Epidermal Growth Factor Receptor Mutations in Cells from Non-Small Cell Lung Cancer Malignant Pleural Effusions

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Background: The prevalence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) patients is about 40~50% in Taiwan, and there are significant correlations between EGFR mutations and clinical responses after gefitinib treatment. For most patients with advanced disease, surgical intervention for tissue sampling is not feasible. We therefore conducted this study to survey EGFR mutations in cells from NSCLC malignant pleural effusions and to evaluate the clinical significance.

Methods: In the present study, malignant pleural effusion cells from 29 NSCLC patients were studied for EGFR mutations. Exons 18, 19, 20, 21 of the EGFR gene were analyzed by polymerase chain reaction (PCR) and automated sequencing. For 11 patients who had received gefitinib therapy, correlations between gefitinib effect and EGFR mutations were also evaluated.

Results: EGFR mutations were detected in 12 of 29 specimens (41%). In-frame deletion mutations in exon 19 (8 of 12 specimens, 67%) and missense mutations in exon 21 (3 of 12 specimens, 25%) were the most frequent mutations detected. The frequency of EGFR mutations was significantly higher in gefitinib responders (4/4) than non-responders (1/7) ($p = 0.015$).

Conclusion: Our results suggest that detecting EGFR mutations in cells from malignant pleural effusions is a feasible adjunct method to finding the subgroup with favorable response to gefitinib therapy among patients with advanced NSCLC.

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Key words: lung cancer, epidermal growth factor receptor, mutations, pleural effusion.

The appearance of malignant pleural effusion is a frequent complication of lung cancer; lung cancer accounts for nearly 36% of all cases with malignant pleural effusion.(1) Although all cell types of lung cancer may cause malignant pleural effusion, adenocarcinoma is the most common cell type.(2) The presence of malignant pleural effusion indicates an advanced stage of non-small cell lung cancer (NSCLC). Chemotherapy slightly prolongs survival of lung cancer patients with advanced disease(3) but is hampered by high relapse rates, significant toxicity and the development of resistance. Recent target therapies that combine anti-tumor activity with better tolerability are beginning to enter clinical practice

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with the purpose of replacing chemotherapy. Epidermal growth factor receptor (EGFR) is an attractive target for therapy, as EGFR signaling is a pathway that plays an important role in the growth, proliferation and survival of many solid tumors, including NSCLC.[4] Gefitinib (Iressa™ or ZD1839, Astra Zeneca Pharmaceuticals, London, Unifed Kingdom), a synthetic anilinoquinazoline, is the first commercially available member of this new class of anticancer drugs. Administered orally, gefitinib competes with adenosine tri-phosphate (ATP) for the tyrosine kinase (TK) binding site on the EGFR, and the resulting inhibition of autophosphorylation blocks downstream signaling.[5] Gefitinib has minimal adverse effects, although tumor responses have been observed in only 10-19% of patients with chemotherapy-refractory advanced NSCLC.[6,7] However, a subgroup of NSCLC with specific mutations in the TK domain of the EGFR gene, which correlates with favorable clinical responsiveness to gefitinib therapy, has been noted.[8,9] All mutations, which are more frequent in adenocarcinomas, appear to be limited to exons 18, 19, 20 and 21 of the EGFR gene.[8-10] Previous studies of EGFR mutations in NSCLC mainly focused on surgical specimens. Since the prognosis of NSCLC patients with malignant pleural effusions is poor, surgical intervention for tissue sampling would not be feasible in most patients. NSCLC patients with advanced disease, in particular adenocarcinoma, commonly have malignant pleural effusion.[2] Obtaining cells from malignant pleural effusion for EGFR study may be a more suitable method for these patients. Recently, EGFR mutations found in malignant pleural effusion cells have been reported[11,12] but the case numbers have been limited for use in further analysis.

In this study, we elucidated the prevalence of EGFR mutations in cells from NSCLC-related malignant pleural effusion. For those patients who had received gefitinib therapy, correlations between EGFR mutations and response to gefitinib were also evaluated.

METHODS

Patients

From February 2005 to August 2005, pleural fluid samples were collected from 29 NSCLC patients undergoing therapeutic or diagnostic thoracentesis at our hospital. After written consent was obtained, thoracentesis was performed under ultrasound guidance. For all 29 patients, the diagnosis of malignant pleural effusion was confirmed by cytological examination of the pleural effusion. For all patients who had received gefitinib therapy, clinical response was evaluated by using chest radiography every 2-4 weeks and classified according to the response evaluation criteria in solid tumors.[13] For patients whose tumor burden could not be quantified with the use of these criteria, the response was assessed as previously described.[8] The clinical response data were updated in October 2005.

