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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].

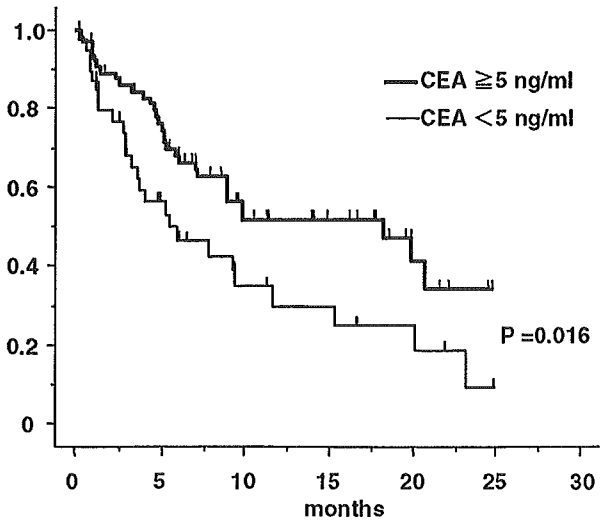

Fig. 1. The survival curves of gefitinib treated patients with elevated serum CEA (⩾5 ng/ml) and normal CEA levels (<5 ng/ml).

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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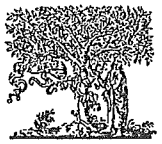

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Mutations in the tyrosine kinase domain of the EGFR gene associated with gefitinib response in non-small-cell lung cancer

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Summary The potential relevance of epidermal growth factor receptor (EGFR) mutations to non-small-cell lung cancer treatment has recently been identified. We have examined the presence of EGFR mutations in Japanese and Spanish gefitinib-treated non-small-cell lung cancer patients. A total of 34 gefitinib-treated patients were screened, 18 from Japan and 16 from Spain. Laser capture microdissection was performed for the accurate procurement of tumor cells. EGFR exons 18, 19 and 21 were amplified from genomic DNA by means of PCR, and the samples were then subjected to bi-directional automatic sequencing. EGFR somatic mutations in the tyrosine kinase domain were found in 8 of 34 patients (23.5%). Gefitinib response was observed in 7 of 8 patients (87.5%) with EGFR mutations and in 3 of 24 (12.5%) with wild-type EGFR ($P=0.0003$). Five deletion mutations were clustered in the region spanning codons 746 to 750 (ELREA) within exon 19. Three additional tumors had amino acid substitutions within exon 18, at codons 718 and 719. Logistic regression analysis showed that response was primarily linked to the presence of EGFR mutations and secondarily linked to female gender, non-smoker status and a greater number of prior chemotherapy regimens. The presence of EGFR mutations is a major determinant of gefitinib response, and EGFR tyrosine kinase inhibitors should be tested in clinical trials of first-line treatment of lung adenocarcinomas harboring EGFR mutations.

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1. Introduction

Epidermal growth factor receptor (EGFR) is surfacing as an important target for therapy. EGFR stimulates cell growth and differentiation after binding of specific ligands, acting as a membrane-bound receptor with intrinsic tyrosine kinase (TK) activity in the intracellular domain. Overexpression of EGFR has been shown to transform NIH 3T3 cells in an EGF-dependent manner [1]. Dimerization with other erbB receptors and the activation of the kinase domain are essential for phosphorylation of a variety of intracellular protein cascades. EGFR is amplified in 9% of NSCLC cases. Therefore, it is broadly accepted that overexpression of EGFR in NSCLC is commonly regulated on the transcriptional level [1]. The Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 trial investigated the efficacy of oral gefitinib in advanced NSCLC patients who had previously received one or two chemotherapy regimens. The response rate was higher for Japanese than for non-Japanese patients (27.5% versus 10.4%; odds ratio = 3.27; $P = 0.0023$). The response rate was also 2.5 times higher in women than in men and 3.5 times higher in adenocarcinoma than in other histologies [2]. The IDEAL 2 study was carried out only in patients in the United States previously treated with two or more regimens containing cisplatin or carboplatin plus docetaxel. The overall response rate was 10%, with a median survival of 6 months and one-year survival of 25%. Response rate was 19% for women and 3% for men, 13% for adenocarcinoma and 4% for other histologies [3]. In addition to the IDEAL 1 and IDEAL 2 trials, 122 patients were treated on the Expanded Access Program, a compassionate use program, at the Memorial Sloan-Kettering Cancer Center. Results confirmed the better response in women (19%) than in men (8%) ($P = 0.14$) and in adenocarcinoma (19%) than in other histologies (0%) ($P = 0.004$). Response was also higher in never-smokers (36%) than in former or current smokers (8%) ($P = 0.001$) [4].

The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 investigated the efficacy of gefitinib versus placebo in combination with cisplatin plus gemcitabine in chemotherapy-naïve patients from Europe (74%), North America (12.7%), Asia (5.3%), South America (4.1%) and South Africa (1.6%). No differences were observed in response, time to progression or median survival [5]. In the INTACT 2 trial, where 80% of the patients were from the United States, patients were randomized to receive paclitaxel plus carboplatin with or without gefitinib. There was no survival advantage in any of the subgroups when gefitinib was added to chemotherapy, but there was a trend toward improved survival in the subgroup of patients with adenocarcinoma who had received chemotherapy for more than 90 days [6].

