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ORIGINAL ARTICLE

Subsequent treatment of epidermal growth factor receptor-tyrosine kinase inhibitor failure in patients with advanced lung adenocarcinoma

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Keywords
Epidermal growth factor receptor; failure; lung adenocarcinoma; tyrosine kinase inhibitor.

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Abstract

Background: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) effectively treat advanced non-small cell lung cancer with EGFR-mutation. However, most patients develop acquired resistance without effective therapy subsequent to EGFR-TKI failure. We evaluated the efficacy of subsequent treatment strategies for EGFR-TKI resistance.

Methods: We retrospectively analyzed 240 patients with advanced lung adenocarcinoma with EGFR-TKI failure and following subsequent treatment. According to the first subsequent strategies after EGFR-TKI failure, patients were divided into groups of EGFR-TKI continuation (21 cases), EGFR-TKI continuation with chemotherapy (23 cases), chemotherapy alone (143 cases), and best supportive care (BSC) (53 cases).

Results: Except for 53 cases of BSC, the disease control rates (DCR) of the remaining 187 patients in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were 66.7%, 73.9%, and 44.8%, respectively. The median post-progression progression-free survival (PFS) for the three groups was 3.0, 3.3, and 2.0 months, respectively. The DCR for the EGFR-TKI continuation with chemotherapy group was significantly higher than the chemotherapy alone group ($P = 0.006$). The post-progression PFS of the EGFR-TKI continuation with chemotherapy group was significantly longer than the chemotherapy alone group ($P = 0.037$). The median overall survival in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups were 6.9, 11.6, 8.8, and 0.9 months, respectively. Compared to the BSC group, all groups achieved a survival benefit ($P < 0.001$).

Conclusions: EGFR-TKI continuation with chemotherapy could provide benefits for patients with acquired resistance to EGFR-TKI.

Introduction

Non-small cell lung cancer (NSCLC) is the main type of lung cancer, accounting for 85% of all lung cancers. Because of the lack of early symptoms and specific clinical manifestations, early diagnosis is very difficult and about 70% of NSCLC patients are diagnosed in advanced stage. Chemotherapy for advanced NSCLC has entered the plateau stage.[1] Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), represented by gefitinib, erlotinib, and icotinib, have changed the treatment model of advanced NSCLC, in which EGFR mutation is the most effective predictor of EGFR-TKI

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efficacy. Many large clinical studies, such as IPASS, WJTOG3405, NEJ002, OPTIMAL, and EURTAC show that EGFR-TKI efficacy in advanced NSCLC with EGFR mutations can reach 60~80%, and progression-free survival (PFS) can be longer than a year.[2–6] However, most patients will inevitably develop EGFR-TKI failure as a result of resistance against EGFR-TKIs. Small sample and single-center studies have found that EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone will benefit some patients.[7-12] This study aimed to conduct a retrospective analysis to further explore the effects of subsequent treatment after EGFR-TKI failure on efficacy and survival in patients with advanced lung adenocarcinoma.

Materials and methods

General information

This retrospective study included 240 patients who had received EGFR-TKIs at the Beijing Chest Hospital for ≥3 months, demonstrated failure, and received subsequent treatment from 6 November 2005 to 20 November 2013. All patients were histologically or cytologically diagnosed with lung adenocarcinoma, and they had reached clinical stage IV after EGFR-TKI failure.[13]

Treatment methods

During initial EGFR-TKI treatment, 104 patients received gefitinib, 84 received erlotinib, and 52 received icotinib with conventional EGFR-TKI doses, including 250 mg of gefitinib once daily, 150 mg of erlotinib once daily, and 125 mg of icotinib three times daily. The first subsequent treatment after EGFR-TKI failure consisted of the following: EGFR-TKI continuation (continuing the same EGFR-TKI agent), EGFR-TKI continuation with chemotherapy, chemotherapy alone, and best supportive care (BSC). We evaluated tumor response in patients who received EGFR-TKI every four weeks based on computed tomography scans, then performed additional assessments every eight weeks. For patients who received chemotherapy, we performed assessments every two cycles. In patients whose symptoms deteriorated over the course of chemotherapy, imaging review was conducted to re-evaluate efficacy.

