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ORIGINAL RESEARCH

Pemetrexed had significantly better clinical efficacy in patients with stage IV lung adenocarcinoma with susceptible *EGFR* mutations receiving platinum-based chemotherapy after developing resistance to the first-line gefitinib treatment

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Background: Increased evidences show that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors such as gefitinib could prolong progression-free survival (PFS) compared with cytotoxic chemotherapy for metastatic lung nonsquamous cell carcinoma harboring susceptible *EGFR* mutation, and gefitinib was served as the first-line therapy. However, acquired resistance is inevitable, but the salvage therapies are still unclear.

Patients and methods: We designed a retrospective study of the salvage therapy and enrolled patients with stage IV lung adenocarcinoma who had mutated *EGFR* and developed an acquired resistance to the first-line gefitinib in two university-affiliated hospitals in Taiwan during June 2011 to December 2014. Age, sex, smoking history, *EGFR* gene mutation, performance statuses, response rate, PFS2 (the PFS in salvage therapy), and overall survival (OS2, the OS in salvage therapy) were recorded.

Results: Two hundred and nine patients with mutated *EGFR* and who took gefitinib as first-line therapy were identified in the period, and a total of 98 patients who had been treated with salvage therapy with cytotoxic chemotherapy or erlotinib were eligible for this study. The overall response rate of second salvage therapy is 13%, and none of them received erlotinib. Patients who received chemotherapy had a trend for better PFS2 than those who received erlotinib (4.3 months vs 3.0 months, P=0.1417) but not in OS. Furthermore, patients who received platinum-based doublet had a trend for better PFS2 and a significantly better OS2 than those who received chemotherapy without platinum (PFS2: 4.9 months vs 2.6 months, P=0.0584; OS2: 16.1 months vs 6.7 months, P=0.0007). Analyses of the patients receiving platinum-based doublet showed that patients receiving pemetrexed had a significantly better PFS2 (6.4 months vs 4.1 months, P=0.0083) and a trend for better OS2 than those without pemetrexed treatment.

Conclusion: Pemetrexed-based platinum chemotherapy may be the most optimal therapy in acquired resistance to gefitinib. Further prospective randomized controlled study is needed urgently.

Keywords: epidermal growth factor receptor, gefitinib, acquired resistance, pemetrexed, chemotherapy

Introduction

Lung cancer continues to be the leading cause of death among patients with malignant tumors worldwide. In 2004, mutations in epidermal growth factor receptor (*EGFR*) that cause oncogene addiction to *EGFR* were discovered in non-small-cell lung cancer

(NSCLC), and these mutations have been found to be strongly associated with the susceptibility to *EGFR*-tyrosine kinase inhibitors (TKIs).[1–4] Several Phase III studies showed that *EGFR*-TKIs were associated with a good response rate of approximately 70% and a progression-free survival (PFS) of 8–13 months in patients with NSCLC harboring *EGFR*-activating mutations.[5–8] These outcomes were much better than those receiving cytotoxic chemotherapy as the first-line therapy.

However, the development of acquired resistance to the first-line *EGFR*-TKI treatment is inevitable, and most of these patients needed subsequent salvage therapy. Some new drugs were designed to conquer the mechanism of acquired resistance such as T790M mutation or MET amplification, and the associated clinical trials were still ongoing.[9–13] In clinical practice, most of these therapies are still not available. Therefore, several retrospective studies were designed to explore the optimal second-line salvage therapy, whereas the results were discrepant.[13–15] Because of the enrollment of heterogeneous study populations (including patients having NSCLC with or without EGFR mutations and even those with unknown *EGFR* mutation status), these studies showed variable outcomes and are, therefore, difficult to be applied to the daily clinical practice. After being covered as the first-line therapy to treat advanced lung adenocarcinoma harboring *EGFR* mutation by the National Health Insurance since June 2011, gefitinib has been the most popular first-line *EGFR*-TKI in Taiwan. Therefore, we conducted a retrospective study in two university-affiliated hospitals to elucidate the best second-line salvage treatment for these patients with stage IV lung adenocarcinoma with susceptible *EGFR* mutation who had disease progression during gefitinib treatment. This study demonstrated the real-world data of the second-line salvage therapy in patients with *EGFR*-mutated lung adenocarcinoma after gefitinib failure in Taiwan.

