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ORIGINAL ARTICLE

Gefitinib as first-line treatment for patients with epidermal growth factor receptor-mutated advanced lung adenocarcinoma: A single institution experience in Taiwan

Shiue-Wei Lai[1], Ching-Liang Ho[1], Ming-Shen Dai[1], Wei-Liang Chen[2,3], Ping-Ying Chang[1], Yi-Ying Wu[1], Cherng-Lih Perng[4,5], Chung-Yu Lai[6]

[1]*Division of Hematology-Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei;* [2]*Department of Medicine,* [3]*Division of Geriatric Medicine, Department of Family and Community Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei;* [4]*Graduate Institute of Pathology, National Defense Medical Center, Taipei;* [5]*Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei;* [6]*Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan*

Summary

Purpose: *Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) represent a new treatment option for patients with advanced lung adenocarcinoma. In this article we assessed the treatment response and tried to identify prognostic factors which may provide some information different from previously published reports in groups with better performance status (PS) than our enrolled patients.*

Methods: *The records of 85 patients with EGFR-mutated advanced lung adenocarcinoma who received gefitinib 250 mg once daily as front-line monotherapy between October 2007 and October 2012 were analysed. Direct sequencing methods were used for detecting EGFR mutations. SPSS (version 20) software was used for all data analysis.*

Results: *The median overall survival (OS) and progression free survival (PFS) were 25.6 and 6.9 months, respectively. No statistical significance between the two groups of exon 19 and exon 21 in OS and PFS was registered (p=0.414 and p=0.519, respectively). The group of patients treated > 3 months had a better median OS survival compared with those treated < 3 months (25.6 vs 4.9 months, p<0.001). In multivariate analysis, significant benefit on OS was observed in patients with ECOG PS scores of 0-2 (p=0.002) and those treated for longer time periods (p<0.001), rather than age, sex and smoking. Among the adverse effects (AEs), skin manifestation was correlated with significantly better OS (p=0.007) but insignificant effect on PFS (p=0.131).*

Conclusions: *Good ECOG PS, longer TKI use and skin rash were significant factors predictive for gefitinib antitumor activity.*

Key words: *epidermal growth factor receptor, gefitinib, lung adenocarcinoma, skin rash*

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases [1] and is one of the leading causes of cancer-related mortality in Taiwan, largely driven by the high frequency of late diagnosis which results in a poor prognosis. Among the NSCLCs histological subclassifications, lung adenocarcinoma, an epithelial malignancy of glandular origin, is the most prevalent [2]. Chemotherapy is the mainstay of treatment in advanced NSCLC [3], including adenocarcinoma. The majority of the existing cytotoxic chemotherapy regimens yield favorable antitumor effects. Platinum-based doublets were well accepted to be the frontline treatments for patients with inoperable adenocarcinoma [4]. However, toxicity with concomitant potential impairment of quality of life is a major concern [5].

EGFR tyrosine kinase (TK) is overexpressed in most NSCLC patients and contributes to cellular proliferation, angiogenesis, metastasis, chemo-re-

Correspondence to: Ching-Liang Ho, MD. Division of Hematology-Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Number 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan.
Tel: +886 2 87923311, Fax:+888 2 87927134, E-mail: w.j.huang512@gmail.com
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sistance and inhibition of apoptosis [6]. EGFR mutations are prevalent in female patients, those who have never smoked, those of Asian ethnicity and those who have adenocarcinoma histology [7]. Several EGFR mutations are correlated with clinical responsiveness to specific TKIs. Most are found in exons 18–21 of the kinase domain of the EGFR gene, representing the ATP-binding cleft, and all lead to increased TK activity [8]. Several different in-frame deletions are found in exon 19, collectively referred to as del 19 mutations, which account for 32% of all mutations [9]. A single-base missense mutation in exon 21 that leads to a leucine-to-arginine substitution (L858R) is the most common reported mutation, accounting for 38% of all mutations [9]. In addition, two mutations in exon 20 conferring drug resistance exist at codon 790 (T790M) and codon 761 (D761Y) [10].

