European Review for Medical and Pharmacological Sciences 2016; 20: 2450-2459

Continued EGFR-TKIs treatment promotes the survival of elderly patients with acquired resistance to EGFR-TKIs therapy

P. WANG[1], D. ZHANG[1], X.-M. LI[1], X.-G. GUO[1], B.-J. SUN[2], X.-Q. FANG[2], G.-P. QU[2], L. AN[2], C.-T. LIU[2]

[1]Department of Nanlou Medical Oncology, Chinese People's Liberation Army General Hospital, Beijing, China
[2]Department of Nanlou Respiratory Diseases, Chinese People's Liberation Army General Hospital, Beijing, China

Abstract. – OBJECTIVE: Continued EGFR-TKIs treatment is still controversial for NSCLC patients with activating EGFR mutations, who acquire resistance to the drug. Of these patients, elderly ones were worth to be investigated to further examine efficacy of continued EGFR-TKIs treatment.

PATIENTS AND METHODS: A total of 232 NSCLC patients (≥ 70-year-old) were recruited from the Chinese People's Liberation Army General Hospital between January 1, 2009, and July 31, 2014. And 44 patients were qualified for further retrospectively investigated, which were divided into dramatic and non-dramatic progression groups based on the characteristics of progression during first-line EGFR-TKIs treatment. And they were also divided into two groups: continued EGFR-TKIs group and discontinued EGFR-TKIs group. Subsequently, progression-free survival (PFS), post-progression survival (PPS), and overall survival (OS) of these groups were investigated by multivariate analysis.

RESULTS: Median OS (28.9 months *vs*. 23.2 months, $p = 0.46$) and median PPS (16.9 months *vs*. 4.4 months, $p = 0.216$) were both not significantly different between continued EGFR-TKIs groups and discontinued ones. However, when focusing on patients with non-dramatic progression, the median OS (29.0 months *vs*. 23.2 months, $p = 0.039$) and median PPS (21.3 months *vs*. 3.9 months, $p = 0.001$) were significantly longer in the continued EGFR-TKIs patients than discontinued ones.

DISCUSSION: Continued EGFR-TKIs beyond PD may be a good option for elderly patients with non-dramatic progression. The characteristic of progression after first-line EGFR-TKIs treatment should be taken into account to determine which part of patients is suitable for continued EGFR-TKIs treatment, especially for the speed of progression.

CONCLUSION: Continued EGFR-TKIs treatment promotes the survival of elderly patients with acquired resistance to EGFR-TKIs therapy.

Key Words:
Continued EGFR-TKIs, Progressive disease, NSCLC, Elderly patients, Non-dramatic progression.

Introduction

Erlotinib or gefitinib is epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), which has led to significant clinical improvement in certain patients with EGFR mutations[1]. Several randomized phase III studies[2-4] had proved that the progression-free survival (PFS) was significantly longer in patients who received EGFR-TKIs than in those who underwent cytotoxic chemotherapy. Despite the marked benefits of EGFR-TKIs in NSCLC with EGFR mutant, most cases ultimately develop resistance to these drugs after a median of 9 to 13 months[5]. In clinical practice, continued EGFR-TKIs still benefited patients with EGFR-mutant lung cancer, who acquired resistance to Erlotinib or gefitinib[6], suggesting that some tumor cells remained sensitive to EGFR-TKIs[7]. However, strategies for the treatment of resistant tumors are still controversial, and have not been investigated well. On the one hand, Nishie et al[8] in 2012 suggested that continued EGFR-TKIs beyond PD prolonged overall survival compared with switching to cytotoxic chemotherapy. And Yoshimura et al[7,9] in 2013 indicated that Erlotinib or gefitinib followed by the addition of pemetrexed showed favorable response and acceptable toxicity for patients beyond PD. On the other hand, Kanda et al[10] in 2015 indicated that platinum-doublet chemotherapy might prevent the development of acquired resistance to EGFR-