Patients and methods

Patient identification

In this retrospective study, patients with stage IV lung adenocarcinoma diagnosed between October 2009 and January 2015 in two university-affiliated hospitals (Kaohsiung Medical University Hospital [KMUH] and Kaohsiung Municipal Ta-Tung Hospital) in Taiwan were identified and followed-up until August 12, 2015. Patients who had susceptible EGFR mutation and received gefitinib as the first-line therapy were enrolled. The diagnosis of lung cancer was confirmed pathologically according to World Health Organization pathology classification, and the tumor staging was made according to the seventh American Joint Committee on Cancer staging system by a special committee including clinical pulmonologists, medical oncologists, chest surgeons, radiologists, pathologists, and radiation oncologists. Patients were included if they 1) had adequate tumor specimens for EGFR mutation examination and had susceptible EGFR mutation, including exon 18 point mutation, exon 19 deletion, and exon 21 point mutation; 2) were treated with gefitinib as the first-line therapy; and 3) subsequently received a second-line treatment. Those who had previous history of other malignancies were excluded.

Baseline clinical characteristics were determined by retrospective chart review, including age at diagnosis, sex, Eastern Cooperative Oncology Group performance status at the beginning of the gefitinib treatment and at the start of the second-line treatment, smoking history, and tumor histology. Smoking history was categorized as current smokers or ever smokers, which included ex-smokers (who had quit $\geq$5 years before diagnosis) and never smokers ($<$100 lifetime cigarettes). Mutations in the *EGFR* gene were analyzed using an *EGFR* RGQ kit (Qiagen NV, Venlo, the Netherlands), which utilized amplification refractory mutation-specific polymerase chain reactions and Scorpion technologies for detection and/or direct sequencing. The detection method was developed and validated by the Division of Molecular Diagnostics, Department of Laboratory Medicine, KMUH.

An initial treatment response was classified as complete response (CR), partial response (PR), stable disease, or progressive disease based on serial imaging studies using the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.[16] The response rate and disease control rate were defined as the percentages of patients with CR and PR and with CR, PR, and stable disease, respectively.

The second-line salvage therapy included erlotinib and cytotoxic chemotherapy, including pemetrexed, gemcitabine, vinorelbine, and taxanes (docetaxel), with or without platinum derivatives (cisplatin or carboplatin). The duration between the start of the second-line treatment to the date of disease progression thereafter and to the date of death were defined as PFS2 and overall survival (OS2).

The Institutional Review Board (IRB) of KMUH approved this study (KMUHIRB-E[II]-20150162) and waived the need for written informed consent from the participants due to the retrospective nature of this study.

Statistical analysis

Age, sex, smoking history, *EGFR* gene mutation site (exon 18, exon 19, and exon 21), thyroid transcription factor 1

immunostaining, metastatic sites on initial diagnosis, performance statuses when starting the treatments, and initial treatment responses were summarized and compared between patients receiving different second-line treatments. Categorical variables and continuous variables were compared using the χ^2-test and the Student's *t*-test, respectively. Survival times were estimated using the Kaplan–Meier method, with differences between the groups compared using the log-rank test. Cox proportional hazards regression analysis was used to identify the effect of different clinical features on PFS2 and OS2, and the results were presented as hazard ratio (HR) with 95% confidence interval (CI). After univariate analyses, all variables were included to obtain a maximal model of multivariable analysis to assess the independent effect of different variables. All statistical analyses were performed using SAS software (Version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a two-sided *P*-value of <0.05.

Results

Patient characteristics

A total of 209 patients with stage IV adenocarcinoma harboring susceptible *EGFR* gene mutations who had been treated with gefitinib as the first-line treatment were identified. After excluding those who remained on gefitinib treatment and those who did not received erlotinib or cytotoxic chemotherapy as the second-line treatment after gefitinib failure, the remaining 98 patients were included for analyses. As shown in Table 1, 12 (12%), 26 (27%), and 60 (61%) patients received erlotinib, chemotherapy without platinum, and platinum-based doublet as their second-line treatment after gefitinib failure, respectively. In the 60 patients who received platinum-based doublet, 34 (57%) of them received pemetrexed (Table 1).