Efficacy assessment

We applied Response Evaluation Criteria in Solid Tumors (1.1) to assess efficacy, which was divided into: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).[14] The evaluation index included: disease control rate (DCR), PFS, and overall survival (OS). The initial EGFR-TKI treatment PFS was defined as the time from the start of EGFR-TKI treatment to PD identification. Post-progression PFS was defined as the time from confirmed PD to the second progression or death. OS was defined as the time from confirmed PD of initial EGFR-TKI failure to death. The survey was conducted using outpatient and telephone follow-up. Follow-up concluded on 30 April 2014, after which data was censored for surviving patients.

Statistical analysis

We performed statistical analysis using SPSS version 19.0 (SSPS Inc., Chicago, IL, USA). We analyzed differences in efficacy using the Chi-square test and a logistic regression model including clinically relevant confounders. We used the Kaplan–Meier method to estimate survival curves, the log-rank test to compare survival curves among different groups, and the multivariate Cox proportional hazards regression model to evaluate independent prognostic factors associated with PFS and OS. As multivariate analysis, all clinical factors were included in the model. All statistical tests were two-sided and values of $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics

During initial EGFR-TKI treatment, the proportions of patients at the first, second, third, fourth, and fifth lines were 32.9%, 43.3%, 21.7%, 1.7%, and 0.4%, respectively. The rate of EGFR mutation testing was 38.75%. The objective response rate (ORR) of initial EGFR-TKI treatment was 30%, and the median PFS was 5.1 months. At initial EGFR-TKI failure, the patients' median age was 57 years (ranging from 26 to 91 years). Women accounted for 49.6% (119/240), non-smokers 58.3% (140/240), and the Eastern Cooperative Oncology Group performance status (PS) 0–1 was 63.3% (152/240). According to the first subsequent treatment after EGFR-TKI failure, patients were divided into four groups: EGFR-TKI continuation (21 cases), EGFR-TKI continuation with chemotherapy (23 cases), chemotherapy alone (143 cases), and BSC groups (53 cases). All 240 patients were evaluable for OS. With the exception of the 53 patients in the BSC group, 187 patients in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were evaluated for post-progression efficacy and PFS.

The median age of patients at initial EGFR-TKI failure in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups were 60, 59, 55, and 58 years, respectively. There were more patients of PS 0–1 at initial EGFR-TKI failure who received EGFR-TKI continuation with chemotherapy (82.6%) and chemotherapy

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Table 1 Clinical characteristics of enrolled patients

Characteristics	TKI n (%)	TKI plus Chemo n (%)	Chemo n (%)	BSC n (%)
Total	21	23	143	53
Characteristics of TKI failure				
Age of TKI failure (years)				
Median (range)	60 (30–85)	59 (45–75)	55 (26–81)	58 (35–91)
≤65	15 (71.4)	17 (73.1)	114 (79.7)	38 (71.7)
>65	6 (28.6)	6 (26.9)	29 (20.3)	15 (28.3)
Gender				
Male	11 (52.4)	15 (65.2)	62 (43.4)	33 (62.3)
Female	10 (47.6)	8 (34.8)	81 (56.6)	20 (37.7)
Smoking status				
Never	11 (52.4)	10 (43.5)	94 (65.7)	25 (47.2)
Smoker	10 (47.6)	13 (56.5)	49 (34.3)	28 (52.8)
ECOG PS of TKI failure				
0–1	9 (42.9)	19 (82.6)	119 (83.2)	5 (9.4)
≥2	12 (57.1)	4 (17.4)	24 (16.8)	48 (90.6)
Characteristics of initial TKI				
EGFR mutation				
Activating mutation	4 (19.0)	9 (39.1)	45 (31.5)	5 (9.4)
Wild type	2 (9.5)	2 (8.7)	14 (9.8)	12 (22.6)
Unknown	15 (71.4)	12 (52.2)	84 (58.7)	36 (67.9)
Line of initial TKI				
1st	8 (38.1)	4 (17.4)	48 (33.6)	19 (35.8)
≥2nd	13 (61.9)	19 (82.6)	95 (66.4)	34 (64.2)
Best response to initial TKI				
PR	6 (28.6)	6 (26.1)	54 (37.8)	6 (11.3)
SD	15 (71.4)	17 (73.9)	89 (62.2)	47 (88.7)
PFS of initial TKI				
≤6 months	13 (61.9)	7 (30.4)	74 (51.7)	42 (79.2)
>6 months	8 (38.1)	16 (69.6)	69 (48.3)	11 (20.8)