Corresponding Author: Chang-ting Liu, Ph.D; e-mail: liuchangting1357@sina.com

TKIs in patients, and prolonged survival compared with continued EGFR-TKIs. We hypothesized that the characteristics of progression of patients during the first-line EGFR-TKIs treatment determined the application of continued EGFR-TKIs. In addition, elderly patients have been underrepresented in clinical trials. The lack of data for elderly patients could result in suboptimal or excessively toxic treatments. These small molecular agents are more easily accepted by elderly patients because they are less toxic, which allows more favorable tolerability. Therefore, continued EGFR-TKIs beyond progression disease (PD) seems a reasonable option for elderly patients whose disease was controlled by first-line EGFR-TKIs treatment.

Lung cancer is the most frequently diagnosed type of cancer and the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) comprises more than 80% of all lung tumors[11]. Approximately two-thirds of NSCLC are diagnosed at advanced stages[12]. 47% of patients with lung cancer are > 70 years[13]. Although the incidence and mortality of lung cancer have decreased in patients with < 50 years, this is not the case for patients with > 70 years[14,15]. For a variety of reasons, only 66% of elderly patients receive any cancer treatment, and only 45% of those are treated with a standard combined chemotherapy and radiation[16]. Therefore, an effective therapeutic approach for lung cancer especially of elderly patients was necessary.

Aim

Here, we investigated whether continued EGFR-TKIs treatment in elderly patients prevented the development of acquired resistance to EGFR-TKIs in patients with advanced NSCLC harboring EGFR. And the characteristics of progression were identified to determine the potential biomarkers for application of EGFR-TKIs treatment beyond PD. Our study further suggested that continued EGFR-TKIs were still potential therapeutic strategy for elderly patients in non-dramatic progression group with acquired resistance to EGFR-TKIs

Patients and Methods

Patients

A total of 232 NSCLC patients (≥ 70-year-old) were recruited from the Chinese People's Liberation Army (PLA) General Hospital between January 1, 2009, and July 31, 2014. The last available follow-up was March 31, 2015. Forty-four patients were qualified for further investigation in our study (Figure 1), and all had experienced disease control for first-line EGFR-TKIs treatments (Partial Response or Stable Disease) after first-line treatment. Three independent radiologists and three oncologists conducted radiological assessments and judgments, and assessment results were all confirmed after careful discussion. The study complied with the Declaration of Helsinki, and was approved by the Institutional Ethics Re-