Personalized treatment can be based on the kinases that are mutationally altered in individual tumors. TKs are central regulators of signaling pathways that control differentiation, transcription, cell cycle progression, apoptosis, motility and invasion. TK mutations have been described in PI3KCA, which encodes the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K) [7,8]. Mutations have also been described in B-raf, the most common of which is a substitution mutation changing valine 599 to glutamic acid (V599E), which dramatically enhances B-raf activity [9]. Recently, EGFR TK mutations have been described and linked to gefitinib sensitivity in NSCLC patients [10,11]. Paez et al. [10] observed mutations in the EGFR TK domain only in responders. These mutations were more frequent in women (9/45, 20%) than in men (7/74, 9%) ($P = 0.009$), in adenocarcinoma (15/70, 21%) than in other histological subtypes (1/49, 2%) ($P = 0.001$), in non-smokers (13/37, 54%) than in smokers (6/62, 11%) ($P = 0.0009$), and in Japanese (15/58, 26%) than in non-Japanese subjects (1/61, 2%) ($P = 0.001$). In addition, no mutations were observed in four patients who progressed on gefitinib, while all five tumors from gefitinib responders harbored EGFR mutations ($P = 0.0027$). Lynch et al. [11] also identified mutations in the EGFR TK domain in eight of nine patients with gefitinib-responsive NSCLC, compared with none of the seven non-responders. In both studies, the majority of mutations was clustered in exons 18, 19 and 21 and were either in-frame deletion or heterozygous missense mutations around the adenosine triphosphate (ATP) binding pocket [12]. Substitution mutations changing leucine 858 to arginine (L858R), guanine 719 to serine (G719S), and leucine 861 to glutamine (L861Q) lay in the activation and glycine-rich P loops, which are important for autoregulation, while multiple deletion mutations clustered in the region spanning codons 746 to 750 (ELREA), around the active site of the kinase [10,11]. Mutant EGFR has also been found in gefitinib-sensitive cell lines [10,11].

These studies demonstrate that mutations around the EGFR TK domain enhance ligand-inducing EGFR autophosphorylation and confer increased sensitivity to gefitinib, suggesting that gefitinib may be highly effective for treating NSCLC patients with somatic EGFR mutations. We have studied EGFR TK mutations in NSCLC patients from Japan and Spain who were treated with gefitinib

after second- or third-line chemotherapy and correlated results with response.

2. Patients and methods

2.1. Patients

Paraffin-embedded tumor tissue was obtained from a total of 34 NSCLC patients who had been treated with gefitinib as part of Expanded Access programs after at least second- or third-line chemotherapy failure. Eighteen samples, including 17 resected primary tumors and one bronchial biopsy of a metastatic tumor, were from the National Kyushu Cancer Center in Fukuoka, Japan, and 16 samples, including eight resected primary tumors and eight bronchial biopsies of metastatic tumors, were from the Catalan Institute of Oncology in Badalona, Spain. Patients were selected retrospectively for the present study based on the availability of tumor specimens. Acquisition of tumor specimens and examination of clinical records were approved by the ethical committees of both institutions. All patients gave their signed informed consent for genetic assessment. Patients were divided into smokers and non-smokers; non-smokers were defined as those who had smoked less than 100 cigarettes in their lifetimes. Tumor response was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [13]. Follow-up was calculated from the start of gefitinib treatment; median follow-up was 8 months (range, 1.05–27.6 months).

2.2. Methods

In order to obtain relatively pure cell samples for DNA extraction, laser capture microdissection was used (Palm, Oberlensheim, Germany). For isolation of DNA from deparaffinated, microdissected tissue, the material was incubated with proteinase K, and DNA was extracted with phenol-chloroform and ethanol precipitation. Primers and cycling conditions for PCR amplification and direct sequencing for exons 18, 19 and 21 of the EGFR gene (GenBank accession number: X00588) were modified from those previously described [10,11]. Primer pairs and PCR conditions utilized are available in the supplementary appendix. Sequencing was performed using forward and reverse primers with the ABI Prism 3100 DNA Analyzer (Perkin-Elmer, Applied Biosystems). Electropherograms were analyzed for the presence of mutations using Seqscape v2.1.1 software in combination with Factura to mark heterozygous positions. Results were confirmed by independent reruns of the same samples.

2.3. Statistical analyses

The primary objective of this study was to compare clinical characteristics, response rates, and survival in patients with and without mutations in the EGFR TK domain treated with gefitinib. Differences in response rates and clinical characteristics between patients with and without somatic EGFR mutations were analyzed using the chi-square, Fisher's exact test, and Student's *t*-test. Time to death was calculated from the start of gefitinib treatment. The Kaplan–Meier method and log-rank test were used to examine survival differences according to response, EGFR mutation status and nationality. Equation of logistic regression models without constant was fit to examine the relationship between the odds of response and each covariate in the whole group and in different sub-groups after adjusting for the following factors: EGFR mutation status, age, gender, smoking status, nationality and number of prior chemotherapy regimens. In the EGFR mutation-response interaction analysis, we used multiple approaches to evaluate consistency of results, including crude and adjusted analyses. The SPSS 11.5 statistical software package was used for all calculations.

3. Results

Patient characteristics are shown in Table 1, broken down by the presence or absence of EGFR mutations. Eight of the 34 patients harbored mutations. All mutations observed were somatic and were found exclusively in adenocarcinomas and more frequently in non-smokers than in smokers. Gefitinib response was observed in 7 of 8 patients (87.5%) with EGFR mutations and in 3 of 24 (12.5%) with wild-type EGFR ($P=0.0003$). Two patients with wild-type EGFR were not evaluable for response. Although mutations were not observed in non-responders, one was found in a Spanish patient with stable disease who had two primary lung cancers. The mutation (W731Stop) was found in the resected specimen of the primary lung adenocarcinoma but not in a second squamous cell carcinoma. Exon sequencing of genomic DNA revealed missense and deletion EGFR mutations in 7 of 9 Japanese responders (Table 2), all within exons 18 and 19. We detected four deletion mutations clustered in the region spanning codons 746 to 750 (ELREA) within exon 19 (Fig. 1). Three of these mutations were

Table 1 Patient characteristics according to EGFR mutations

	EGFR mutation	Wild-type EGFR	*P*
No.	8	26	
Age (years)			
≤60	6 (75)	14 (53.8)	0.42
>60	2 (25)	12 (46.2)	
Sex			
Male	4 (50)	19 (73.1)	0.38
Female	4 (50)	7 (26.9)	
Ethnicity			
Caucasian	1 (12.5)	14 (53.8)	0.05
Asian	7 (87.5)	12 (46.2)	
Histology			
Adenocarcinoma	8 (100)	20 (76.9)	0.001[a]
Large cell carcinoma	0 (0)	4 (15.4)	
Squamous cell carcinoma	0 (0)	2 (7.7)	
Smokers	3 (37.5)	21 (80.8)	0.03
No. of prior regimens	2 (0–6)	2 (0–6)	0.65
Response to gefitinib			
Yes	7 (87.5)	3 (12.5)	0.0003
No	1 (12.5)	21 (87.5)	
NE		2	
Skin toxicity			0.47
None	2 (25)	12 (46.2)	
G1	2 (25)	7 (26.9)	
G2	4 (50)	6 (23.1)	
G3	0 (0)	1 (3.8)	
Duration of gefitinib, weeks (range)	31.2 (4–62.4)	11.2 (0.8–119.8)	0.35

NE, non-evaluable; CR, complete response; PR, partial response; SD, stable disease.
[a] Adenocarcinomas with EGFR mutations compared to adenocarcinomas with wild-type EGFR.