The clinical characteristics and treatment responses of all patients were summarized in Tables 2 and 3. No significant difference was noted in the baseline characteristics between patients receiving erlotinib and those receiving chemotherapy as the second-line treatment (Table 1). However, the disease control rate was significantly higher in those receiving chemotherapy than in those receiving erlotinib (79% vs 50%, *P*=0.0283). Although no significant differences in PFS2 and OS2 were noted between those receiving chemotherapy and those taking erlotinib, patients receiving chemotherapy had a trend for better PFS2 (median of PFS2: 4.3 months vs 3.0 months, log-rank *P*=0.1417) (Figure 1A and B).

To identify the chemotherapy regimen with better outcome, we performed further analyses with the 86 patients receiving chemotherapy as the second-line treatment, including 60 (70%) and 26 (30%) patients receiving platinum-based doublets and chemotherapy without platinum, respectively. As expected, those receiving platinum-based doublets were significantly younger in age than those receiving chemotherapy without platinum ($P<0.0001$), whereas no significant difference in the performance status was noted between groups (Table 3). The disease control rate was significantly higher in those receiving platinum-based doublet than in those receiving chemotherapy without platinum (90% vs 54%, *P*=0.0002) (Table 3). Patients receiving platinum-based doublet had a trend for better PFS2 and a significantly better OS2 than those receiving chemotherapy without platinum (median PFS2: 4.9 months vs 2.6 months, log-rank *P*=0.0584; median OS2: 16.1 months vs 6.7 months, log-rank *P*=0.0007) (Figure 1C and D). Cox regression analyses showed that platinum-based doublet was associated with a borderline effect for better PFS2 (HR: 0.52 [95% CI: 0.26–1.01], *P*=0.0545), after controlling for sex, age, and performance status while starting the second-line treatment (Table 4).

Table 1 Regimens used as the second-line treatment after gefitinib failure

Regimen	All patients	Patients receiving chemotherapy	Patients receiving platinum-based doublet
Erlotinib	12 (12%)	Not applicable	Not applicable
Chemotherapy without platinum			
Pemetrexed	2 (2%)	2 (2%)	Not applicable
Gemcitabine	2 (2%)	2 (2%)	Not applicable
Vinorelbine	21 (21%)	21 (24%)	Not applicable
Taxanes	1 (1%)	1 (1%)	Not applicable
Platinum-based doublet			
Pemetrexed + platinum	34 (35%)	34 (40%)	34 (57%)
Gemcitabine + platinum	16 (16%)	16 (19%)	16 (27%)
Vinorelbine + platinum	7 (7%)	7 (8%)	7 (12%)
Taxanes + platinum	3 (3%)	3 (3%)	3 (5%)
Total	98 (100%)	86 (100%)	60 (100%)

Note: Data are presented as n (%).

Table 2 Clinical characteristics and treatment responses of all patients

Variables	All patients	Chemotherapy	Erlotinib	*P*-value
Patients	98 (100%)	86 (87.8%)	12 (12.2%)	
Age (years), mean ± SD	63±10.9	63±10.8	62.8±12.2	0.9465
Age				0.2958
<65 years old	60 (61%)	51 (59%)	9 (75%)	
≥65 years old	38 (39%)	35 (41%)	3 (25%)	
Sex				0.0474
Female	65 (66%)	54 (63%)	11 (92%)	
Male	33 (34%)	32 (37%)	1 (8%)	
Smoking history				0.1451
Never smoker	73 (74%)	62 (72%)	11 (92%)	
Ever smoker	25 (26%)	24 (28%)	1 (8%)	
TTF-1 staining				0.7196
Negative	2 (2%)	2 (2%)	0 (0%)	
Positive	85 (87%)	75 (87%)	10 (83%)	
Not performed	11 (11%)	9 (10%)	2 (17%)	
EGFR gene mutation site				0.7277
Exon 18	4 (4%)	4 (5%)	0 (0%)	
Exon 19	48 (49%)	43 (50%)	5 (42%)	
Exon 19 + exon 21	1 (1%)	1 (1%)	0 (0%)	
Exon 21	45 (46%)	38 (44%)	7 (58%)	
Performance status while starting gefitinib				0.3011
ECOG score ≤1	79 (81%)	68 (79%)	11 (92%)	
ECOG score ≥2	19 (19%)	18 (21%)	1 (8%)	
Metastatic sites on initial diagnosis				0.6525
≤1	30 (31%)	27 (31%)	3 (25%)	
≥2	68 (69%)	59 (69%)	9 (75%)	
Progression-free survival of gefitinib (months), median (IQR)	9.8 (6.2–13.6)	10.1 (6.2–13.8)	8.8 (5.1–12.4)	0.5728
Performance status while starting the second-line treatment				0.6967
ECOG score ≤1	70 (71%)	62 (72%)	8 (67%)	
ECOG score ≥2	28 (29%)	24 (28%)	4 (33%)	
Response to the second-line treatment				0.0557
Partial response	13 (13%)	13 (15%)	0 (0%)	
Stable disease	61 (62%)	55 (64%)	6 (50%)	
Progressive disease	24 (24%)	18 (21%)	6 (50%)	
Disease control rate with the second-line treatment (%)	76%	79%	50%	0.0283
Response rate with the second-line treatment (%)	13%	15%	0%	0.1481

