination of CEA and CYFRA 21-1				
Group C	11 (42.3)	12 (46.2)	3 (11.5)	0.005
Group B	17 (25.8)	26 (39.4)	23 (34.8)	
Group A	4 (16.7)	5 (20.8)	15 (62.5)	
EGFR mutation (n=84)				
Negative	7 (15.6)	12 (26.7)	26 (57.8)	<0.001
Positive	18 (52.9)	10 (29.4)	6 (17.6)	

Group A, CEA <5 and CYFRA 21-1 ≥3.3 ng/ml. Group B, CEA <5 and CYFRA 21-1 <3.3 or CEA ≥5 and CYFRA 21-1 ≥3.3 ng/ml. Group C, CEA ≥5 and CYFRA 21-1 <3.3 ng/ml. PR, partial remission; SD, stable disease; PD, progression of disease; CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin-19 fragments; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor.

low CYFRA 21-1 (l-CYFRA) levels (P=0.104). To evaluate whether the combination of CEA and CYFRA 21-1 levels improved the prediction accuracy, patients were divided into three groups according to their CEA and CYFRA 21-1 levels. Patients with a l-CEA and a h-CYFRA 21-1 level were defined as group A (CEA <5 ng/ml and CYFRA 21-1 ≥3.3 ng/ml, n=24), while those with l-CEA and l-CYFRA 21-1 levels or h-CEA and h-CYFRA 21-1 levels were considered group B (CEA <5 ng/ml and CYFRA 21-1 <3.3 ng/ml, or CEA ≥5 ng/ml and CYFRA 21-1 ≥3.3 ng/ml, n=66). Finally, patients with h-CEA and l-CYFRA 21-1 levels were defined as group C (CEA ≥5 ng/ml and CYFRA 21-1 <3.3 ng/ml, n=26). The three groups showed significantly different response rates, with the most favorable responses noted in group C (42.3 vs. 25.8 vs. 16.7%, P=0.005, for groups C, B and A, respectively) (Table II).

Association of serum markers with survival. Patients with a h-CEA level had significantly better PFS than those with a l-CEA level (7.0 vs. 4.0 months, P=0.021). In contrast, patients with a l-CYFRA 21-1 level also had significantly better PFS than those with h-CYFRA 21-1 (8.1 vs. 3.0 months, P=0.006).

Table III. Univariate predictions of survival.

Category	PFS			OS		
	Median (months)	95% CI	P-value	Median (months)	95% CI	P-value
Total	5.0	3.3-6.7		16.0	8.7-23.3	
Age (years)						
<65	4.1	2.0-6.2	0.982	15.1	10.5-19.7	0.843
≥65	5.6	2.8-8.4		22.0	5.5-38-5	
Gender						
Male	4.1	2.7-5.6	0.985	15.1	9.3-20.9	0.902
Female	6.0	2.5-9.50		18.1	5.7-30.6	
Histologic type						
Adenocarcinoma	5.6	3.3-7.8	0.942	18.1	0.0-36.3	0.716
Non-adenocarcinoma	4.1	1.2-7.0		16.0	8.3-23.7	
Performance status						
0-1	6.1	3.2-9.0	0.016	29.6	19.9-39.4	<0.001
2	3.0	1.0-5.0		6.1	1.7-10.6	
Smoking history						
None	5.0	2.8-7.2	0.331	16.0	7.0-25.0	0.780
Current + former	4.9	3.1-6.7		14.1	1.7-26.5	
No. of prior regimens						
0-1	8.1	3.2-13.0	0.176	29.6	3.3-55.3	0.447
≥ 2	4.0	2.0-6.0		15.0	9.1-20.9	
TKI						
Gefitinib	5.6	3.6-7.5	0.679	16.0	8.9-23.1	0.935
Erlotinib	3.9	1.5-6.3		24.0	13.2-34.9	
Serum CEA level (ng/ml)						
<5	4.0	1.7-6.3	0.021	14.0	2.2-25.8	0.505
≥5	7.0	2.5-11.5		18.0	10.3-25.7	
Serum CYFRA 21-1 level (ng/ml)						
<3.3	8.1	2.9-13.3	0.006	NR		<0.001
≥3.3	3.0	2.0-4.0		8.0	5.2-10.8	
Combination of CEA and CYFRA 21-1 (ng/ml)						
CEA ≥5 and CYFRA 21-1 <3.3	15.0	5.7-24.3	<0.001	NR		0.002
CEA <5 and CYFRA 21-1 <3.3 or CEA ≥5 and CYFRA 21-1 ≥3.3	4.0	3.1-4.9		14.1	5.0-23.2	
CEA <5 and CYFRA 21-1 >3.3	2.0	0.9-3.1		8.0	4.8-11.2	
EGFR mutation (n=84)						
Negative	2.0	1.4-2.7	<0.001	7.1	3.9-10.3	0.038
Positive	11.0	5.3-16.7		22.0	13.1-31.0	

PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin-19 fragments; NR, not reached; EGFR, epidermal growth factor receptor.

When subgrouped by combined CEA and CYFRA 21-1 levels, the three groups showed significantly different PFS, and group C showed the longest PFS among the three groups (15.0 vs. 4.0 vs. 2.0 months, P<0.001, for groups C, B and A, respectively) (Fig. 1). Particularly, group C had the longest PFS among the patients with squamous cell carcinoma (Fig. 2). In addition, a h-CEA and a l-CYFRA 21-1 level was a significant prognostic marker, not only in patients with EGFR-mutant

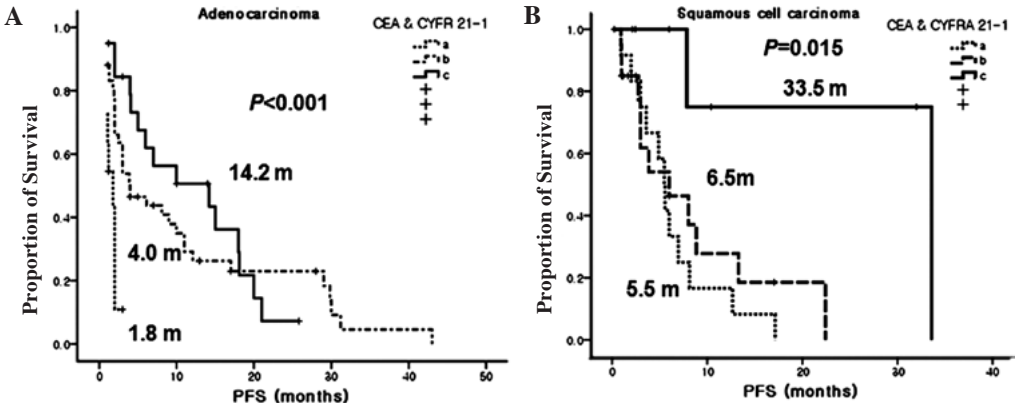

Figure 2. Progression-free survival (PFS) curves according to pre-treatment serum levels of a combination of carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1) according to histologic type. (a) Patients with l-CEA and h-CYFRA 21-1, (b) patients with l-CEA and l-CYFRA 21-1 or h-CEA and h-CYFRA 21-1 and (c) patients with h-CEA and l-CYFRA 21-1. (A) Patients with adenocarcinoma. (B) Patients with squamous cell carcinoma.