Table 2 Patient characteristics and EGFR mutations for gefitinib responders

Country	Sex	Age[a]	Histology	No. of prior regimens	Smoking status	Duration of therapy	Overall survival (months)	EGFR mutations
Japan	F	71	adeno	1	No	5.6	5.6+	719 (GGC → GC)
Japan	F	68	adeno	2	No	17.7	17.7+	No
Japan[b]	F	60	adeno	3	No	3.5	6.9+	718 (CTG → CCG)
Japan	F	53	LCC	3	No	16.9	17.8+	719 (GGC → GCC)
Japan	F	42	adeno	2	No	10.6	10.6+	In-frame deletion (746–750)
Japan	M	50	adeno	0	No	10.4	10.4+	In-frame deletion (747–751) insertion of A
Japan	M	76	adeno	3	Yes	2.2	2.2+	No
Japan	M	52	adeno	1	Yes	1.1	1.1+	In-frame deletion (745–750)
Japan	F	54	adeno	2	No	15.6	18.7	In-frame deletion (746–750)
Spain	M	63	adeno	3	Yes	10.1	10.1+	In-frame deletion (746–751) insertion of F

[a] Age at start of gefitinib treatment.
[b] This patient has no measurable disease and suffered an increase of CEA levels adeno, adenocarcinoma; LCC, large cell carcinoma.

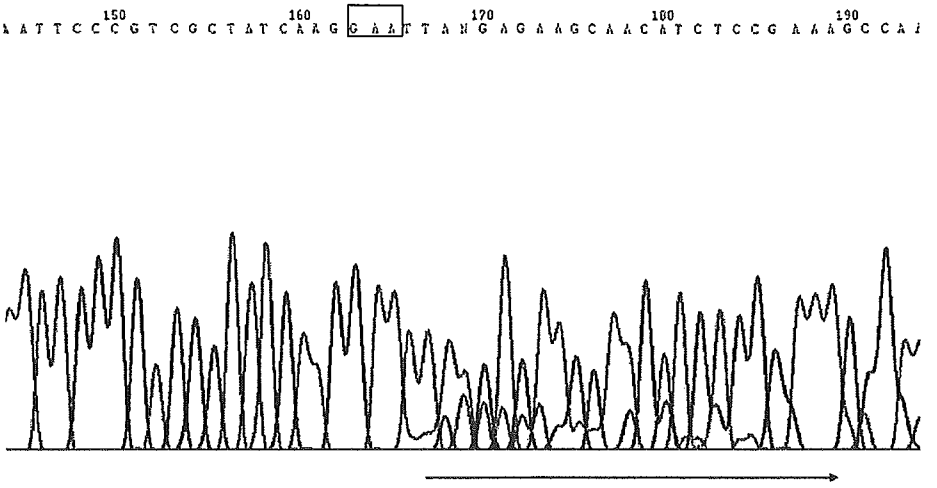

Fig. 1 Partial electropherogram after direct DNA sequencing of PCR products for heterozygous deletion at codons 747–751. Loss of amino acids L R E A T of exon 19 is indicated by the arrow.

homozygous in-frame deletion (745–750), and one was a heterozygous in-frame deletion (747–751) and insertion of a phenylalanine residue. The only Spanish gefitinib responder also harbored a heterozygous in-frame deletion (746–751) and insertion of alanine residue. Three additional tumors had amino acid substitutions within exon 18, at codons 718 (Fig. 2) and 719 (Fig. 3).

Table 3 shows the adjusted odds ratio for the joint effect on response of different variates and covariates. Response was primarily linked to the presence of EGFR mutations. The odds ratio was slightly lower in males than in females and increased 23-fold in non-smokers. In addition, patients who had received more prior chemotherapy lines showed a 11-fold increased probability of response. Other variates are shown in Table 3.

Median survival for all patients, calculated from the start of gefitinib treatment, was 14.1 months (95% CI, 7.8–20.5). Median survival was 15.6 months (95% CI, 0–38.1) for the Japanese patients

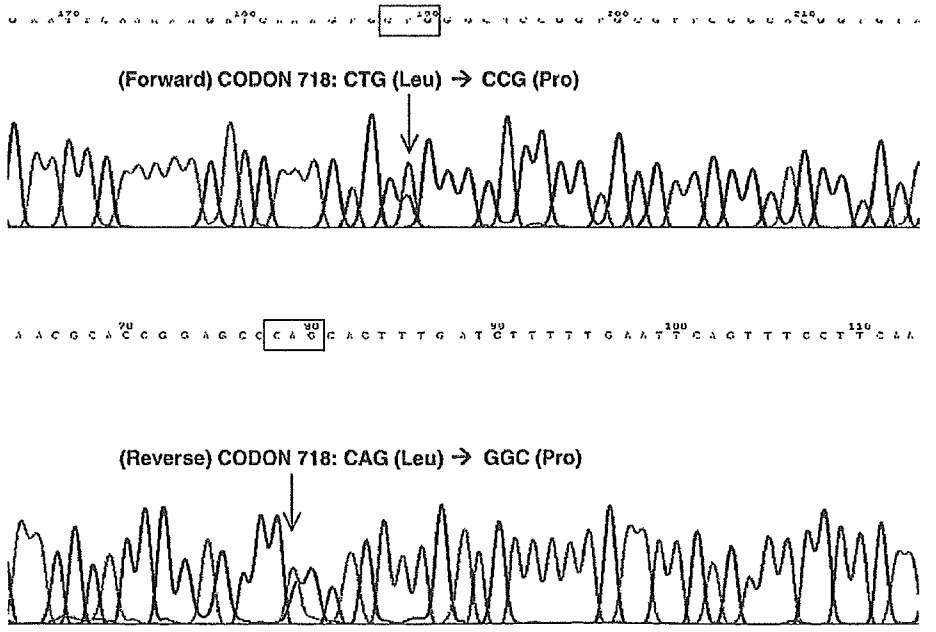

Fig. 2 Partial electropherogram after direct and reverse DNA sequencing of PCR products for a heterozygous missense mutation (T to C) at codon 718 of exon 18 yielding a leucine (Leu) to proline (Pro) amino acid change.