BSC, best supportive care; chemo, chemotherapy; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI plus chemo, EGFR-TKI continuation with chemotherapy; TKI, tyrosine kinase inhibitors.

alone (83.2%) compared with patients of PS 2 at initial EGFR-TKI failure who received EGFR-TKI continuation (57.1%) and BSC (90.6%). Four patients (19%) had activating EGFR mutations in the EGFR-TKI continuation group, nine (39.1%) in the EGFR-TKI continuation with chemotherapy, 45 (31.5%) in the chemotherapy alone, and five patients (9.4%) in the BSC group. The majority of patients in the four groups accepted initial EGFR-TKI as a second-line and above therapy. The characteristics of the four groups are listed in Table 1.

Efficacy of different therapeutic strategies after epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) failure

Among 187 patients, there was no complete response, seven PR (3.7%), 88 SD (47.1%), and 92 PD cases (49.2%). The ORR was 3.7%. The ORR of the EGFR-TKI continuation group was 14.3% and the chemotherapy alone group 2.8%. There were no PR patients in the EGFR-TKI continuation with chemotherapy group. Because cases of PR were rare, we performed no further statistical analysis. The overall DCR was 50.8%, and the rates in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were 66.7%, 73.9%, and 44.8%, respectively. The difference among these three groups was significant ($P = 0.01$) (Table 2). The DCR of the EGFR-TKI continuation with chemotherapy group was significantly higher than the chemotherapy alone group (odds ratio [OR] = 1.651, 95% confidence interval [CI] = 1.219–2.237, $P = 0.009$). The DCR difference between the EGFR-TKI continuation and EGFR-TKI continuation with chemotherapy groups, and that between the EGFR-TKI continuation and chemotherapy alone groups, was not significant ($P = 0.559$; $P = 0.06$). Results after balancing confounding factors showed that the DCR of the EGFR-TKI continuation with chemotherapy group was significantly higher than the che-

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Table 2 Efficacy of different treatment strategies after EGFR-TKI failure

Group	TKI	TKI plus Chemo	Chemo	*P*
PR	3	0	4	
SD	11	17	60	
PD	7	6	79	
DCR	66.7%	73.9%	44.8%	0.01†

†Comparison among the three groups. DCR, disease control rate; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; TKI plus chemo, EGFR-TKI continuation with chemotherapy.

motherapy alone group (OR = 4.057, 95% CI = 1.485–11.083, $P = 0.006$). Logistic multivariate analysis indicated that initial EGFR-TKI as a first-line therapy (OR = 2.146, 95% CI = 1.123–4.102, $P = 0.021$) was an independent predictor of improved efficacy.

Progression-free survival of different treatment strategies after EGFR-TKI failure

The median PFS of 187 patients who received treatment after EGFR-TKI failure was 2.2 months, and six patients were without progression at the last follow-up. The post-progression median PFS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups was 3.0 (95% CI: 1.4–4.6 months), 3.3 (95% CI: 1.6–5.0 months), and 2.0 months (95% CI: 1.6–2.4 months), respectively, and the difference among these three groups was not significant ($P = 0.203$) (Fig 1a, Table 3). The Cox proportional hazards regression model indicated that the post-progression PFS of the EGFR-TKI continuation with chemotherapy group was significantly longer than that of the chemotherapy alone group (hazard ratio [HR] = 0.611, 95% CI = 0.385–0.971, $P = 0.037$) (Table 4). The Cox proportional hazards regression model also showed that initial EGFR-TKI treatment as a first-line therapy (HR = 0.705, 95% CI = 0.508–0.978, $P = 0.036$) and PS 0–1 at initial EGFR-TKI failure (HR = 0.469, 95% CI = 0.319–0.689, $P < 0.001$), were independent prognostic factors reducing the risk of disease progression.