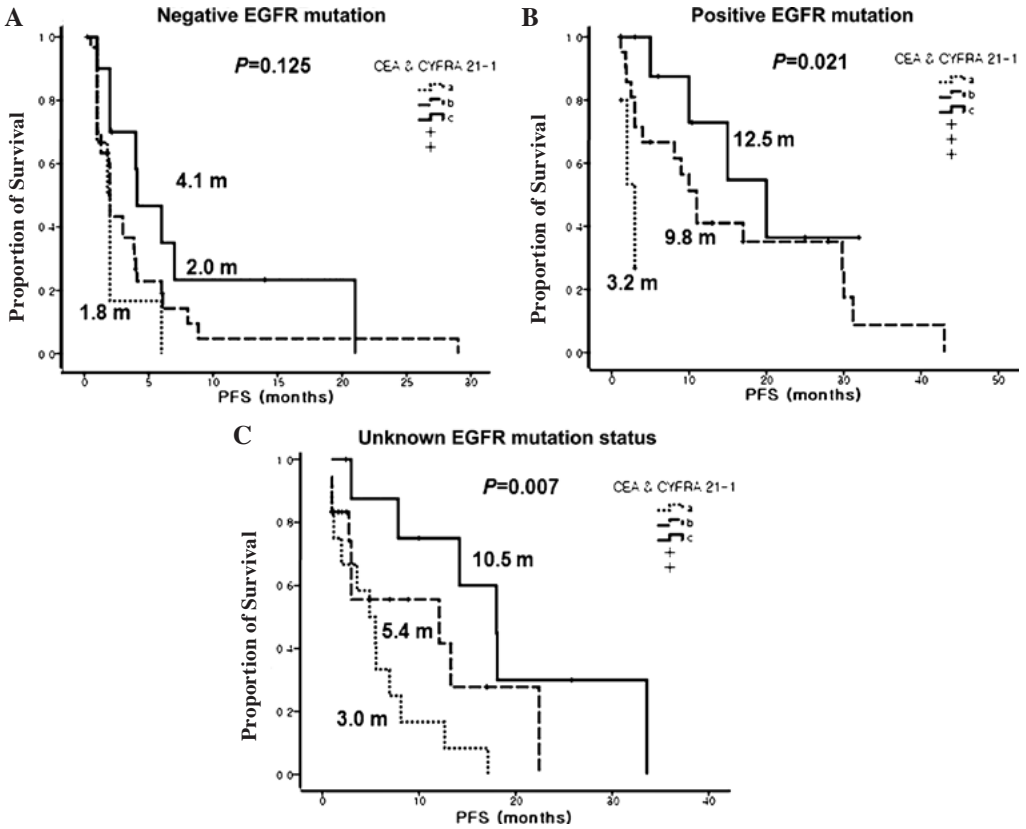

Figure 3. Progression-free survival (PFS) curves according to pre-treatment serum levels of a combination of carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1) according to epidermal growth factor receptor (EGFR) mutation status. (a) Patients with l-CEA and h-CYFRA 21-1, (b) patients with l-CEA and l-CYFRA 21-1 or h-CEA and h-CYFRA 21-1 and (c) patients with h-CEA and l-CYFRA 21-1. (A) Patients with a negative EGFR mutation. (B) Patients with a positive EGFR mutation. (C) Patients with unknown EGFR mutation status.

tumors, but in patients with an unknown EGFR mutation status (Fig. 3). Finally, univariate analysis revealed several significant factors for PFS including good ECOG PS (6.1 vs. 3.0 months, P=0.016) and positive EGFR mutation status (11.0 vs. 2.0 months, P<0.001) (Table III).

Patients with good ECOG PS and a positive EGFR mutation status also had significantly longer OS than those who had a poor ECOG PS and a negative EGFR mutation status (ECOG PS, 29.6 vs. 6.1 months, P<0.001; EGFR mutation status, 22.0 vs. 7.1 months, P=0.038, respectively). However, OS did not differ according to pre-treatment CEA levels. Patients with a l-CYFRA 21-1 level had a longer OS than those with h-CYFRA 21-1 (not reached vs. 8.0 months, P<0.001). Patients in group C also had the longest OS among the three groups (Table IV and Fig. 4).

Multivariate analysis using a Cox proportional hazards model indicated that a good ECOG PS, positive EGFR mutation status, high pre-treatment CEA levels, and low pre-treatment CYFRA 21-1 levels are independent predictive factors for PFS. Meanwhile, predictive factors for OS

Table IV. Multivariate predictions of survival.

	PFS			OS		
Category	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age (years)						
<65 vs. ≥65	1.23	0.67-2.28	0.506	1.18	0.64-2.29	0.633
Gender						
Female vs. male	2.86	0.75-10.89	0.124	1.24	0.27-6.75	0.808
Histologic type						
Non-adeno vs. adeno	0.80	0.41-1.56	0.521	1.59	0.81-3.14	0.182
Clinical stage						
IV vs. III	0.64	0.35-1.15	0.134	0.80	0.40-1.60	0.534
Performance status						
0-1 vs. 2	2.02	1.13-3.61	0.017	2.13	1.14-3.98	0.018
Smoking history						
None vs. current + former	1.48	0.39-5.56	0.57	1.38	0.25-7.61	0.706
Serum CEA level (ng/ml)						
<5 vs. ≥5	0.41	0.24-0.78	0.007	0.55	0.25-1.21	0.554
Serum CYFRA 21-1 level (ng/ml)						
<3.3 vs. ≥3.3	1.93	1.09-3.44	0.025	2.76	1.38-5.53	0.004
EGFR mutation (n=84)						
Negative vs. positive	0.22	0.11-0.42	<0.001	0.53	0.28-1.004	0.051

PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; CEA, carcinoembryonic antigen; CYFRA 21-1, cytokeratin-19 fragments; EGFR, epidermal growth factor receptor.

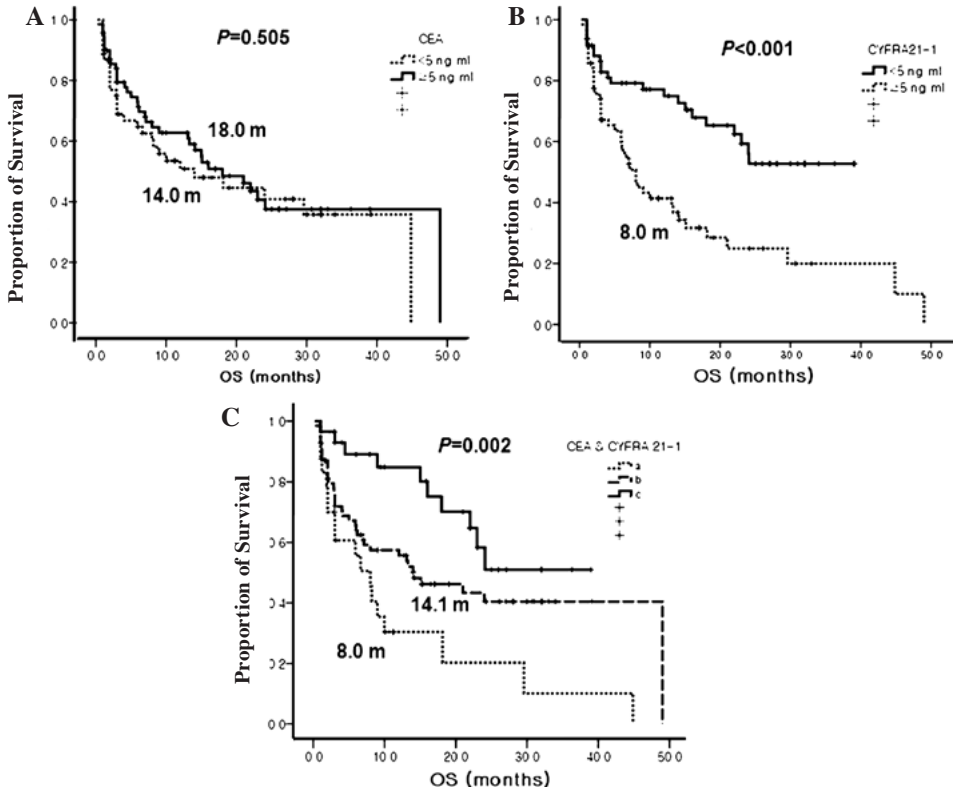

Figure 4. Overall survival (OS) curves according to pre-treatment serum levels of carcinoembryonic antigen (CEA) and cytokeratin-19 fragments (CYFRA 21-1). (A) CEA. (B) CYFRA 21-1. (C) Combinations of CEA and CYFRA 21-1 by group: (a) patients with l-CEA and h-CYFRA 21-1, (b) patients with l-CEA and l-CYFRA 21-2 or h-CEA and h-CYFRA 21-1 and (c) patients with h-CEA and l-CYFRA 21-1.

included a good ECOG PS, positive EGFR mutation status and l-CYFRA 21-1, but not h-CEA (Table IV).

Discussion

Detection of a mutation in the EGFR gene in NSCLC patients treated with an EGFR TKI is the most important factor for the prediction of a good response to these drugs (4). However, the detection of an EGFR mutation may be difficult due to the limited amount of available tissue (2-4). Therefore, a surrogate biomarker that can improve the prediction of response to these targeted drugs is needed.