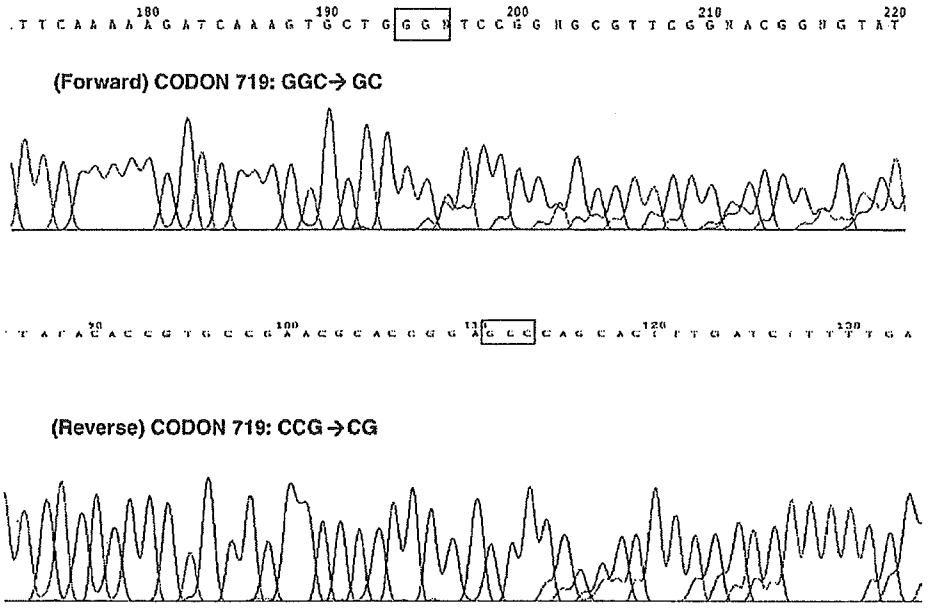

Fig. 3 Partial electropherogram after direct and reverse DNA sequencing of PCR products showing a nucleotide deletion (G) at codon 719 that disrupts the wild-type reading frame of exon 18.

Table 3 Adjusted odds ratios (OR) for the joint effect on response of different covariates

Variates/covariates	OR (95% CI)	*P*
EGFR mutations	7 (1.1–56)	0.05
EGFR mutations by sex (male)	6.6 (1.3–33.3)	0.02
EGFR mutations by smoking status (non-smoker)	23.3 (3.1–166.7)	0.002
EGFR mutations by no. prior chemotherapy regimens	11.6 (2.12–62.5)	0.005
EGFR mutations by ethnicity	4 (1.05–15.6)	0.04
EGFR mutations by age	7 (4.8–1000)	0.002
Sex (male)	0.23 (0.08–0.69)	0.009
Smoking status (smoker)	0.15 (0.04–0.5)	0.002
No. of prior chemotherapy regimens	0.7 (0.5–0.9)	0.04
Ethnicity (Asian)	7 (1.7–100)	0.01
Age	1.03 (0.9–1.1)	0.07

Odds ratio was calculated according to the logistic regression model without constant.

Table 4 Patient characteristics of 12 Spanish patients with stable disease after gefitinib treatment

Sex	Age[a]	Histology	No. of prior regimens	Smoking status	Duration of therapy	Overall survival (months)	EGFR mutations
M	62	adeno	3	Yes	3.2	3.2+	No
F	42	adeno	2	Yes	2.5	2.5+	No
M	52	adeno	3	Yes	20.4	20.4+	No
M	40	LCC	3	Yes	19.1	19.1	No
F	51	adeno	1	Yes	12.8	23.7+	No
M	49	adeno	2	Yes	27.6	27.6	No
M	50	adeno	2	Yes	14.1	14.1	No
M	70	LCC	2	Yes	11.3	11.3	No
M	56	adeno	5	Yes	9.6	11.6	No
M	52	SCC	2	Yes	6.9	18.9	No
M	65	adeno	2	Yes	1.4	2.1	No
M	56	adeno	6	Yes	6.0	7.6	W731Stop

[a] Age at start of gefitinib treatment adeno, adenocarcinoma; LCC, large cell carcinoma; SCC, squamous cell carcinoma.

Table 5 EGFR mutations according to patient characteristics in Japanese patients

	EGFR mutation	Wild-type EGFR	*P*
Age, years			
≤60	6 (66.7)	3 (33.3)	0.05
>60	1 (12.5)	7 (87.5)	
Sex			
Male	2 (25)	6 (75)	0.33
Female	5 (44.4)	4 (55.6)	
Histology			
Adenocarcinoma	6 (40)	9 (60)	0.9[a]
Large cell carcinoma	1 (100)	0 (0)	
Squamous cell carcinoma	0 (0)	1 (100)	
Smoking status			
Smoker	1 (12.5)	7 (87.5)	0.05
Non-smoker	6 (66.7)	3 (33.3)	

[a] Adenocarcinomas with EGFR mutations compared to adenocarcinomas with wild-type EGFR.

and 11.3 months (95% CI, 5.4–17.2) for the Spanish patients ($P=0.8$). Median survival for responders has not been reached, while for non-responders, it is 6.9 months (95% CI, 0–13.9). Twelve Spanish patients had stable disease after gefitinib treatment (Table 4). Median survival for these patients was 14.1 months (95% CI, 7.9–20.4).