Overall survival of different treatment strategies after EGFR-TKI failure

The median OS of the 240 patients was 6.5 months. Twenty-four of those patients survived until the final follow-up and 16 patients were lost to follow-up, resulting in a loss to follow-up rate of 6.7%. The median OS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups was 6.9 (95% CI: 2.9–10.9 months), 11.6 (95% CI: 4.0–19.2 months), 8.8 (95% CI: 6.7–10.9 months), and 0.9 months (95% CI: 0.6–1.2 months), respectively, and the difference among these groups was significant ($P < 0.001$) (Fig 1b, Table 3). Compared with the BSC group, the OS of the EGFR-TKI continuation ($P < 0.001$), EGFR-TKI continuation with chemotherapy ($P < 0.001$), and chemotherapy alone groups ($P < 0.001$) were significantly prolonged. The OS of the EGFR-TKI

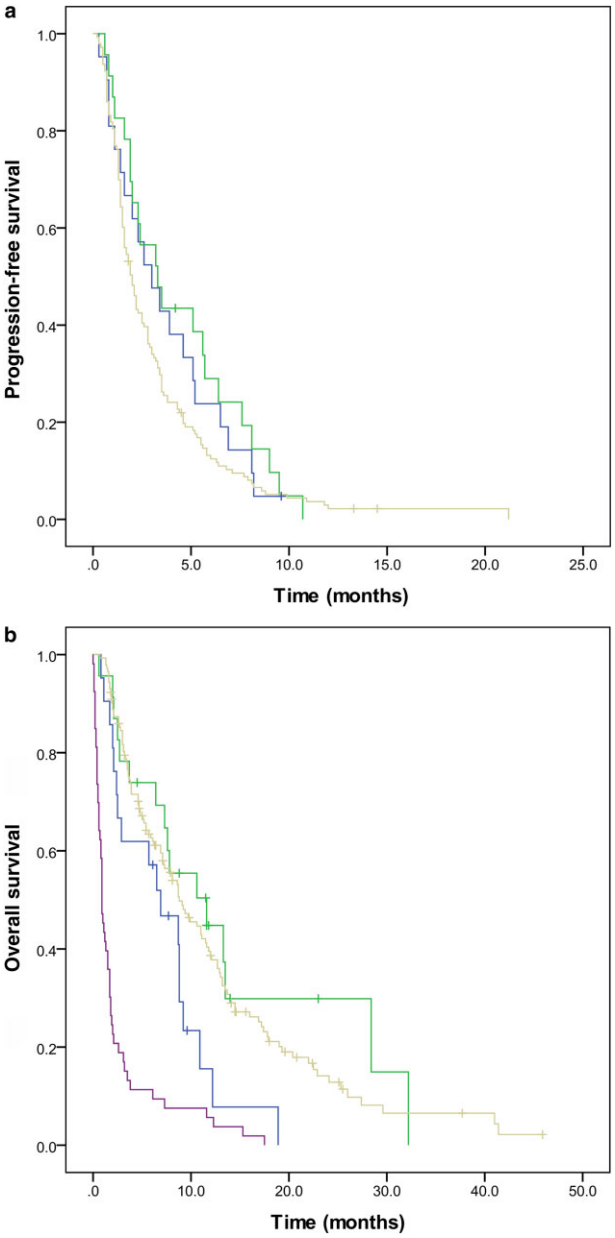

Figure 1 Progression-free survival (PFS) and overall survival (OS) curves after epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) progression. (**a**) PFS curve: TKI *versus* TKI plus chemo *versus* chemo; (**b**) OS curve: TKI *versus* TKI plus chemo *versus* chemo *versus* best supportive care. , TKI; , TKI plus; , Chemo; , TKI-censoring; , TKI plus-censoring; , Chemo-censoring.

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Table 3 Univariate analysis of progression-free survival and overall survival after EGFR-TKI failure

	PFS (month)			OS (month)		
Group	Median	95% CI	*P*	Median	95% CI	*P*
Characteristics of initial TKI						
EGFR mutation			0.718			0.063
Activating mutation	2.6	1.5–3.7		10.6	6.7–14.5	
Wild type	1.6	1.0–2.2		4.6	0.1–9.6	
Unknown	2.1	1.6–2.6		5.1	3.3–6.9	
Line of initial TKI			0.059			0.189
1st	2.8	1.7–3.9		6.1	3.7–8.5	
≥2nd	2.0	1.6–2.4		6.9	4.6–9.2	
Best response to initial TKI			0.448			0.157
PR	2.8	1.4–4.2		10.6	7.9–13.3	
SD	2.1	1.8–2.4		7.3	6.08–.6	
PFS of initial TKI			0.887			0.003
≤6 months	2.1	1.6–2.6		3.8	2.6–5.0	
>6 months	2.2	1.5–2.9		8.8	6.4–11.2	
Characteristics of TKI failure						
Age of TKI failure (years)			0.806			0.002
≤65	2.2	1.8–2.6		7.2	5.3–9.1	
>65	2.0	1.0–3.0		3.5	2.5–4.5	
Gender			0.952			0.323
Male	2.1	1.7–2.5		4.6	2.66–.6	
Female	2.2	1.5–2.9		8.6	6.7–10.5	
Smoking status			0.783			0.120
Never	2.0	1.3–2.7		7.3	5.5–9.1	
Smoker	2.2	1.7–2.7		4.6	2.17–.1	
ECOG PS of TKI failure			0.000			0.000
0-1	2.5	1.8–3.2		10.9	8.81–3.0	
≥2	1.7	0.8–2.6		1.7	1.3–2.1	
Subsequent treatment			0.203			0.000
TKI	3.0	1.4–4.6		6.9	2.9–10.9	
TKI plus	3.3	1.6–5.0		11.6	4.01–9.2	
Chemo	2.0	1.6–2.4		8.8	6.7–10.9	
BSC	–	–		0.9	0.61–.2	