Note: Data are presented as n (%) unless otherwise stated.
Abbreviations: SD, standard deviation; TTF-1, thyroid transcription factor 1; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Platinum-based doublet was associated with a significantly better OS2 on the univariate analysis (HR: 0.38 [95% CI: 0.21–0.68], *P*=0.0011), whereas the significance was not seen in the multivariable analysis controlling for sex, age, and performance status while starting the second-line treatment (HR: 0.59 [95% CI: 0.26–1.33], *P*=0.2021).

We further investigated whether pemetrexed provides better effect than other chemotherapy agents in the 60 patients receiving platinum-based doublet. The baseline characteristics were similar between patients receiving a platinum derivative with pemetrexed and those receiving a platinum derivative with cytotoxic chemotherapeutic agents other than pemetrexed (Table 3), while patients receiving a platinum derivative with pemetrexed had longer progression-free survival on gefitinib treatment. The disease control rate and response rate were similar in both groups (Table 3). In patients receiving platinum-based doublet, those receiving pemetrexed had a significantly better PFS2 and a trend for better OS2 than those without pemetrexed treatment (median PFS2: 6.4 months vs 4.1 months, log-rank *P*=0.0083; median OS2: 19.2 months vs 14.1 months, log-rank *P*=0.1639) (Figure 1E and F). Cox regression analyses showed that pemetrexed, as compared with other cytotoxic chemotherapeutic agents, was associated with a significantly better PFS2 (HR: 0.47 [95% CI: 0.26–0.84], *P*=0.0101) and a trend for better OS2 (HR: 0.50 [95% CI: 0.22–1.13],

Table 3 Clinical characteristics and treatment response of all patients receiving chemotherapy as the second-line treatment