Gefitinib is an orally active and selective EGFR-TKI and high response rates (RR) to EGFR-TKI treatment have been reported among chemonaive, EGFR-mutated patients with PFS around 10.7 months and RR of 79.3% [11]. No significant difference in median OS among patients treated with gefitinib and platinum-based systemic chemotherapy has been reported [12,13]. Therefore, gefitinib has become a promising agent for first-line treatment in Asian population with advanced lung adenocarcinoma [14].

The purpose of this retrospective analysis was to assess the RR of advanced EGFR-mutated lung adenocarcinoma to gefitinib, and to identify clinical parameters that may predict or affect treatment outcomes. The results may expand our experience that were different from some previously published reports in groups with better PS than our enrolled patients.

Methods

Patients and study design

This retrospective study enrolled a total of 85 patients with advanced EGFR-mutated lung adenocarcinoma at the Tri-Service General Hospital between October 2007 and October 2012. All patients received oral gefitinib 250 mg once daily as front-line monotherapy. The clinical data retrieved from medical records included sex, age, smoking, ECOG PS, tumor grade, TNM stage (AJCC staging system, 7th Edn), pleural metastases, CEA levels, duration of gefitinib treatment, types of EGFR mutations and AEs. The study was approved by the Research Ethics Committee of the Tri-Service General Hospital.

Direct sequencing methods for detecting EGFR mutations

Lung cancer tissue specimens were formalin-fixed and paraffin-embedded at the Tri-Service General Hospital. DNA was extracted by proteinase K digestion and isopropanol precipitation. Briefly, the formalin-fixed, paraffin-embedded block was sliced into 35-µm-thick sections. Each section was macro-dissected from the tumor region identified by a pathologist with hematoxylin & eosin staining and processed by proteinase K digestion at 56 ºC for more than 16 h. The lysate was then purified by salt-chloroform method and DNA was precipitated by isopropanol. After two washes with 70% alcohol, DNA was redissolved with 50 µl TE buffer (10 mM Tris, pH8.0; 0.1 mM EDTA) [15]. Fragments of exons 18-21 of EGFR gene were amplified and sequenced by BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystem, Life Technologies, Foster City, CA, USA) and analyzed in both sense and antisense directions [16].

Definitions and statistics

The Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) was used for response evaluation [17]. A computed tomography scan of measurable tumor sites was performed every 3 months. The response criteria were defined as follows: complete response (CR): disappearance of all target lesions; partial response (PR): 30% decrease in the sum of the longest diameter (LD) of target lesions; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD; progressive disease (PD): at least 20% increase in the sum of the LD of target lesions, or appearance of new lesion(s). RR was the sum of PR and CR. Disease control rate was the sum of PR, CR and SD. PFS was defined as the time from TKI treatment to the date of documented clinical progression or to patient's death. OS was defined as the time from TKI therapy to the patient's death. AEs were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Log rank test and Kaplan–Meier estimates of survival curves were computed for OS and PFS. Adjusted hazard ratio for survival of the participants was evaluated by multivariate Cox regression model. SPSS software (version 20) was used for all data analyses.

Results

Clinical features

The demographic characteristics of the 85 patients enrolled are summarized in Table 1. The female to male ratio was 1.43 and their median age was 63 years (range 33-90). Seventeen patients (20.0 %) were smokers and 18 (21.2%) had an ECOG PS 3-4. Thirty-one patients (36.4%) had normal serum CEA levels, 49 (57.6%) had elevated

Table 1. Patient and disease characteristics (N=85)

Characteristics	*Patients, N*	*%*
Sex		
Male	35	41.2
Female	50	58.8
Age (years)		
Median	63	
Range	33-90	
Smoking status		
Never	68	80.0
Ever	17	20.0
ECOG performance status		
0-2	67	78.8
3-4	18	21.2
TNM stage		
IIIb	9	10.6
IV	76	89.4
Pleural metastases		
Yes	19	22.4
No	66	77.6
Metastatic sites		
Brain	38	44.7
Bone	28	32.9
Lung to lung	14	16.5
Liver	11	12.9
Spine	4	4.7
Adrenals	1	1.2
CEA levels (ng/ml)		
< 5	31	36.4
≥ 5	49	57.6
Unknown	5	6.0
Pathological grade		
1	13	15.3
2	44	51.8
3	28	32.9
Gefitinib use (months)		
Median (range)	6.4 (0.2-59.3)	
Time to progression (months)		
Median (range)	5.7 (1.4-26.3)	