continuation with chemotherapy and chemotherapy-alone groups were both significantly longer than in the EGFR-TKI continuation group ($P = 0.024$; $P = 0.022$), while the OS differences in the EGFR-TKI continuation with chemotherapy group and chemotherapy alone group were not statistically significant. The Cox proportional hazards regression model indicated that the OS of the EGFR-TKI continuation (HR = 0.332, 95% CI = 0.192–0.573, $P < 0.001$), EGFR-TKI continuation with chemotherapy (HR = 0.265, 95% CI = 0.145–0.485, $P < 0.001$), and chemotherapy alone groups (HR = 0.331, 95% CI = 0.220–0.498, $P < 0.001$) were significantly longer than the BSC group (Table 4). The Cox proportional hazards regression model also revealed that an age of ≤ 65 years (HR = 0.653, 95% CI = 0.469–0.910, $P = 0.012$) and PS 0–1 at initial EGFR-TKI failure (HR = 0.378, 95% CI = 0.263–0.542, $P < 0.001$) were independent prognostic factors reducing the risk of death.

Discussion

Subsequent treatment after EGFR-TKI failure has attracted much attention from researchers. Current studies have shown that among patients with acquired resistance against EGFR-TKI, 50–60% of cases were a result of a second T790M mutation,[15] 5–22% were a result of mesenchymal-epithelial transition (MET) gene amplification,[16] and others were caused by factors such as excessive hepatocyte growth factor expression,[17] Gas6-Axl activation,[18] phosphatase and tensin homolog gene expression loss in the downstream pathway,[19] phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha mutation,[20] small-cell lung cancer transformation,[21] and epithelial-to-mesenchymal transition.[22] For patients resistant to EGFR-TKI, the most ideal treatment is to conduct a subsequent biopsy to clarify the resistance mechanism in order to select a targeted therapeutic strategy.

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Table 4 Cox analysis of progression-free survival and overall survival after EGFR-TKI failure

	PFS			OS		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Line of initial TKI	0.705	0.508–0.978	0.036			
1st						
≥2nd						
Age of TKI failure (years)				0.653	0.469–0.910	0.012
≤65						
>65						
ECOG PS of TKI failure	0.469	0.319–0.689	<0.001	0.378	0.263–0.542	<0.001
0–1						
≥2						
Subsequent treatment			0.017			<0.001
TKI	0.566	0.343–0.935		0.332	0.192–0.573	
TKI plus	0.611	0.385–0.971		0.265	0.145–0.485	
Chemo†	–	–		0.331	0.220–0.498	
BSC‡				–	–	

†Reference group of subsequent treatment in Cox proportional hazards regression model of PFS. ‡Reference group of subsequent treatment in Cox proportional hazards regression model of OS. BSC, best supportive care; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI plus chemo, EGFR-TKI continuation with chemotherapy; TKI, tyrosine kinase inhibitors.

However, in clinical practice, collecting subsequent specimens after EGFR-TKI failure is not possible, and drugs based on the EGFR-TKI resistance mechanism are still in various clinical trial stages. At the 2014 American Society of Clinical Oncology conference, the results of a phase I study of AZD9291 and Lux-lung-5 were reported.[23,24] However, only a handful of research centers are able to participate in clinical research for new drugs after the first generation of EGFR-TKI resistance. Only a small percentage of patients are suitable for and receive new drug treatment, while most patients resistant to EGFR-TKI have no optional new drug. Therefore, clinical treatment after EGFR-TKI failure mainly adopts existing treatment methods, such as EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone. This study retrospectively analyzed EGFR-TKI failure cases and investigated the effects of subsequent therapeutic strategies on efficacy and patient survival. Our results showed that after EGFR-TKI failure, the EGFR-TKI continuation with chemotherapy group achieved the highest DCR, and the median PFS and median OS were the longest, indicating that EGFR-TKI continuation with chemotherapy might provide benefits for a small percentage of patients.