Variables	All chemotherapy patients			Patients receiving platinum-based doublet		
	Chemotherapy without platinum	Platinum-based doublet	*P*-value	Without pemetrexed	With pemetrexed	*P*-value
Patients, n	26	60		26	34	
Age (years), mean ± SD	71.9±8.5	59.1±9.4	<0.0001	57.6±9.5	60.3±9.2	0.2657
Age			<0.0001			0.3668
<65 years old	6 (23%)	45 (75%)		21 (81%)	24 (71%)	
≥65 years old	20 (77%)	15 (25%)		5 (19%)	10 (29%)	
Sex			0.5196			0.5480
Female	15 (58%)	39 (65%)		18 (69%)	21 (62%)	
Male	11 (42%)	21 (35%)		8 (31%)	13 (38%)	
Smoking history			0.6969			0.9687
Never smoker	18 (69%)	44 (73%)		19 (73%)	25 (74%)	
Ever smoker	8 (31%)	16 (27%)		7 (27%)	9 (26%)	
TTF-1 staining			0.3603			0.6344
Negative	1 (4%)	1 (2%)		0 (0%)	1 (3%)	
Positive	24 (92%)	51 (85%)		22 (85%)	29 (85%)	
Not performed	1 (4%)	8 (13%)		4 (15%)	4 (12%)	
EGFR gene mutation site			0.1415			0.7115
Exon 18	2 (8%)	2 (3%)		1 (4%)	1 (3%)	
Exon 19	17 (65%)	26 (43%)		10 (38%)	16 (47%)	
Exon 19 + exon 21	0 (0%)	1 (2%)		0 (0%)	1 (3%)	
Exon 21	7 (27%)	31 (52%)		15 (58%)	16 (47%)	
Performance status while starting gefitinib			0.1398			0.6412
ECOG score ≤1	18 (69%)	50 (83%)		21 (81%)	29 (85%)	
ECOG score ≥2	8 (31%)	10 (17%)		5 (19%)	5 (15%)	
Metastatic sites on initial diagnosis			0.2739			0.9564
≤1	6 (23%)	21 (35%)		9 (35%)	12 (35%)	
≥2	20 (77%)	39 (65%)		17 (65%)	22 (65%)	
Progression-free survival of gefitinib (months), median (IQR)	9.1 (6.1–12)	10.9 (6.9–14.8)	0.5641	9.1 (4.9–11.7)	11.8 (7.7–15.4)	0.0217
Performance status while starting the second-line treatment			0.0500			0.8166
ECOG score ≤1	15 (58%)	47 (78%)		20 (77%)	27 (79%)	
ECOG score ≥2	11 (42%)	13 (22%)		6 (23%)	7 (21%)	0.4865
Response to the second-line treatment			0.0007			
Partial response	2 (8%)	11 (18%)		3 (12%)	8 (24%)	
Stable disease	12 (46%)	43 (72%)		20 (77%)	23 (68%)	
Progressive disease	12 (46%)	6 (10%)		3 (12%)	3 (9%)	
Disease control rate with the second-line treatment (%)	54%	90%	0.0002	23 (88%)	31 (91%)	0.7283
Response rate with the second-line treatment (%)	8%	18%	0.2058	3 (12%)	8 (24%)	0.2342

Note: Data are presented as n (%) unless otherwise stated.
Abbreviations: SD, standard deviation; TTF-1, thyroid transcription factor 1; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

P=0.0972), after controlling for sex, age, and performance status while starting the second-line platinum-based doublet treatment (Table 4).

Discussion

Our study is one of the largest retrospective studies to investigate the treatment strategies for patients who initially harbored susceptible *EGFR* mutation and developed an acquired resistance to the initial *EGFR*-TKI treatment. For patients with stage IV adenocarcinoma harboring susceptible *EGFR* mutation who developed acquired resistance to the first-line gefitinib treatment, cytotoxic chemotherapy seemed more effective than a subsequent *EGFR*-TKI as the second-line salvage therapy. Platinum-based doublet chemotherapy