Table 2. Summary of EGFR mutations and treatment response

	EGFR mutation (85 patients)		
	Exon 18 (N=1, 1.2%)	*Exon 19 (N=45, 52.9%)*	*Exon 21 (N=39, 45.9%)*
CR	0	0	1
PR	0	21	15
SD	1	17	17
PD	0	7	6

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

serum CEA and 5 patients (6.0 %) were not evaluated. Grade 1 tumors had 13 (15.3%) patients, grade 2 44 (51.8%) and 28 (32.9%) patients had grade 3 tumors. The mean and median time of gefitinib use were 7.7 and 6.4 months, respectively (range 0.2-59.3). The frequencies of the different types of EGFR mutations were as follows: 1 out of 85 (1.2%) exon 18 deletions, 45 out of 85 (52.9%) exon 19 deletions, 39 out of 85 (45.9%) exon 21 deletions (Figure 1). All of the exon 21 deletions were L858R point mutations. The EGFR mutation groups and treatment response are presented in Table 2.

Treatment outcomes

Overall RR was 43.5% and disease control rate (DCR) 84.7%. Among the subgroups, the RR and DCR of exon 19 mutation were 46.7% and 84.4%. The RR and DCR of exon 21 mutation were 41.0% and 84.6%, respectively. No statistical significance was seen between the two groups in OS and PFS (p=0.414 and p=0.519, respectively). The first reported exon 19 mutation with K739_I744dupLysIleProValAlaIle was found in a patient who had SD with OS of 5.1 months. The relatively rare exon 19 mutation with K754E was found in another patient who had SD and OS of 3.1 months. All others had common mutations previously reported (Figure 1).

The patients' median OS and PFS were 25.6 and 6.9 months, respectively. The group of patients treated with gefitinib >3 months had significantly better median OS compared with those treated < 3 months (25.6 vs 4.9 months, p<0.001) (Figure 2).

Demographic groups were stratified by treatment duration (< 3 months vs ≥ 3 months; Table 3). Significant clinical benefit was observed for those with ECOG PS 0-2 and those treated for longer time period (Table 4).

Treatment-related AEs are shown in Table 5, with the majority of AEs being of grade 1/2 by CTCAE criteria. The most common toxic effects of gefitinib treatment were dermatologic manifestations such as skin rash or acne (43.5%), diarrhea (35.3%), normocytic anemia (29.4%) and elevated liver transaminases (24.7%). Grade 3 AEs were elevated liver transaminases (5.9%), normocytic anemia (4.7%), rash or acne and thrombocytopenia (1.2% each). Grade 4 AEs were elevated liver transaminases (3.5%) and thrombocytopenia (1.2%). Nine patients (10.6%) experienced transient thrombocytosis during gefitinib treatment. Among the AEs, skin manifestations were corre-

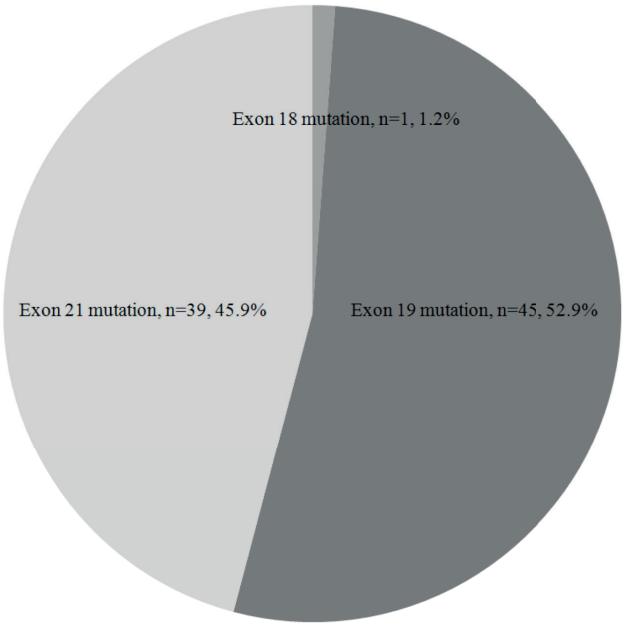

Figure 1. Distribution of EGFR mutations.