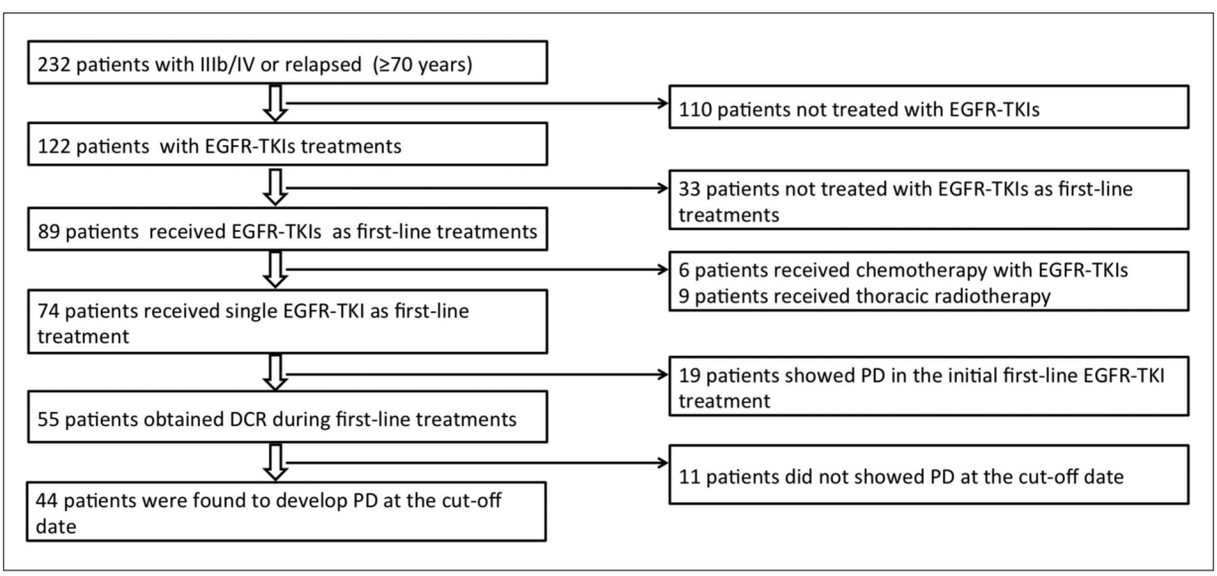

Figure 1. The screening process of qualified patients.

view Board at the Chinese PLA General Hospital. Written informed consent was obtained from all patients.

Evaluative Criteria

Response to continued EGFR-TKIs treatment was evaluated using RECIST version 1.1. Overall survival (OS) was defined as a period from the start of first-line EGFR-TKIs treatment to the date of death or to the date at which the patient was last known to be alive. Post-progression survival (PPS) was defined as the period from the first PD after first-line treatment of EGFR-TKIs to the date of death. Progression-free survival 1 (PFS1) was identified as the period from the start of EGFR-TKIs treatment to the first PD. PFS2 was defined as the period from the first PD to the second PD or death. Here, PFS1 was categorized into two modes: non-dramatic and dramatic progression. Dramatic progression was defined as rapid tumor progression with sudden worsening of symptoms during first-line EGFR-TKIs treatment. The other was identified as non-dramatic progression.

Statistical Analysis

Clinical characteristics were analyzed using Fisher's exact test. Survival analyses were analyzed using Kaplan-Meier method. The differences between the two groups were tested using the log-rank test. Multivariate analysis for survival was performed using a Cox regression model. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

The median age of these 44 patients was 81.2 years (70-96 years). 32/44(72.7%) patients were ≥ 80 years and the majority was male (90.9%). Nearly 20% patients were non-adenocarcinoma, including five patients with squamous cell carcinoma. Thirty-three patients were treated with continued EGFR-TKIs beyond PD. Of these patients, 14 patients (42.4%) discontinued any treatment after PFS2, and the other 19 patients (57.6%) received subsequent treatments after PFS2. Of these 19 patients, 10 patients switched from EGFR-TKIs to cytotoxic chemotherapy: gemcitabine/carboplatin (1), nab-paclitaxel/carboplatin (2), pemetrexed/cisplatin (3), docetaxel (4), pemetrexed (5), S-1 (6) and nab-paclitaxel (7). The other 9 patients' subsequent treatment included: radiotherapy (1), CIK (2), sunitinib (3), sorafenib (4), TACE (transhepatic arterial chemotherapy and embolization) (5), everolimus (6). In addition, of these 44 patients, EGFR mutation status was identified in 20 patients, 16 patients of whom were harboring active driver mutation (including 5 patients with exon 19 deletion, and 11 patients with exon 21 L858R point mutation). In order to further investigate the role of continued EGFR-TKIs in this group of patients, the median duration of continued EGFR-TKIs treatment beyond PD was calculated (5.9 months), and consequently served as the time used to divide the patients into two groups, including long-term EGFR-TKIs group and short-term EGFR-TKIs group (Table I).

According to the comparison of patients who continued EGFR-TKIs beyond PD and those who did not, we identified that only the characteristic "the duration of EGFR-TKIs treatment beyond PD" showed a significant difference (detailed in Table II).