Since almost 90% of mutations were in the Japanese patients, further analyses were performed on this group. EGFR mutations were found in 62% in Japanese female non-smokers with adenocarcinoma. In Japanese patients, mutations were more frequently observed in patients younger than 60 years ($P=0.05$), in non-smokers ($P=0.05$), in women and in adenocarcinoma (Table 5). Median survival for the seven Japanese patients with EGFR mutations was 15.6 months (95% CI, 0–53) and for the 10 Japanese patients with wild-type EGFR, it was 2.3 months ($P=0.04$) (Fig. 4).

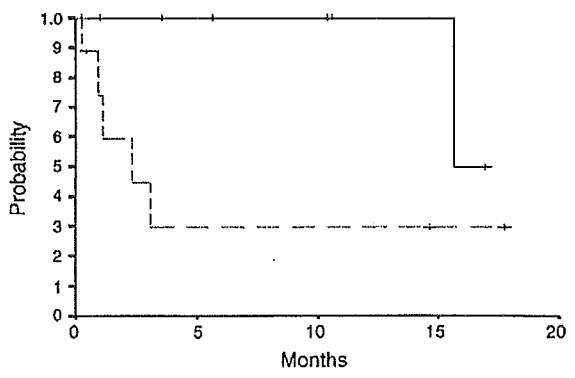

Fig. 4 Survival in Japanese patients according to the presence of EGFR mutations. The solid line represents the seven patients with mutations, and the broken line represents the 10 patients with wild-type EGFR.

4. Discussion

In the present study, we have observed that EGFR mutations are a strong predictor of gefitinib response in chemoresistant NSCLC patients. Seven of eight patients (87.5%) with EGFR mutations attained an objective response, in contrast with only three of 24 patients (12.5%) with wild-type EGFR ($P<0.0003$). These results mirror accumulated data from three studies [10,11,14], in which 25 of 31 (81%) NSCLC patients with EGFR mutations attained objective response, while none of 29 non-responders had mutations. In addition, recent work [15] has demonstrated that NSCLC cell lines containing EGFR mutations are chemoresistant but highly sensitive to gefitinib. In our study, an increased number of prior chemotherapy regimens reduced the chances of response to gefitinib in general but increased chances of response in the presence of EGFR mutations.

To date, it has not been clearly demonstrated that gene mutations in general can be predictive markers of response. For example, K-ras gene mutations in cell lines derived from NSCLC patients were associated with shorter survival when treated with chemotherapy [16], but this was not confirmed in studies where K-ras mutations were analyzed in archival pathology blocks [17]. In human tumor cell lines, the presence of ras mutations enhances gemcitabine sensitivity in comparison to tumor cells with wild-type ras alleles [18]. A single nucleotide

polymorphism in exon 4 (arginine allele), together with wild-type p53, has been associated with favorable response to chemoradiotherapy of squamous cell carcinoma [19].

It seems that in non-smokers and some adenocarcinoma patients, the EGFR signaling pathway can be selectively activated, as has been observed in gefitinib-sensitive human NSCLC cell lines, like PC9 [20] and others harboring EGFR mutations [10,11]. Homo- and/or heterodimerization of EGFR activates several intracellular signal transducing elements, such as phospholipase Cγ, PI3K, protein kinase B/AKT (Akt), a small G-protein (Ras), the Ras GTPase-activating protein extracellular signal-regulated kinase (ERK) 1/2, Src family kinases, and signal transducers and activators of transcription (STATs). Experimentally, tobacco carcinogen exposure (NNK) has been shown to promote the activation of PI3K/Akt pathway [21], and it is thus plausible that the PI3K signaling pathway is activated in heavy smokers through the stimulation of other TKs [22]. In MDA-468 human breast cancer cells overexpressing EGFR, the concomitant amplification of the PI3K/Akt pathway as a consequence of loss of PTEN increased Akt activity and led to resistance to EGFR TK inhibitors; the re-introduction of PTEN restored sensitivity to EGFR TK inhibitors [23].

Although these results may be biased due to the small number of patients studied and because they were selected on the basis of availability of tumor tissue, they are in line with those reported [10,11,14]. The discovery of EGFR mutations in the TK domain that predict response to gefitinib is a breakthrough in the implementation of predictive markers for selecting treatment. Screening for EGFR mutations may be particularly useful in non-smokers, patients younger than 60 years, females and patients with adenocarcinoma, especially Japanese patients. The low response rate to gefitinib observed in Spanish patients may be explained by the low frequency of EGFR mutation in these patients. However, stable disease was observed in a meaningful number of gefitinib-treated Spanish patients, resulting in a median survival that was close to that of Japanese responders. Further research should be carried out in Caucasians to elucidate the predictive markers for the significant number of patients who can obtain a clinical benefit from gefitinib. A polymorphic CA repeat located at the 5′-regulatory sequence in intron 1 of the EGFR gene has been associated with its transcriptional activity with interethnic differences. Shorter CA repeats are associated with higher transcription activity and are observed more frequently in Caucasian than in Japanese patients [24]. In conclusion, previous studies [10,11,14] and our present study concur that the presence of EGFR mutations is a major determinant of gefitinib response. In future clinical trials, therefore, EGFR TK inhibitors should be considered in preference to chemotherapy as first-line treatment in lung adenocarcinomas harboring EGFR mutations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.lungcan.2005.05.017.

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Case report

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Long-term survival after an aggressive surgical resection and chemotherapy for stage IV pulmonary giant cell carcinoma

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Abstract

Background: Pulmonary giant cell carcinoma is one of the rare histological subtypes with pleomorphic, sarcomatoid or sarcomatous elements. The prognosis of patients with this tumor tends to be poor, because surgery, irradiation and chemotherapy are not usually effective.

Case presentation: We herein report a patient with pulmonary giant cell carcinoma with stage IV disease in whom aggressive multi-modality therapy resulted in a long-term survival. A 51-year-old male underwent an emergent operation with a partial resection of small intestinal metastases due to bleeding from the tumor. The patient also underwent a left pneumonectomy due to hemothorax as a result of the rapid growth of the primary tumor. Thereafter, two different regimens of chemotherapy and a partial resection for other site of small intestinal metastases and a splenectomy for splenic metastases were performed. The patient is presently doing well without any evidence of recurrence for 3 years after the initial operation.