Pre-clinical studies suggest that EGFR-TKI combined with chemotherapy has synergistic effects on EGFR-TKI acquiring resistant cells.[25] Yoshimura *et al*. reported a phase II study, the results of which showed that 27 NSCLC patients with stage III-IV EGFR mutations who received EGFR-TKI continuation with pemetrexed after EGFR-TKI failure obtained a favorable response.[9] Shukuya *et al*. retrospectively analyzed 16 NSCLC patients with gefitinib failure who had obtained CR or PR during gefitinib therapy, and they then received subsequent gefitinib treatment plus paclitaxel.[10] The results demonstrated an ORR of 13%, DCR 75%, median PFS 4.3 months, and median OS of 8.1 months. Our study showed that the EGFR-TKI continuation with chemotherapy group received the most significant clinical benefits among 187 patients with advanced NSCLC who developed EGFR-TKI failure and received subsequent treatment. Our data demonstrated a DCR of 73.9%, and median PFS and OS values of 3.3 and 11.6 months, respectively. However, in our study, the DCR and median PFS of the EGFR-TKI continuation with chemotherapy group were lower than in previous reports, and there were no PR patients. Meanwhile, the median PFS of the EGFR-TKI continuation and chemotherapy alone groups were also lower than in previous retrospective reports, which may be related to the enrolled population.[7,12] Most patients from previous studies were a selective population, while in this study, patients with sensitive EGFR mutations accounted for 31%; the efficacy of initial EGFR-TKI evaluated as PR accounted for 30%, and without CR; and post-progression treatment as a third-line or above therapy accounted for 66.8%. The difference in OS may be a result of different OS definitions.

Our data showed that the DCR and median PFS and OS of the EGFR-TKI continuation with chemotherapy group were higher than those of the chemotherapy alone group, and the differences in DCR and median PFS were statistically significant. This was similar to another retrospective study, but inconsistent with the preliminary findings of IMPRESS, a phase III randomized study.[26] Goldberg *et al*. conducted a retrospective study on 78 patients resistant to EGFR-TKIs in a single center, and the results revealed that the efficiency and PFS of the EGFR-TKI continuation with chemotherapy group were both superior to those of chemotherapy alone

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(41% vs. 18%, $P = 0.02$; 4.4 vs. 4.2 months, $P = 0.34$); however, the PFS difference was not statistically significant and OS was not prolonged.[27,30] The preliminary findings of IMPRESS showed that the clinical benefit of gefitinib continuation with chemotherapy after progression on first-line gefitinib was no better than chemotherapy in NSCLC patients with EGFR mutation-positive. The interpretation of our results was limited by the small sample and the retrospective nature of the study. However, subsequent treatment in the IMPRESS study was unbalanced between the chemotherapy and gefitinib continuation with chemotherapy groups. In the chemotherapy group, 12.9% and 33% of patients received subsequent platinum-based chemotherapy and EGFR-TKI, respectively, compared to 3.8% and 22.6%, respectively, in the gefitinib continuation with chemotherapy group. Therefore, further prospective studies are required to explore the resistance mechanism of patients who achieved a benefit from the EGFR-TKI continuation with chemotherapy, and to determine the specific beneficiaries.

Our study also analyzed the efficacy and survival between the EGFR-TKI continuation and chemotherapy alone groups. OS of the chemotherapy alone groups were significantly longer than in the EGFR-TKI continuation group. However, between the EGFR-TKI continuation and chemotherapy alone groups, the difference of DCR and the post-progression median PFS was not significant. [Correction added on 18 May 2015, after first online publication: The statements above have been amended for further clarification.] Wu *et al*. retrospectively analyzed the subsequent treatment and prognosis of 195 patients with advanced NSCLC whose first-line therapy with gefitinib had failed. Their results showed that second-line platinum-based chemotherapy achieved significantly improved survival rates compared with other therapies, including erlotinib.[28] Therefore, it is necessary to expand the sample for further stratification exploration.