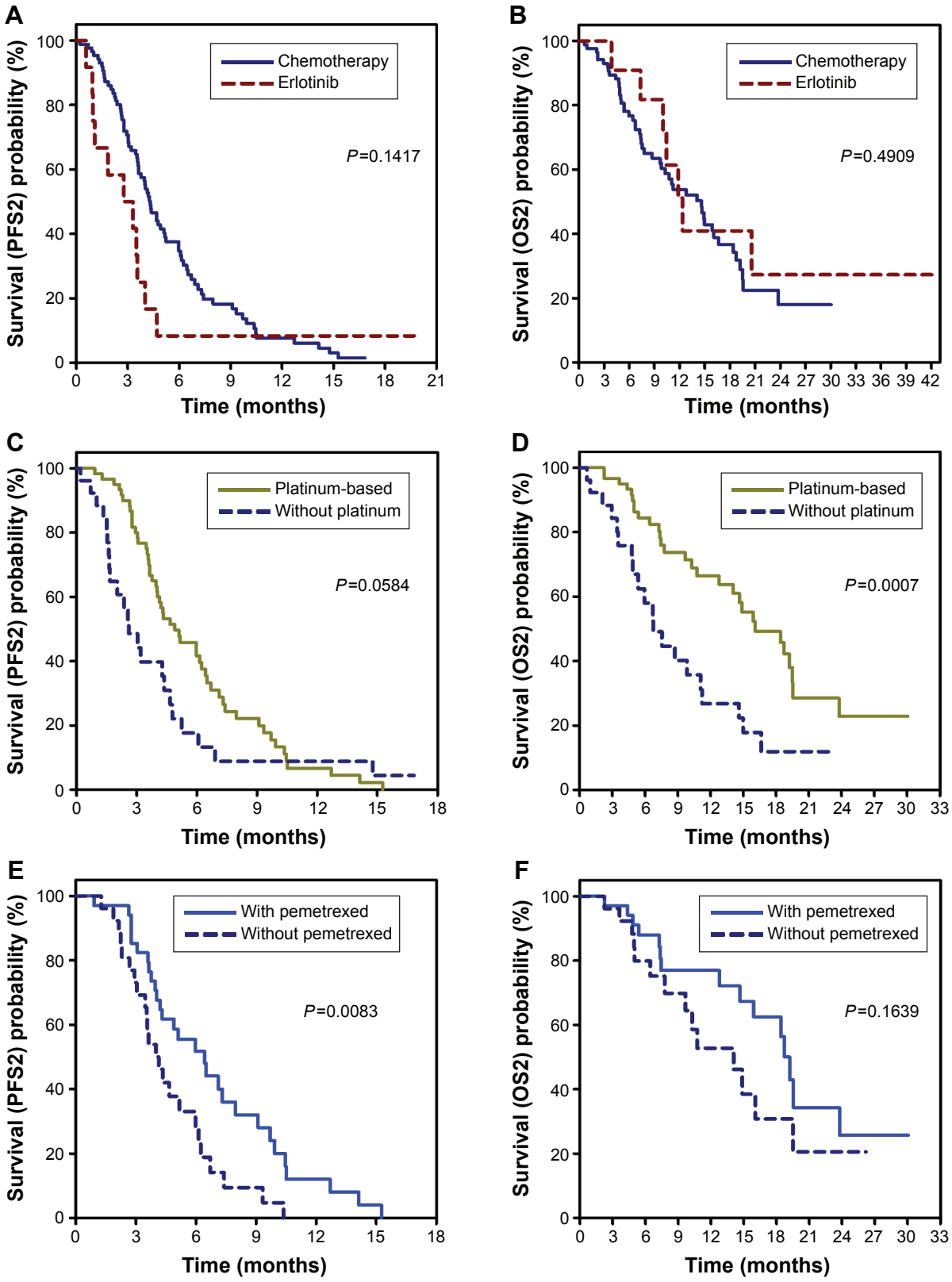

Figure 1 Kaplan–Meier curves of progression-free survival (PFS2; **A**, **C**, and **E**) and overall survival (OS2; **B**, **D**, and **F**) with the second-line treatment.

Notes: (**A** and **B**) Analyses of the whole study population showed that patients receiving chemotherapy had a trend for better PFS2 than those receiving erlotinib (MST of PFS2: 4.3 months vs 3.0 months, log-rank *P*=0.1417), whereas no significant difference in OS2 was noted (MST of OS2: 14.6 months vs 12.3 months, log-rank *P*=0.4909). (**C** and **D**) Analyses of the patients receiving chemotherapy showed that patients receiving platinum-based doublet had a trend for better PFS2 and a significantly better OS2 than those receiving chemotherapy without platinum (MST of PFS2: 4.9 months vs 2.6 months, log-rank *P*=0.0584; MST of OS2: 16.1 months vs 6.7 months, log-rank *P*=0.0007). (**E** and **F**) Analyses of the patients receiving platinum-based doublet showed that patients receiving pemetrexed had a significantly better PFS2 and a trend for better OS2 than those without pemetrexed treatment (MST of PFS2: 6.4 months vs 4.1 months, log-rank *P*=0.0083; MST of OS2: 19.2 months vs 14.1 months, log-rank *P*=0.1639).

Abbreviations: PFS, progression-free survival; PFS2, the PFS in salvage therapy; OS, overall survival; OS2, the OS in salvage therapy; MST, median survival time.