CEA was first described by Gold and Freedman in 1965 as an antigen expressed by gastrointestinal carcinoma cells (17). Although CEA was often falsely elevated in smokers and in patients with restrictive or obstructive pulmonary disease (18-20), abnormally elevated CEA levels were reported in 30-70% of patients with NSCLC and were most frequently observed in patients with adenocarcinoma and advanced stage carcinoma (21). In addition, several studies have shown that h-CEA is a potential marker of poor prognosis in NSCLC regardless of treatment (7,21).

On the contrary, Okamoto *et al* (11) reported that patients treated with EGFR TKIs with high pre-treatment levels of CEA had a longer survival and a better response than those with l-CEA. They attributed this to a possible anti-apoptotic signal of the mutant EGFR pathway that may elevate the expression level of CEA protein. Our data are similar to the data of Okamato *et al* (11). Shoji *et al* (22) reported that the rate of the EGFR gene mutation significantly increased as the serum CEA level increased (for serum CEA levels of <5, ≥5 but <20, and ≥20, the rate of the EGFR gene mutation was 35, 55 and 87.5%, respectively; P=0.040). However, our data showed that the status of the EGFR mutation made no difference in the CEA levels. Based on previous reports, the function of CEA has not been elucidated but may include the following: i) CEA is a cell surface adhesion protein and may play a role in cell-to-cell adhesion (23); ii) overexpression of CEA is thought to play a role in tumorigenesis (24); iii) CEA has a dominant effect in blocking differentiation, and it also cooperates with Myc and Bcl-2 in cellular transformation (25); and iv) it can inhibit cell death induced by a loss of anchorage to the extracellular matrix (anoikis) (26). Although these findings suggest that CEA has anti-apoptotic effects in cancer cells, a direct relationship between h-CEA and response to EGFR TKIs has not yet been established.

CYFRA 21-1, a fragment of cytokeratin subunit 19, was first identified in 1993 as a valuable marker in lung cancer patients (27). CYFRA 21-1 was found to be associated with TNM stage and ECOG PS, reflecting an unfavorable prognosis for NSCLC patients regardless of treatment (8,21,28-30). In our study, patients with a poor ECOG PS had a higher CYFRA 21-1 level than patients with a good ECOG PS (6.4 vs. 3.0 ng/ml; P=0.03). Patients with h-CYFRA 21-1 levels were more likely to have a history of smoking; however, this association was not significant (P=0.072). Previous studies have also reported that smoking has no effect on serum CYFRA 21-1 levels (31,32). Univariate and multivariate analyses demonstrated that CYFRA 21-1 levels higher than 3.3 ng/ml had an independent negative impact on PFS (HR=1.93, 95% CI 1.09-3.44; P=0.025) and OS (HR=2.76, 95% CI 1.38-5.53; P=0.0004). Therefore, CYFRA 21-1 is an independent marker for poor prognosis in NSCLC patients receiving an EGFR TKI, which is consistent with a previous study (12).

We demonstrated that pre-treatment levels of CEA and CYFRA 21-1 serve as prognostic and predictive markers in NSCLC patients treated with gefitinib or erlotinib. Patients with a high pre-treatment CEA level showed better responses and longer PFS, and patients with a low pre-treatment CYFRA 21-1 level showed longer PFS and OS. In addition, the prediction accuracy of the EGFR TKI response and prognosis improved when all patients were divided into three groups according to combined levels of CEA and CYFRA 21-1.

It is difficult to predict high efficacy of EGFR TKIs when they are used in patients with non-adenocarcinoma histology since the incidence of EGFR mutation is extremely rare in these tumors (33). However, the present study revealed that CEA and CYFRA 21-1 levels can also be prognostic markers in patients with squamous cell carcinoma or patients with unknown EGFR mutation status (Figs. 2 and 3).

In conclusion, pre-treatment serum levels of CEA and CYFRA 21-1 are simple and easy to detect, and can serve as predictive and prognostic factors for advanced NSCLC patients being treated with EGFR TKIs, particularly in patients with squamous cell carcinoma or patients with an unknown EGFR mutation status.

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