A therapeutic strategy after EGFR-TKI failure is still being explored. This study showed that EGFR-TKI continuation with chemotherapy may benefit a small portion of patients. The clinical benefits of this therapy may be related to tumor heterogeneity. *In vitro* studies have shown that mutations were resistant in only a portion of cells when EGFR-TKI resistance occurs, while a certain percentage of tumor cells remain sensitive to EGFR-TKI therapy.[29] Clinical studies have confirmed that ceasing EGFR-TKI continuation treatment after EGFR-TKI failure in EGFR-TKI-sensitive tumors increases tumor progression, which stabilizes once EGFR-TKI is re-applied.[30,31] EGFR-TKIs combined with chemotherapy can inhibit EGFR mutation-sensitive cells and kill tumor cells independent of EGFR mutation by chemotherapy at the same time. Thus, it can control different tumor clones and is likely a method that can improve efficacy and survival.

This study analyzed OS in 240 NSCLC patients who developed EGFR-TKI failure, including BSC. The results showed that the median OS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were all superior to those of the BSC group, in which the median OS increased at least 6.9 months. Kuo *et al*. enrolled 114 first-line EGFR-TKI-resistant patients with advanced NSCLC, of which 67 cases received sequential chemotherapy and 47 BSC.[12] Their results revealed that, compared with the BSC group, the median OS of the chemotherapy group increased by 7.4 months (11.2 vs. 3.8 months, $P < 0.01$). Kim *et al*. also demonstrated that in 417 patients who benefitted from gefitinib and received subsequent treatment after gefitinib failure, the survival benefit of the chemotherapy group was more significant than for the BSC group (HR = 0.38, 95% CI = 0.27–0.53).[32] Conversely, Kim *et al*. found no significant difference between the EGFR-TKI continuation and BSC groups, which may be relevant to retrospective and small sample studies. Our study indicated that patients who are qualified for and capable of continuing treatment should adopt active treatment as they may achieve survival benefits.

In this study, multivariate analysis showed that EGFR-TKI as a first-line therapy is an independent predictive factor that improves efficacy and a prognostic factor that reduces disease progression. The results indicated that efficacy of and survival rates for post-progression treatment were related to initial EGFR-TKI treatments, where earlier EGFR-TKI application may result in higher control rates and longer survival benefits after EGFR-TKI failure. A PS of 0–1 at initial EGFR-TKI failure is an independent prognostic factor reducing disease progression and risk of death, where patients with a good PS at initial EGFR-TKI failure can achieve greater clinical benefits with active treatment. However, this study also showed that EGFR mutation status was not related to the efficacy of and survival rates for post-progression treatment.

This retrospective study had some limitations. Our data were from a small sample size with strong case heterogeneity. Furthermore, as cases of EGFR mutation-sensitive patients were rare, we performed no further stratified analyses.

Conclusions

This study showed that a small portion of patients with advanced lung adenocarcinoma resistant to EGFR-TKIs may benefit from the combination of EGFR-TKIs with chemotherapy, which may become a valuable therapeutic strategy for suitable patients. Patients who are qualified for and capable of continuing treatment should adopt active treatment. It is necessary to conduct future prospective and large sample studies to explore the resistance mechanism of patients who benefited from EGFR-TKI

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continuation with chemotherapy in order to screen for probable beneficiaries.

Disclosure

No authors report any conflict of interest.

References

1 Ohe Y, Ohashi Y, Kubota K *et al*. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; **18**: 317–23.

2 Mok TS, Wu YL, Thongprasert S *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.

3 Mitsudomi T, Morita S, Yatabe Y *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 121–28.

4 Maemondo M, Inoue A, Kobayashi K *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362**: 2380–88.

5 Zhou C, Wu YL, Chen G *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.

6 Rosell R, Carcereny E, Gervais R *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 239–46.

7 Asami K, Okuma T, Hirashima T *et al*. Continued treatment with gefitinib beyond progressive disease benefits patients with activating EGFR mutations. *Lung Cancer* 2013; **79**: 276–82.

8 Cho BC, Im CK, Park MS *et al*. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol* 2007; **25**: 2528–33.

9 Yoshimura N, Okishio K, Mitsuoka S *et al*. Prospective assessment of continuation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of pemetrexed. *J Thorac Oncol* 2013; **8**: 96–101.