Table 4 Cox regression analyses for the factors predicting progression-free survival (PFS2) and overall survival (OS2) with the second-line treatment

Clinical features	Progression-free survival with the second-line treatment (PFS2)		Overall survival with the second-line treatment (OS2)	
	Univariate analysis	Multivariable analysis	Univariate analysis	Multivariable analysis
All chemotherapy patients				
Sex (male vs female)	0.65 (0.40–1.04)	0.63 (0.39–1.01)	0.66 (0.36–1.21)	0.64 (0.35–1.17)
Age (≥65 vs <65 years old)	1.16 (0.73–1.84)	0.83 (0.45–1.55)	2.47 (1.37–4.44)	1.75 (0.77–3.98)
Performance status while starting the second-line treatment (ECOG ≥2 vs ≤1)	1.32 (0.81–2.15)	1.34 (0.82–2.18)	2.34 (1.32–4.18)	2.42 (1.35–4.35)
The second-line treatment (platinum-based doublet vs chemotherapy without platinum)	0.62 (0.38–1.02)	0.52 (0.26–1.01)	0.38 (0.21–0.68)	0.59 (0.26–1.33)
Patients receiving platinum-based doublet				
Sex (male vs female)	0.63 (0.35–1.11)	0.62 (0.34–1.12)	0.41 (0.17–0.96)	0.39 (0.16–0.93)
Age (≥65 vs <65 years old)	1.23 (0.65–2.33)	1.69 (0.86–3.33)	4.21 (1.77–10.0)	5.96 (2.28–15.59)
Performance status while starting the second-line treatment (ECOG score ≥2 vs ≤1)	0.82 (0.43–1.55)	0.59 (0.30–1.17)	1.48 (0.65–3.34)	1.45 (0.61–3.45)
The second-line treatment (with pemetrexed vs without pemetrexed)	0.47 (0.26–0.84)	0.42 (0.23–0.77)	0.60 (0.29–1.25)	0.50 (0.22–1.13)

Note: Data are presented as hazard ratio (95% confidence interval).
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

was superior to non-platinum-based chemotherapy in terms of disease control rate, PFS2, and OS2. Among patients receiving platinum-based doublet, pemetrexed seemed better than other cytotoxic chemotherapeutic agents in terms of PFS2. Therefore, a platinum derivative with pemetrexed might be the best regimen for second-line salvage therapy.

Because of its great efficacy shown by several Phase III prospective studies, gefitinib has been covered by the National Health Insurance in Taiwan since June 2011 as the first-line treatment for patients with advanced lung adenocarcinoma harboring susceptible *EGFR* mutation. As a result, most of these patients received gefitinib as the first-line therapy in Taiwan. Despite gefitinib showed good efficacy and longer PFS than cytotoxic chemotherapy in this population, acquired resistance to *EGFR*-TKI almost always eventually occurred, resulting in the need of subsequent salvage therapy. Some strategies to overcome acquired resistance were proposed, including new-generation *EGFR*-TKIs for T790M mutation, MET inhibitors for MET amplification, and so on. However, these treatment strategies are still under investigation and are not currently available in daily clinical practice. In the real world, the lack of an established therapeutic strategy for patients with NSCLC who have disease progression after receiving the first-line *EGFR*-TKI treatment remains a great challenge for physicians. Shifting to erlotinib after gefitinib failure had been proposed but had modest efficacy,[8,17,18] as shown in our study. Cytotoxic chemotherapy, based on the current concept, is the optimal salvage therapy to these patients with acquired resistance, and the researchers were trying to identify the best regimens to improve the outcome.

Several retrospective studies were designed to explore the most optimal salvage therapy for patients with advanced NSCLC, while most of them enrolled unselected patients (including those with mutated, nonmutated, and unknown *EGFR* mutation status).[10,14,15,19] Kuo et al showed that patients who received cytotoxic chemotherapy had better PFS and OS than those who just received best supportive care. Furthermore, they also indicated that patients who received taxane-based subsequent chemotherapy exhibited a higher response rate (48.7%), higher disease control rate (79.5%), longer PFS (median: 5.1 months), and longer OS (median: 12.7 months) than those who received non-taxane-based regimens, including pemetrexed-based therapy.[14] In contrast to their study, we found no significant difference in PFS and OS in patients receiving chemotherapy with or without taxanes as the second-line treatment (data not shown).