Conclusion: This is a first report of a rare case with stage IV pulmonary giant cell carcinoma who has survived long-term after undergoing aggressive surgical treatment and chemotherapy.

Background

The recent World Health Organization (WHO) classification of lung tumors has unified the heterogeneous group of non-small cell lung carcinomas that contains sarcoma or sarcoma-like components under the designation of "carcinomas with pleomorphic, sarcomatoid or sarcomatous elements" [1]. This group includes different entities, such as pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma. In general, these tumors are rare, comprising approximately from 0.1–0.4% of all lung malignancies [2-4]. The patients with these tumors tend to demonstrate a despondent clinical course and the prognosis for them is gernally poor [5], because surgery, irradiation and chemotherapy are ineffective. We experienced a pulmonary giant cell carcinoma patient with stage IV disease in whom aggressive multi-modality therapy consisting of surgical resections for the primary lesion and multi-organ metastases and also chemotherapy which together resulted in a long-term survival.

Case presentation

A 51-year-old male was admitted in June 2001, due to hemosputum, cough, hemo-stool and an abnormal shadow on a chest roentgenogram. Laboratory results showed severe anemia with hemoglobin of 4.0 g/dl (13.6 < normal range < 16.8 g/dl) and hematocrit of 16.0 % (40 < normal range < 48 %). The patient's chest X-ray demonstrated a huge mass lesion in the left upper lung field (Figure 1). Computed tomography (CT) of the chest showed a mass shadow, measuring 7.0 × 7.0 cm in size in the left upper lobe (S^{1+2}) without any invasion of the surrounding tissue such as the vessels, plexus or thoracic wall and with no mediastinal lymph node swelling. Abdominal CT revealed a huge mass, measuring 12.7 × 7.5 cm in size in the small intestine. Prior to performing any treatment for the presumed lung cancer, we tried to stop the continuous bleeding from tumor in the small intestine. As a result, we performed an emergency operation. The tumor was observed in the jejunum at a location about 30 cm from the ligament of Treitz on the anal side and a 25 cm length of the jejunum, including the tumor, was thus resected. Six days later, the patient experienced sudden chest pain, dyspnoea and hemoptysis. The patient's chest X ray showed the left lung mass shadow to have rapidly increased in size, while the broncho-fiberscopy findings showed bleeding from the left upper bronchus and an obstruction of the left lower bronchus due to coagulation. Hemothorax due to a rupture of the lung induced by the rapid growth of the tumor was found after an emergency thoracotmy. The tumor was so large that it was difficult to approach the interlobular pulmonary artery. Therefore, a left pneumonectomy with mediastinal lymph nodal dissection was performed. Thereafter, intraoperative intrapleural hypotonic cisplatin treatment [6] was performed because some tumor cells were suspected to exist in the pleural cavity due to the rupture of the tumor. A histological examination revealed pure giant cell carcinoma containing no sarcomatoid component, similar to that found in the small intestine (Figure 2). As a result, we diagnosed the patient to have stage IV disease (pathological stage T2N0M1) according to the TNM classification [1]. The patient had an uneventful recovery without any complications. However, about 4 months after the first operation, the patient was diagnosed to have a recurrence at another site in the small intestine and spleen by abdominal CT. The patient received 2 cycles of chemotherapy (cisplatin 40 mg/m^2 + gemcitabine 800 mg/m^2+ vinorelbine 20 mg/m^2), at days 1 and 8, and thereafter every 4 weeks). The splenic metastases increased in size while the size of the tumor in the small intestine decreased. At this time, no recurrence site except for those in the small intestine and spleen were found, therefore, to avoid the risk of bleeding either from tumors in the small intestine or a rupture of spleen in the future, surgical treatment consisting of a partial resection of the small intestine and a splenectomy was performed. The intestinal tumor was found in the jejunum at a location about 10 cm from the ligament of Treitz on the anal side and a total 20 cm length of the jejunum, including the tumor, was resected. A pathological examination revealed a proliferation of pure giant cell carcinoma with extensive necrosis both in the small intestine and the spleen, thus suggesting the chemotherapy to be effective in the both organs. Thereafter, the patient received 2 additional cycles of this triplet chemotherapy. The patient experienced neither any hematological nor severe non-hematological adverse events. About 6 months later, metastases in multiple abdominal lymph nodes were found (Figure 3A). The patient was started on chemotherapy (carboplatin AUC = 2 + paclitaxel 60 mg/m^2, on days 1 and 8, and thereafter every 3 weeks). After receiving a total of 10 cycles of chemotherapy on an outpatient basis, abdominal CT showed the chemotherapeutic effect to be a complete response (Figure 3B), without any severe hematological or non-hematological adverse events. At present, the patient has survived for about 3-years since the first operation and a complete response has been maintained for 15 months.

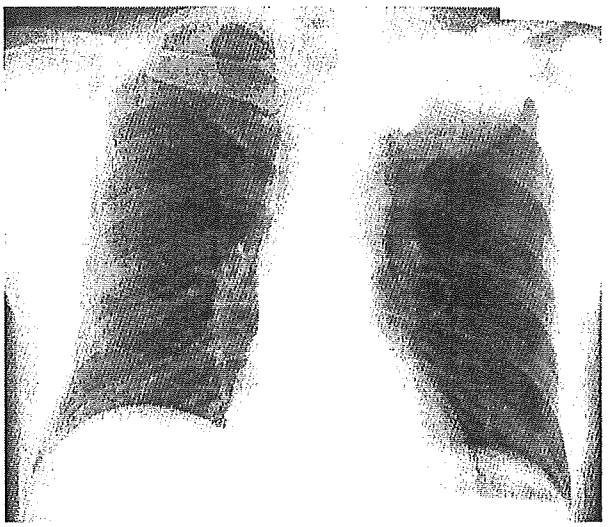

Figure 1
Posterior-anterior view of a chest X-ray film demonstrated a huge mass shadow in the left upper lung field.