Pleural effusion

Pleural effusion from each patient was collected with a volume of 100 to 150 ml. Another 50 ml of pleural effusion was also collected and submitted for cell-block cytology study by pathologists. Cancer cells and other mononuclear cells were then separated by Ficoll gradient as previously described.[14,15] Soon after collection, the specimen was centrifuged at 250 g for 15 minutes at 4°C. The cell pellet was resuspended in 5 ml of phosphate buffer solution (PBS) and then layered onto 5 ml of Ficoll-Hypaque (Histopaque-1077, Sigma-Aldrich, Inc., St. Louis, MO, USA) in a 15 ml collection tube. After centrifuging at 250 g for 30 minutes at room temperature, mononuclear cells in the opaque interface between Ficoll-Hypaque and supernatant were aspirated with a Pasteur pipette. Cells were then washed with PBS and centrifuged at 250 g for 10 minutes twice. Finally, the cell pellets were stored at –80°C for DNA extraction.

DNA extraction, polymerase chain reaction and sequencing

DNA was extracted with a commercialized kit (QIAmp Blood Mini Kit, QIAGEN, Hilden, Germany) from cell pellets according to the manufacturer's instructions. Polymerase chain reaction (PCR) was then performed to amplify the targeted exons. Primers used for amplification of exon 18-21 of the EGFR genes were exon18, GCTCTGTAGAG AAGGCGT (sense) and GTAATCAGTGGTCCT-GTG (antisense); exon19, GATTCGTGGAGCC-CAACA (sense) and CCTTAGAGACAGCACTGG (antisense); exon20, TGCACAAATCAGTGCCTG (sense) and TGCACAAATCAGTGCCTG (anti-

sense); exon 21, CAGCAGCGGGTTACATCT (sense) and TGGGACAGTGAATGAGGA (antisense). PCR was performed for 40 cycles in a programmable thermal cycler (GeneAmp PCR System 9600, Applied Biosystems Foster City, CA, USA) with a volume of 50 μL. Each cycle consisted of steps of denaturation at 95°C for 1 minute, primers annealing at 55°C for 1 minute and elongation at 72°C for 1 minute. The final step was extended at 72°C for 10 minutes. The PCR fragments were sequenced and analyzed in both sense and antisense directions for the presence of heterozygous mutations. Results that were not determined by the first sequencing were then reconfirmed by a second PCR and subsequent sequencing.

Statistical analysis

The chi-square test was conducted to analyze associations between EGFR mutation frequency and the different clinical variables, including clinical response to gefitinib therapy. Statistical analysis was carried out by SPSS (version 10.0, Chicago, IL, USA). Significance was defined as $p < 0.05$ with two-sided analysis.

RESULTS

Patients

Fourteen male and 15 female patients were enrolled for study. The average age was 63±14 years. Twenty-one patients had no history of cigarette smoking; the eight current smokers were all male. There were 26 cases of adenocarinomas and three cases of NSCLC in pathological classification of primary tumors. Fourteen patients had received systemic chemotherapy previously and 15 were chemotherapy naive (Table 1). Eleven patients received gefitinib in our study, one patient before and 10 patients after collection of pleural fluid.

Correlations between EGFR mutations and clinicopathological features

EGFR mutations were detected in 12 of 29 effusion cell specimens (41%); all mutations were heterozygous (Table 2). Eight specimens (67%) contained in-frame deletions within exon 19, resulting in the loss of codons 746 through 750 (delE746-A750) in seven specimens and the loss of codons 746 through 752 with insertion of a valine residue (delE746-S752insV) in the other two specimens. Three specimens (25%) were found to have missense mutations with amino acid substitutions within exon 21, leucine to arginine at codon 858 (L858R) in two specimens and leucine to glutamine at codon 861 (L861Q) in one specimen. Only one specimen (8%) contained in-frame duplication within exon 20, resulting in the duplication of codons 768 to 770 (S768-D770dup). No significant correlation was found between prevalence of EGFR mutations and clinical characteristics including gender, age, pathology, current smoking status and previous chemotherapy (Table 1).