Wu et al[10] showed that the salvage platinum-based chemotherapy was associated with a better OS than non-platinum-based chemotherapy (median: 21.7 months vs 8.9 months, P=0.006). In line with their finding, our study showed a trend for better PFS and a significantly longer OS in patients receiving platinum-based chemotherapy than those receiving non-platinum-based chemotherapy. Wu et al[10] also indicated that platinum-based chemotherapy with gemcitabine provided longer OS than platinum-based therapy with taxane did. Kim et al[15] suggested that pemetrexed-based therapy provided significantly longer

OS (18.5 months vs 8.5 months, *P*=0.008) in unselected patients, while *EGFR* mutation status was unknown in most of them. In contrast to these studies enrolling unselected patients, we found that the pemetrexed use, along with platinum-based doublet, was associated with a significantly longer PFS and a trend for better OS in patients with stage IV lung adenocarcinoma with susceptible tumor *EGFR* mutation who received platinum-based doublet after gefitinib failure.

Recently, some studies enrolled patients who had tumors with *EGFR* mutation and received *EGFR*-TKI as the first-line therapy. Tseng et al[11] indicated that using cytotoxic chemotherapy as the second-line therapy resulted in a median PFS of 4.5 months and OS of 14.6 months. Similarly, this study showed that patients treated with cytotoxic chemotherapy as the second-line treatment after gefitinib failure had a median PFS of 4.3 months and OS of 14.6 months.

Pemetrexed is a multiple antifolate drug for nonsquamous cell NSCLC and is currently regarded as one of the most effective and safest cytotoxic chemotherapeutic agents. Clinical trials showed that pemetrexed-based chemotherapy provided longer PFS and OS than gemcitabine-based chemotherapy did, while the regimen was used as the first-line therapy for patients with advanced NSCLC.[20] Basically, high-level expression of thymidylate synthase in NSCLC conferred a reduced susceptibility to pemetrexed.[21–23] However, NSCLC harboring *EGFR* mutation had decreased the expression of thymidylate synthase,[24] which might lead to a better response to pemetrexed.[25] Indeed, Park et al[19] recently showed that pemetrexed used alone as a salvage drug after gefitinib failure provided significantly longer PPS than platinum-based doublet chemotherapy did (PFS: 4.2 months vs 2.7 months, *P*=0.008). Tseng et al[11] also demonstrated that chemotherapy with pemetrexed as the second-line chemotherapy for patients having acquired resistance to the first-line *EGFR*-TKI seemed to provide better PFS (4.7 months vs 3.3 months, *P*=0.62) and better OS (15.1 months vs 8.1 months, *P*=0.17) than chemotherapy without pemetrexed did, but the differences were nonsignificant and inconclusive. In our study population, chemotherapy with pemetrexed was associated with a significantly longer PFS and OS in patients with stage IV lung adenocarcinoma receiving salvage chemotherapy as the second-line treatment after gefitinib failure (data not shown). Furthermore, in patients receiving platinum-based doublet as the second-line treatment, pemetrexed, along with a platinum derivative, provided a significantly longer PFS and a trend for better OS. Therefore, platinum-based doublet with pemetrexed might be the most optimal regimen for patients with stage IV lung adenocarcinoma with acquired resistance to gefitinib. Further prospective randomized studies might be needed to confirm our findings.

There were several limitations in this study. First, our study was a retrospective study, and selection bias was inevitable. Also, due to the retrospective nature of this study, almost no rebiopsy specimens were collected from the patients after developing acquired resistance to gefitinib, so the molecular mechanism underlying our findings could not be assessed. However, this retrospective study demonstrated the clinical conditions in the real world. Second, only patients with stage IV lung adenocarcinoma harboring susceptible *EGFR* mutation who received gefitinib as their first-line treatment were included in our analyses. Several *EGFR*-TKIs available nowadays, such as gefitinib, erlotinib, and afatinib, had different potency, resulting in different PFS and OS. Therefore, it remained questionable whether our findings could be applied in patients with stage IIIB adenocarcinoma, in patients with NSCLC other than adenocarcinoma, or in patients receiving *EGFR*-TKI other than gefitinib. However, the inclusion of a specific population receiving gefitinib as the first-line treatment reduced the heterogeneity of our study population, resulting in easier application of the results in daily clinical practice.

Conclusion

Our study demonstrated the real-world data in Taiwan, showing that platinum-based doublet chemotherapy with pemetrexed might be the most optimal second-line treatment for patients with stage IV adenocarcinoma harboring susceptible *EGFR* mutation after gefitinib failure. Further prospective studies are required to confirm our findings and uncover the underlying mechanisms.

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Disclosure

The authors report no conflicts of interest in this work.

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