10 Shukuya T, Takahashi T, Tamiya A *et al*. Gefitinib plus paclitaxel after failure of gefitinib in non-small cell lung cancer initially responding to gefitinib. *Anticancer Res* 2009; **29**: 2747–51.

11 Chang MH, Ahn JS, Lee J *et al*. The efficacy of pemetrexed as a third- or fourth-line therapy and the significance of thymidylate synthase expression in patients with advanced non-small cell lung cancer. *Lung Cancer* 2010; **69**: 323–29.

12 Kuo CH, Lin SM, Lee KY *et al*. Subsequent chemotherapy improves survival outcome in advanced non-small-cell lung cancer with acquired tyrosine kinase inhibitor resistance. *Clin Lung Cancer* 2010; **11**: 51–6.

13 Goldstraw P, Crowley J, Chansky K *et al*. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; **2**: 706–14.

14 Eisenhauer EA, Therasse P, Bogaerts J *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.

15 Kobayashi S, Boggon TJ, Dayaram T *et al*. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005; **352**: 786–92.

16 Engelman JA, Zejnullahu K, Mitsudomi T *et al*. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007; **316**: 1039–43.

17 Yano S, Wang W, Li Q *et al*. Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. *Cancer Res* 2008; **68**: 9479–87.

18 Zhang Z, Lee JC, Lin L *et al*. Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. *Nat Genet* 2012; **44**: 852–60.

19 Yamamoto C, Basaki Y, Kawahara A *et al*. Loss of PTEN expression by blocking nuclear translocation of EGR1 in gefitinib-resistant lung cancer cells harboring epidermal growth factor receptor-activating mutations. *Cancer Res* 2010; **70**: 8715–25.

20 Ludovini V, Bianconi F, Pistola L *et al*. Phosphoinositide-3-kinase catalytic alpha and KRAS mutations are important predictors of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2011; **6**: 707–15.

21 Sequist LV, Waltman BA, Dias-Santagata D *et al*. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011; **3**: 75ra26.

22 Suda K, Tomizawa K, Fujii M *et al*. Epithelial to mesenchymal transition in an epidermal growth factor receptor-mutant lung cancer cell line with acquired resistance to erlotinib. *J Thorac Oncol* 2011; **6**: 1152–61.

23 Janne PA. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC). 2014 ASCO Annual Meeting Proceedings, *J Clin Oncol* 2014; **32** (Suppl.): Abstract 8009.

24 Schuler MH, Yang CH, Park K *et al*. Continuation of afatinib beyond progression: Results of a randomized, open-label, phase III trial of afatanib plus paclitaxel (P) versus investigator's choice chemotherapy (CT) in patients (pts)

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with metastatic non-small cell lung cancer (NSCLC) progressed on erlotinib/gefitinib (E/G) and afatanib – LUX-Lung 5 (LL5). 2014 ASCO Annual Meeting Proceedings, *J Clin Oncol* 2014; **32** (Suppl.): Abstract 8019.
25 Wu M, Yuan Y, Pan YY, Zhang Y. Combined gefitinib and pemetrexed overcome the acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. *Mol Med Rep* 2014; **10**: 931–38.
26 Mok T, Wu Y, Nakagawa K *et al*. Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: the Phase III, randomised IMPRESS study. 2014 ESMO Congress, 2014, Abstract LBA2_PR.
27 Goldberg SB, Oxnard GR, Digumarthy S *et al*. Chemotherapy with erlotinib or chemotherapy alone in advanced non-small cell lung cancer with acquired resistance to EGFR tyrosine kinase inhibitors. *Oncologist* 2013; **18**: 1214–20.
28 Wu JY, Shih JY, Yang CH *et al*. Second-line treatments after first-line gefitinib therapy in advanced nonsmall cell lung cancer. *Int J Cancer* 2010; **126**: 247–55.
29 Chmielecki J, Foo J, Oxnard GR *et al*. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. *Sci Transl Med* 2011; **3**: 90ra59.
30 Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: Implications for clinical trial design. *Clin Cancer Res* 2011; **17**: 6298–303.
31 Riely GJ, Kris MG, Zhao B *et al*. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res* 2007; **13**: 5150–55.
32 Kim HR, Lee JC, Kim YC *et al*. Clinical characteristics of non-small cell lung cancer patients who experienced acquired resistance during gefitinib treatment. *Lung Cancer* 2014; **83**: 252–58.

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