Table 1. Patients' Characteristics and Frequency of Epidermal Growth Factor Receptor (EGFR) Mutations

Variables		Patient No.	Mutations No. (%)	*p*-value
Total		29	12 (41)	
Gender	Male	14	5 (36)	0.55
	Female	15	7 (46)	
Age (yr)	Median	63±14		
	≦65	15	8 (53)	0.878
	>65	14	5 (38)	
Smoking	Current smoker	8	2 (25)	0.269
	Never smoker	21	10 (48)	
Pathology	Adenocarcinoma	26	11 (42)	0.765
	Non-small cell carcinoma	3	1 (33)	
Chemotherapy	Chemotherapy naive	15	7 (46)	0.55
	Previous chemotherapy	14	5 (36)	

Correlations between EGFR mutations and response to gefitinib

For patients who had received gefitinib therapy, EGFR mutations were detected in cells from malignant pleural effusion in five of 11 patients (Table 3). Among those with EGFR mutations, four patients had partial response and one had stable disease after 28-days gefitinib therapy. Among patients with partial response to gegitinib therapy, two patients showed both decreased tumor size and amount of pleural effusion, and two patients showed decreased amount of pleural effusion. All six patients without EGFR mutations had progressive disease either due to increased tumor size or the amount of pleural effusion. While defining a patient with complete or partial response as a responder, the frequency of EGFR mutations was significantly higher in gefitinib

Table 2. Epidermal Growth Factor Receptor (EGFR) Mutations in 12 Patients with Malignant Pleural Effusion

Patient	Age (yr)	Gender	Smoker	Pleural Effusion Cytology	Primary Tumor Pathology	Exon	Mutation
2	68	F	No	Suggestive of malignancy	Adenocarcinoma	21	L861Q
5	59	F	No	Adenocarcinoma	Adenocarcinoma	21	L858R
6	57	F	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
7	70	M	No	Suggestive of malignancy	Non small cell lung cancer	19	delE746 S752insV
9	83	M	Yes	Suggestive of malignancy	Adenocarcinoma	20	S768-D770dup
12	59	F	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
23	77	F	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
25	58	M	Yes	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
26	78	M	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
27	54	F	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750
28	68	M	No	Adenocarcinoma	Adenocarcinoma	21	L858R
28	34	F	No	Adenocarcinoma	Adenocarcinoma	19	delE746-A750

Abbreviations: F: female; M: male.

Table 3. Epidermal Growth Factor Receptor (EGFR) Mutations and Gefitinib Response in 11 Patients

Patient	Gender	Age (yr)	EGFR Mutation	Tumor Size	Pleural Effusion	Response
2	F	68	L861Q(21)	Unmeasurable	Decreased	PR
23	F	77	delE746-A750(19)	Decreased	Decreased	PR
28	M	68	L858R(21)	Decreased	Decreased	PR
29	F	34	delE746-A750(19)	Decreased	Decreased	PR
6	F	57	delE746-A750(19)	Unmeasurable	Unchanged	SD
1	M	83	WT	Unmeasurable	Increased	PD
4	M	50	WT	Increased	Increased	PD
8	M	62	WT	Increased	Unchanged	PD
17	F	40	WT	Increased	Increased	PD
21	F	67	WT	Unchanged	Increased	PD
30	M	49	WT	Increased	Unchanged	PD

Abbreviations: F: female; M: male; WT: wild type; PR: partial response; SD: stable disease; PD: progressive disease.

responders (4/4) than non-responders (1/7) (p = 0.015).

DISCUSSION

Recently, Tsai et al.[16] reported that mutations in the TK domain of EGFR were found in 53.7% of Taiwanese patients with NSCLC by DNA sequencing in paraffin-embedded tumor tissues. Compared with patients whose tumors were non-mutant EGFR, patients with EGFR mutations had better progression-free survival and overall survival after gefitinib treatment.[16] In another survey done by Gow et al.,[11] EGFR mutations in exons 18, 19 and 21 were detected in 49% of NSCLC specimens from Taiwanese patients. There was significantly longer survival after gefitinib treatment for men with EGFR mutations than those without mutations. The work collaborated between the National Health Research Institutes and the Chang Gung Memorial Hospital revealed that EGFR mutations were found in 39 of 101 surgical specimens of NSCLC. There were 38 adenocarcinomas among these 39 cancer samples with EGFR mutations.[17] All the above data indicate that the incidence of EGFR mutations in NSCLC is about 40~50% in Taiwanese patients, the mutation incidence is particularly high in adenocarcinomas, and there is significant correlation of EGFR mutations and clinical features including tumor response, response duration, progression-free survival and overall survival after gefitinib treatment. In the present study, the frequency of EGFR mutations was 41% in malignant pleural effusion cells from 29 Taiwanese patients with NSCLC. This data is comparable to the prevalence rates in other EGFR studies focusing on mutations in surgical[8,9,18-20] and non-surgical[21] specimens from Japanese, Chinese and Taiwanese patients (32% to 55%). EGFR mutations

have also been reported to occur more frequently in female patients and never smokers.[18,21] However, our data does not show any statistically significant difference between the frequency of mutations and clinical characteristics. This may be due to a small patient number, resulting in a lack of statistic significance.