Discussion

According to the treatment guidelines for unresectable non-small cell lung cancer of American Society of Clinical Oncology (ASCO)[7], chemotherapy prolongs survival and is the most appropriate treatment for stage IV patients with a good performance status. Although both resections of primary lung cancer and either brain or adrenal

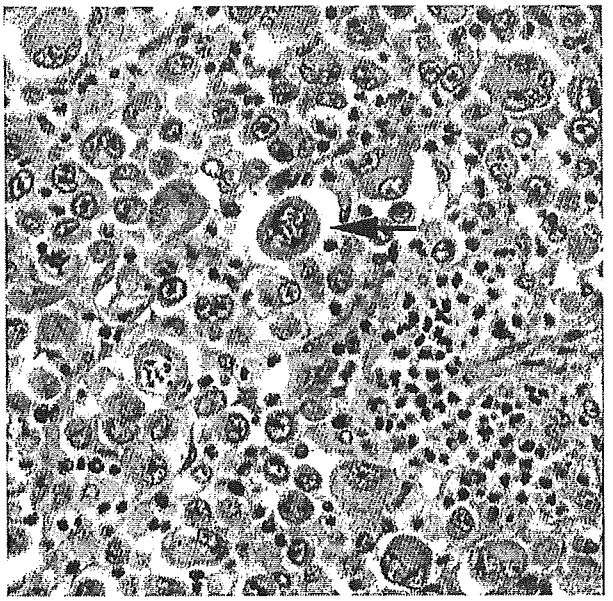

Figure 2
Pathological findings of the left lung. The section consists of a diffuse proliferation of atypical, giant and bizarre cells (arrowhead). No sarcomatoid component is seen.

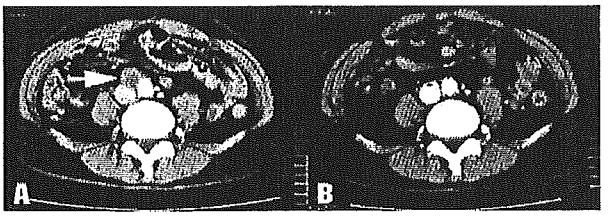

Figure 3
Computerised tomographic scan before and after treatment. A) Abdominal CT showed multiple lymph node swelling, suggesting the presence of metastases (arrowhead). B) Abdominal CT showed the lymph nodes metastases to have completely disappeared.

metastases are occasionally recommended in highly selected patients, a surgical resection of other metastasized sites is hardly ever performed. Therefore, the present patient is an extremely rare case because he underwent an emergency surgical resection of small intestinal metastases and a primary tumor due to bleeding from both tumors, as well as a surgical resection of other metastases in the small intestine and spleen in order to avoid a risk of bleeding from the recurrent site in the future.

Fishback *et al*, reported the overall survival of total 78 patients with pleomorphic (spindle/ giant cell) carcinoma (stage I-IV), among whom 57 patients received a surgical resection, to be poor with a median survival time of 10 months and a survival rate of 10% at 5 years [8]. According to Chang *et al*, the mean survival time of resected pleomorphic carcinoma patients was 5 months while the median survival time of pleomorphic carcinoma patients treated with concurrent or sequential chemo-radiotherapy was 2.7 months [9]. To our knowledge, a case of a long-term survivor with stage IV pleomorphic (spindle/ giant cell) carcinoma has never been previously reported. The tumor histology of the present case was very rare, pure giant cell carcinoma, which belongs to the category of carcinomas with pleomorphic, sarcomatoid or sarcomatous elements according to new WHO classification, and the prognosis is estimated to be poor. Although pleomorphic carcinoma has been reported to usually be resistant to chemotherapy, we first chose chemotherapy including cisplatin, gemcitabine and vinorelbine, which has been shown to demonstrate the highest response rate in advanced non-small cell lung cancer based on our experience. In our prior phase II trial using this combination chemotherapy in 79 advanced non-small cell lung cancer patients, the response rate was 56% and the 1-year survival rate was 75% while the toxicity levels were acceptable [10]. After recurrence, we chose chemotherapy with carboplatin and paclitaxel, which is most frequently used for the treatment of advanced non-small cell lung cancer. Since the standard treatment method using carboplatin and paclitaxel in Japan is the administration of AUC of 6 and 200 mg/m^2, respectively once every 3 weeks [11], the administered regimen (carboplatin AUC = 2 and paclitaxel 60 mg/m^2, on days 1 and 8, and thereafter every 3 weeks) in this patient was unusual and the dose intensity was relatively small. However, this regimen nevertheless effectively treated his disease and he was also able to work normally during the treatment process. At present, the patient has survived for 3 years since the first operation and has remained healthy without any signs of recurrence for 15 months after the last treatment.

Conclusion

This is a first report of a rare case with stage IV pulmonary giant cell carcinoma who has survived long-term after undergoing aggressive surgical treatment and chemotherapy.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

FS: Conceived the study, participated in its design and coordination and drafted the manuscript.

RM and TO: carried out the literature search and helped in drafting the manuscript

JI, TN and HW: participated in the study design and helped with preparation of the manuscript

YI: Shaped the idea for the manuscript, coordinated the study and edited the manuscript.

All authors conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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Written consent was obtained from the patient for the publication of this case.

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Case report

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Malignant schwannoma of the upper mediastinum originating from the vagus nerve

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Abstract

Background: Malignant schwannoma of the upper mediastinum originating from the vagus nerve is extremely rare.

Case presentation: A 46-year-old female was admitted for a left cervical mass which was associated with both hoarseness and Horner's syndrome. Chest computed tomography showed a mass extending from the left upper mediastinum to the left supraclavicular area. A fine needle aspiration cytological examination suggested primary lung cancer stage IIIB large cell carcinoma. After administering induction chemo-radiotherapy, a complete surgical resection was performed. The tumor was found to involve both the left vagus nerve and the left sympathetic nerve. Histological examination of the resected specimen revealed the tumor to be malignant schwannoma.