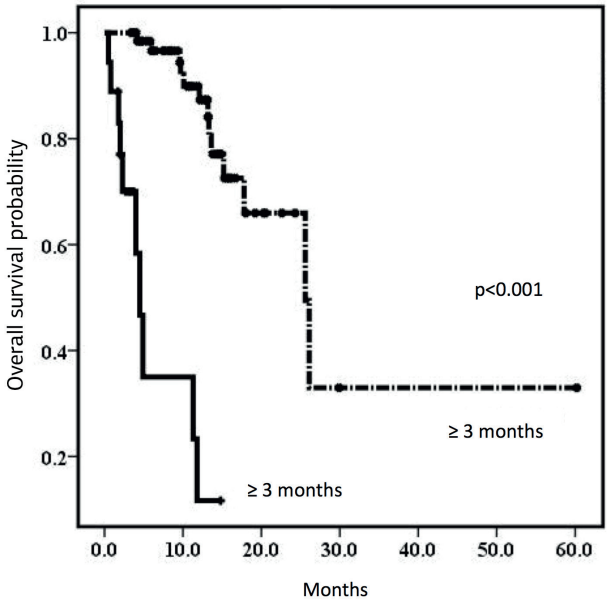

Figure 2. Kaplan-Meier overall survival of patients with advanced lung adenocarcinoma in different gefinitib treatment duration. Median survival time ≥ 3 months = 25.6 months; <3 months = 4.5 months.

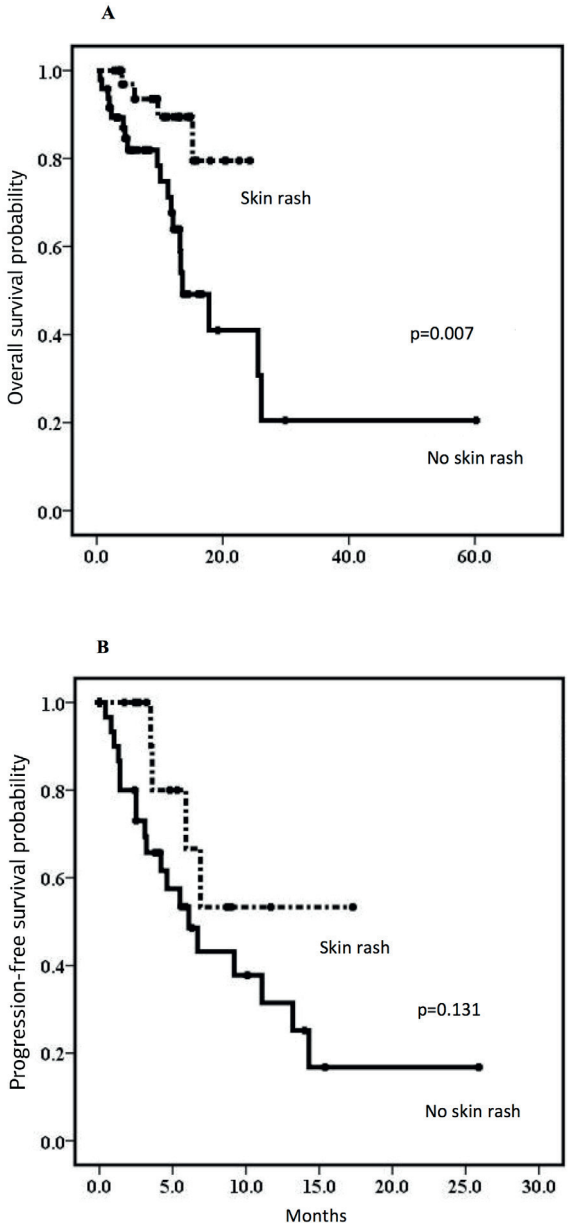

Figure 3. Kaplan–Meier overall survival in patients with and without skin rash. **A**: Patients with skin rash had a median overall survival of 11.3 months compared to 8.3 months for patients without a rash. **B**: Kaplan-Meier progression free survival showing insignificant differences between patients with or without skin rash.

lated with the better OS (p=0.007) but insignificant effect on PFS (p=0.131; Figure 3A and 3B).