In-frame deletion in exon 19 was the most frequent mutation found in the present study. The prevalence (67%) is almost the same as the findings in previous studies (60-68%).[8,9] Missense mutations in exon 21 and in-frame deletions within exon 19 have been shown to be the most frequent EGFR mutations in NSCLC[17,18,21] and have been demonstrated to be associated with anti-apoptotic pathways in cancer cell lines.[22] The role of in-frame duplication in exon 20 (S768-D770dup) in tumorigenesis, another mutation found in this study, remains unclear and needs further study. Further survey for the correlations between the mutation types and clinical outcomes, including the development of resistance to gefitinib, is currently underway in our laboratory.

As mentioned above, EFGR mutations in the TK domain were associated with favorable clinical response to gefitinib therapy in NSCLC patients.[8,9] Our data demonstrate significantly higher prevalence of EGFR mutations in gefitinib responders than non-responders, which is consistent with recent findings.[8,9,11,17,20,21] As the cost of gefitinib treatment for NSCLC is quite high, more than NT$60,000 per month per patient, and this agent is very specifically active to cancer cells with EGFR mutations in the TK domain, it is important to screen the genetic status of EGFR in cancer samples before treatment. Since the majority of NSCLC patients are in an advanced stage at the time of diagnosis,[23] it is not feasible to obtain surgical specimens for mutation analysis from most lung cancer patients. Pleural effusion is a common complication of lung cancer; about 50% of patients with disseminated disease will develop pleural effusion.[24] Clinically, ultrasound guided thoracentesis is a generally easy and safe procedure for sampling pleural effusion.[25] Though we did not compare the EGFR mutations between effusion cells and primary tumor or pleural biopsy specimens to find if there was any discrepancy, the detection rate of EGFR mutations in cells from malignant pleural effusion was comparable with that in surgical samples. Our data suggest that obtaining cells from malignant pleural effusions for genetic screening of EGFR is a sensitive and more feasible method for those patients with advanced NSCLC. It may offer an alternative way to find a patient group better suitable to this target therapy.

There are limitations in this study. Some previously reported significant differences of clinicopathologic features[18,21] (e.g. gender, smoking status) between patients with and without EGFR mutations are not shown in our results because of the small patient number. Also, the correlation of EGFR mutations between effusion cells and primary tumors was not available in our study and there might be false negative results. Our results warrant further studies with larger patient numbers and correlation of EGFR mutations between pleural effusion cells and primary tumors.

In conclusion, detection of EGFR mutations in cells from malignant pleural effusion is a feasible adjunct method in determining those patients with a probable better response to target therapy among NSCLC patients with advanced disease.

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非小細胞肺癌所引起的惡性肋膜積液細胞中上皮生長因子受器基因突變分析

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背 景： 臺灣的非小細胞肺癌中有40~50% 伴有上皮生長因子受器基因的突變，而且此一突變與gefitinib 治療的臨床表現有顯著關聯。對多數後期患者而言，用外科手術去做組織取樣並不可行。我們因此設計本研究來研究非小細胞肺癌的惡性肋膜積液細胞中上皮生長因子受器基因的突變，並探討其臨床意義。

方 法： 此研究包括了 29 個非小細胞肺癌併發之惡性肋膜積液的病例。我們分析在惡性肋膜積液細胞中上皮生長因子受器基因 Exon18 至 19 的基因突變狀況，以及在其中接受 gefitinib 治療的 11 個病例中，臨床的療效與上皮生長因子受器基因突變的相關性。

結 果： 在 29 個非小細胞肺癌併發之惡性肋膜積液的病例中，12 例的肋膜積液細胞檢測出有上皮生長因子受器基因突變，佔總比率的 41%。突變的形式以 Exon19 的框架轉移缺失突變 (8 例) 和 Exon21 的點突變 (3 例) 爲主。對 gefitinib 治療有療效的 4 例都有上皮生長因子受器基因突變，相對於無療效的另外 7 例 (1 例有上皮生長因子受器基因突變) 在統計上有明顯的差別 ($p = 0.015$)。

結 論： 檢測惡性肋膜積液細胞中上皮生長因子受器基因突變狀態是一個可行的輔助方式，用以在後期非小細胞肺癌患者中找出對gefitinib 治療可能有較佳療效者。

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