Conclusion: Despite incorrect preoperative diagnosis, the multimodality treatment administered in this case, including induction chemo-radiotherapy and surgery, proved to be effective.

Background

According to a collected series of 2399 cases of mediastinal tumors reported in the literature [1], 496 cases (20.7%) were of neurogenic tumors, and most of them occurred in the posterior mediastinum. Neurogenic tumors can be divided into two groups depending on their origin: those that arise from the nerve sheath and those that arise from nerve cells. The majority of the tumors of nerve sheath origin in adults are either benign schwannomas or neurofibromas, and they usually arise from either an intercostal nerve or a sympathetic nerve. Intrathoracic schwannoma originating from the vagus nerve, is extremely rare.

Case presentation

A 46-year-old female with symptoms of hoarseness and Horner's syndrome presented with a left cervical mass that was diagnosed to be undifferentiated carcinoma based on the findings of aspiration cytology (Figure 1). The patient's chest computed tomography (CT) findings showed a mass measuring 5.0 cm in size spreading from the left upper mediastinum to the left supraclavicular area, which pressed against both the trachea and

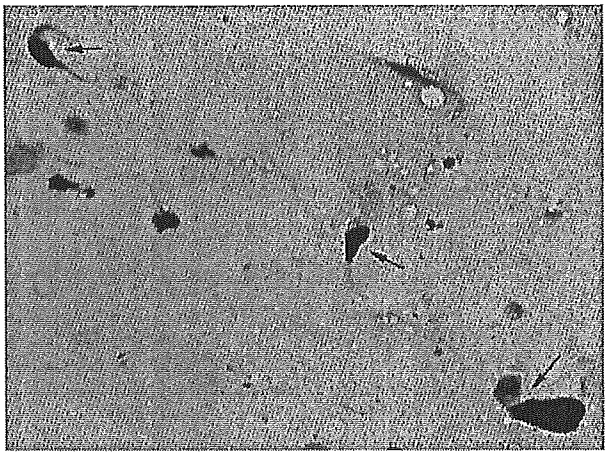

Figure 1
Aspiration cytology of the tumor before treatment showing scattered atypical spindle cells (arrows) (Giemsa staining, high power view x400).

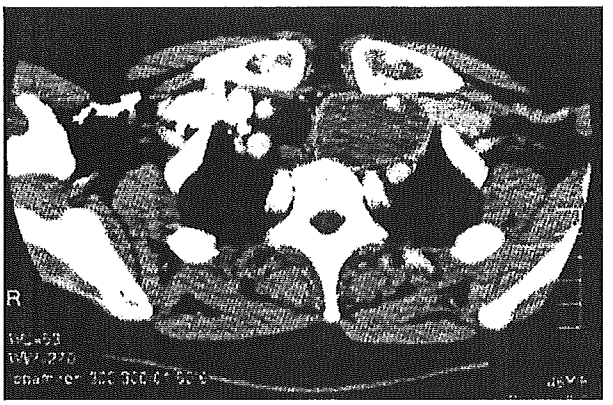

Figure 2
Chest CT showed a mass, measuring 5.0 cm in size in the upper mediastinum.

esophagus and it seemed to involve the left common carotid artery (Figure 2). Based on these findings, and cytology findings a clinical diagnosis of stage IIIB (T4N3M0) non-small cell lung cancer (NSCLC) originating from the apex of the left lung involving both the mediastinum and the supraclavicular lymph nodes was made [2]. The patient received concurrent chemo-radiotherapy (cisplatin 80 mg/m^2 for days 8 and 36 + UFT 400 mg/m^2, both on days 1–14 and on days 29–42 plus radiotherapy, 2 Gy/day on days 1–20 for a total of 40 Gy) [3]. After this treatment regimen, the tumor size decreased by 35.0%. Thereafter, the patient underwent a surgical resection though a median sternotomy with a combined resection of the left clavicle. During the operation, an encapsulated tumor was detected in the mediastinum. Although the tumor was easily ablated from the left common carotid artery, it involved both the left vagus and the sympathetic nerves. As a result, both nerves had to be sacrificed in order to achieve a complete resection of the tumor. Grossly, the tumor was in continuity of the vagus nerve was whitish in color and oval shaped measuring 5 × 3 cm in diameter (Figure 3). Both cytological and histological examinations revealed 1) Continuity between the vagus nerve and tumor was seen, while the no continuity between the tumor and the sympathetic nerve was found. 2) The findings of aspiration cytology of the tumor diagnosing it to be undifferentiated carcinoma before the treatment included an atypical spindle cell. (Figure 1). 3) The predominantly tumor consisted of necrotic tissue and a few viable atypical spindle cells (Figure 4A) which were positive for S-100 protein (Figure 4B). As a result, the tumor was considered to arise from the left vagus nerve while invading the left sympathetic ganglion, and was therefore diagnosed it to be a malignant schwannoma. At present, the patient has survived for about 2 years since operation without any recurrence.

Discussion

Tumors of vagus nerve origin are observed in about 2% of all neurogenic tumors of the mediastinum [4], however, no instace of malignant schwannoma was reported in this review. To our knowledge, only a few such cases have been previously reported [5-7]. As a result, malignant schwannoma originating from the vagus nerve is therefore considered to be extremely rare.

Malignant peripheral nerve sheath tumors (MPNST) including malignant schwannoma are the malignant variants of schwannomas and neurofibromas. Although the 5-year survival rates have been reported to be up to 75 % in MPNST's patients, MPNST often advance locally and can also occasionally metastasize to the lung or other organs [8]. Therefore, in addition to a complete surgical resection, adjuvant therapy is usually advocated. However, in an adjuvant setting, the efficacy of chemotherapy or radiotherapy appears to provide little additional benefit [9,10]. We previously reported concurrent chemo-radiotherapy with UFT plus cisplatin as an induction treatment followed by a surgical resection for patients with marginally resectable stage IIIB NSCLC to be both a feasible and promising treatment [3]. Since we preoperatively considered the disease to be marginally resectable stage IIIB NSCLC, we performed concurrent induction chemo-radiotherapy followed by surgery. As a result, this