Discussion

Gefitinib is an orally active, selective EGFR-TKI that blocks signal transduction pathways involved in cell proliferation. This drug demonstrated impressive and durable responses in patients with heavily pretreated NSCLC [18]. The IPASS study demonstrated that gefitinib monotherapy is superior to carboplatin/paclitaxel as first-line therapy in East Asian patients with NSCLC harboring an activating EGFR mutation [19].

This retrospective analysis demonstrated clear antitumor activity of gefitinib (RR 43.5% and DCR 84.7%). These results corresponded to Iressa Survival Evaluation in Lung cancer (ISEL) trial (RR 37.5%) [20], but somewhat inferior to those of the intent-to-treat population in IPASS

Table 3. Comparison of treatment duration in relation with demographic variables

Variable	*Gefinitib < 3mos (N=18)*	*Gefinitib ≥ 3mos (N=67)*	*Log rank, p-value*
Age, years (%)			
<65	6 (33.3)	38 (56.7)	0.134
≥65	12 (66.7)	29 (43.3)	
Sex (%)			
Female	9 (50.0)	41 (61.5)	0.557
Male	9 (50.0)	26 (38.8)	
TNM stage (%)			
3	2 (11.1)	7 (10.4)	1.000
4	16 (88.9)	60 (89.6)	
ECOG PS (%)			
0-2	9 (50.0)	58 (86.6)	0.002
3-4	9 (50.0)	9 (13.4)	
Smoking (%)			
No	14 (77.8)	54 (80.6)	0.750
Yes	4 (22.2)	13 (19.4)	
Response (%)			
CR or PR	5 (27.8)	32 (47.8)	0.045
SD	7 (38.9)	28 (41.8)	
PD	6 (33.3)	7 (10.4)	
*PD (%)			
No	13 (72.2)	36 (53.7)	0.254
Yes	5 (27.8)	31 (46.3)	
PleuMeta (%)			
0	4 (22.2)	15 (22.4)	1.000
1 and 3	14 (77.8)	52 (77.6)	
Patients alive (%)			
Yes	8 (44.4)	54 (80.6)	0.005
No	10 (55.6)	13 (19.4)	
Follow-up (mo)[1]	4.3±4.1	12.6±8.4	0.001[2]

mos: months, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, PleuMeta: pleural metastasis, [1]mean±standard deviation, [2]independent *t* tests. *PD during follow up, even if patients had received 2nd or 3rd line treatment

Table 4. Adjusted hazard ratio in multivariate Cox regression analysis

Variable	*Survival N (%)*	*Death N (%)*	*aHR* †	*95%CI*
ECOG PS				
0-2	52 (83.9)	15 (65.2)	1	ref
3-4	10 (16.1)	8 (34.8)	5.62	1.90-16.64
Gefinitib use (mos)				
<3	8 (12.9)	10 (43.5)	1	ref
≥3	54 (87.1)	13 (56.5)	0.10	0.03-0.28
Response				
CR or PR	30 (48.4)	7 (30.4)	1	ref
SD	29 (46.8)	6 (26.1)	0.65	0.21-1.97
PD	3 (4.8)	10 (43.5)	1.33	0.43-4.15

†: adjusted hazard ratio, CI: confidence interval, mos: months, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 5. Adverse effects and their grades with gefitinib treatment

Adverse effects	*Patients, N (%)*	*Grade*	*%*
Rash or acne	37 (43.5)	1	32.9
		2	9.4
		3	1.2
Diarrhea	30 (35.3)	1	30.6
		2	4.7
Normocytic	25 (29.4)	1	16.5
anemia		2	8.2
		3	4.7
Elevated liver	21 (24.7)	1	12.9
transaminases		2	2.4
		3	5.9
		4	3.5
Thrombocytopenia	15 (17.6)	1	11.7
		2	3.5
		3	1.2
		4	1.2
Leukopenia	9 (10.6)	1	8.2
		2	2.4
Thrombocytosis*	9 (10.6)	-	-
Neurotoxicity	2 (2.4)	1	2.4
None	22 (25.9)	-	-