Survival

For these 44 patients, the median PFS1 was 11.8 months (95% confidence interval [CI]: 7.8-15.8 months) and median OS was 24.1 months (95% CI: 17.7-30.5 months) (Figure 2). Univariate analysis showed that median OS was 28.9 months in patients who continued to take EGFR-TKIs beyond PD, and 22.5 months in those who discontinued EGFR-TKIs. There was no significant difference between the two groups (p = 0.131). However, there was a significant difference in the median PPS between the two groups (16.9 months *vs.* 3.9 months, p = 0.006). Moreover, when we further investigated the progression in PFS1, we found in non-dramatic progression group, those patients who treated with continued EGFR-TKIs achieved better median PPS and OS outcomes than those who discontinued EGFR-TKIs treatment (Figure 3A&B; PPS: 21.3 months *vs.* 3.9 months, p = 0.001; OS: 29.0 months *vs.* 23.2 months, p = 0.039, respectively), but we did not conclude the same results in dramatic progression group.

Here, 33 (75%) patients continued EGFR-TKIs beyond PD after their first-line treatment. Of these 33 patients, 6 patients (75.0%) had oligo-metastasis, 12 patients (66.7%) showed existing lesion progression, and 15 patients (83.3%) showed dramatic progression. The median PFS1 of these patients was 12.1 months (95% CI 10.0-

Table I. Characteristics of 44 patients.

	Characteristics	Number (%)
Age group	70-80	12 (27.3)
	≥ 80[a]	32 (72.7)
Sex	Male	40 (90.9)
	Female	4 (9.1)
Smoking status	Never	18 (40.9)
	Ex/Current	26 (59.1)
ECOG PS	0-2	25 (56.8)
	≥ 3	19 (43.2)
Histology	Adenocarcinoma	36 (81.8)
	Non-adenocarcinoma[b]	8 (18.2)
Stage	Recurrence[c]	19 (43.2)
	IIIb/IV	25 (56.8)
First-line EGFR-TKIs	Gefitinib	28 (63.6)
	Erlotinib	16 (36.4)
EGFR-TKIs Response	Partial Response (PR)	16 (36.4)
	Stable Disease (SD)	28 (63.6)
Type of progression	Oligo-metastasis[d]	8 (18.2)
	Existing lesion	18 (40.9)
	Dramatic progression	18 (40.9)
Continued EGFR-TKIs	YES[e]	33 (75)
	No[f]	11 (25)
Duration of EGFR-TKIs administration beyond PD	≥ 5.9 m	22 (50%)
	< 5.9 m	22 (50%)

[a]Range: 80-96 years old. $s \pm \bar{x}$: 83.86 ± 4.036. [b]Five patients were diagnosed as squamous cell carcinoma. Two patients were diagnosed as large cell carcinoma. One patient was diagnosed as atypical carcinoid mixed with bronchioloalveolar carcinoma (BAC). [c]Eleven patients were relapsed after prior to surgery, and eight patients were relapsed prior to definitive radiotherapy. [d]One patient was diagnosed as adrenal gland metastases. Two patients were diagnosed as contra-lateral lung metastases. Two patients were diagnosed as brain metastases. One patient was diagnosed as liver metastases. Two patients were diagnosed as spine or bone metastases. [e]Seven patients received gefitinib as first-line treatment and continued gefitinib treatment beyond PD, whereas eight patients switched to erlotinib. Six patients received erlotinib as first-line treatment and continued erlotinib beyond PD, where two patients switched to gefitinib. [f]Two patients switched to chemotherapy, one patients received radiochemotherapy. Three patients received palliative local radiotherapy. Two patients received bio-treatments and three patients discontinued treatments.

Table II. The comparison of patients of continued EGFR-TKIs beyond PD with those of discontinued EGFR-TKIs.