*No grade and percent is presented due to lack of relative information

(ITT-IPASS) study (RR 71.2%, DCR 91.7%) [21]. There are several possible reasons for this. First, we included patients in poor ECOG PS and smokers. Second, the percentage of enrolled patients < 65 years in ITT-IPASS was higher (72.0 vs 51.8% in our group). Third, the female to male ratio was more prominent in ITT-IPASS (4.49 vs 1.43 in our group), and this has to do with the fact that women showed better response to TKI as shown in previous studies [20,22].

Results from our institution showed OS of 25.6 months with gefitinib and PFS of 6.9 months, which were better than the median survival observed in Asian patients in the IPASS study (OS 18.6 months, PFS 5.7 months). It seems possible that these results are due to longer median duration of gefitinib use (7.7 vs 6.4 months in IPASS) [21] and more intensive supportive care.

The EGFR mutations were either small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the TK domain [16]. Lynch et al. found that the highest RR to these TKIs were seen in patients with deletion mutations within exon 19, missense mutations in exon 21 (L858R), and exon 18 (G719X) [16]. In

our study, 52.9 % patients had exon 19 mutation and 45.9 % patients had exon 21 mutation. The RR and DCR of exon 19 mutation were 46.7% and 84.4%, respectively. The RR and DCR of patients with exon 21 mutation were 41.0% and 84.6%, respectively. There was no OS or PFS benefit observed among the subgroups (p=0.185, p=0.25 respectively). In the rare exon 19 mutation sites, neither K739_I744 dup KIPVAI nor K754E were associated with clinical benefit.

In the 7th edition of the TNM Classification for Lung and Pleural Tumors, the pathological diagnosis of patients with pleural metastasis is classified as stage M1a. Patients in our series with M1a stage did not have significantly different OS or PFS compared to other stages.

Among our patient groups, 74.1% experienced AEs with the majority being grade 1 or 2 events that resolved spontaneously with supportive care. Of the patients, 43.5% developed dermatological symptoms (rash or acne) which were associated with longer OS (p=0.002), but not PFS (p=0.131). The correlation between skin rash due to gefitinib and clinical outcomes were reported in previous studies [23,24]. There is limited published information on the clinical impact of individual AEs, their severity and pathogenesis. The relatively rare recorded AEs in our series were transient thrombocytosis (10.6%) and two patients developed thrombocytosis ($708x10^3$/ul and $908x10^3$/ul, respectively) which subsided without specific medical treatment.

In a recent review, Grunnet et al. found that serum CEA carried prognostic and predictive significance over the risk of recurrence and death in NSCLC, independent of treatment or study design [25]. However, there are some previous studies with negative results which might affect the initial assessment plan by some clinicians [26-29]. In our institution, this may be the reason why 6.0% of the patients were not evaluated initially and no prognostic or predictive significance was revealed by our analysis (p=0.238). Sex, TNM stage, smoking history and PD during treatment showed the same trivial influence on survival. A possible explanation may result from the mutual effects of these variables and the latent prognostic factors may be masked. After adjusting for other confounders, the aHR in multivariate Cox regression analysis showed significant poor prognosis in patients with ECOG PS 3-4, gefinitib use < 3 months and the effect of initial treatment response, including CR or PR, was not observed. In our patients, gefinitib administration > 3 months showed significant survival benefit (25.6 vs 4.9 months, p<0.001) which clearly points to continued gefitinib administration for at least 3 months in advanced lung adenocarcinoma with EGFR mutations.

Because of the retrospective design, there are limits in the strength of our study. However, the results of our analyses provide valuable practical experience to clinicians who care for this high-risk population.

In summary, the current study confirmed the efficacy and safety of gefitinib therapy in Taiwanese patients with EGFR-mutated advanced adenocarcinoma at our institution, with favorable median OS of 25.6 months and median PFS of 6.9 months. From our results, good PS, longer gefitinib administration use and skin rash were predictive factors of gefitinib antitumor activity rather than age, sex and smoking in multivariate analysis.

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