		Continued EGFR-TKIs beyond PD		
		Yes	No	p
Age	< 80	10	1	0.408
	≥ 80	24	9	
Stage	IIIb/IV	16	3	0.474
	Recurrence	18	7	
Smoking	No	14	4	0.892
	Yes	19	6	
Initial EGFR-TKIs response	PR	15	1	0.067
	SD	19	9	
PS score	0-2	22	3	0.074
	≥ 3	12	7	
Dramatic progression	No	19	7	0.489
	Yes	15	3	
Duration of EGFR-TKIs administration beyond PD	≥ 5.9 m	22	0	0.001
	< 5.9 m	12	10	

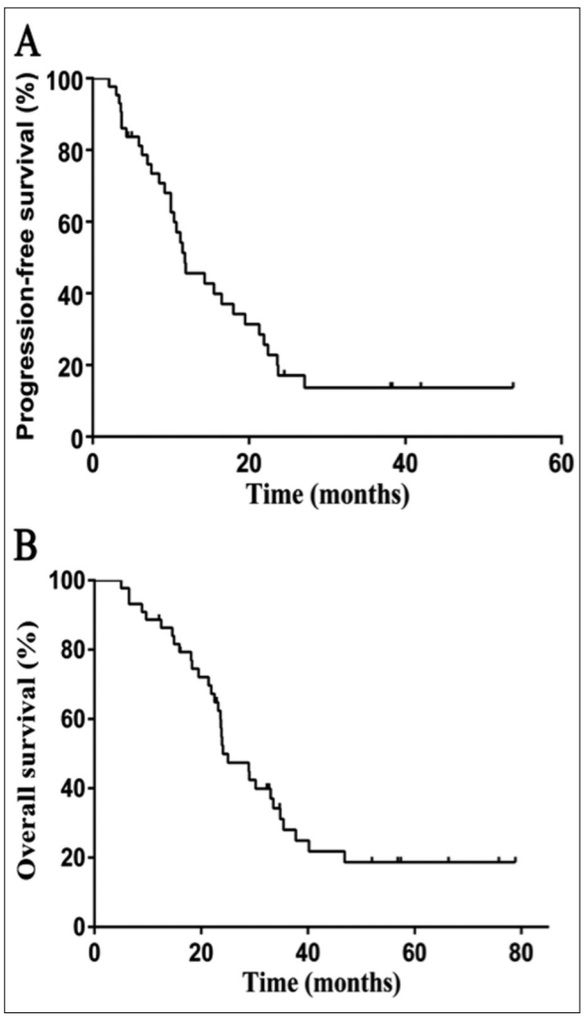

Figure 2. Kaplan-Meier analysis for PFS1 ***(A)*** and OS ***(B)*** in all patients (n = 44).

12.9 months) and median PFS2 was 4.7 months (95% CI: 2.9-6.5 months). Median PFS1 did not differ significantly between non-dramatic and dramatic progression groups (14.3 months *vs.* 11.2 months, $p = 0.227$). Moreover, the median PFS2 of patients with non-dramatic progression showed 7.0 months (95% CI: 2.3-11.7), and patients who showed dramatic progression were 4.6 months (95% CI: 0.6-3.4). This difference was statistically significant, $p = 0.037$ (Figure 3C). PPS showed similar results. The median PPS was 21.3 months (95% CI: 13.0-29.6 months) in the non-dramatic progression group and 12.0 months (4.7-19.3 months) in the dramatic progression group ($p = 0.003$) (Figure 3D).

The range of continued EGFR-TKIs treatment beyond PD was 0-35 months and the median duration beyond PD was 5.9 months. According to this time, the patients were divided into long-term (≥ 5.9 months) and short-term (< 5.9 months) groups. It was here noted that median PPS and median OS were significantly longer in patients who underwent long-term EGFR-TKIs treatment than in those who underwent short-term treatment (PPS 19.8 months *vs.* 6.1 months, $p = 0.013$; OS 33.0 months *vs.* 21.9 months, $p = 0.034$) (Figure 3E & 3F).

Results of univariate analysis for median OS are shown in Table III. Multivariate analysis of prognostic factors was performed in a Cox proportional-hazards model. Results showed that a good PS (0-2) (hazard ratio [HR] 6.8, 2.5-18.4, $p = 0.000$), adenocarcinoma (hazard ratio [HR] 3.9, 1.7-9.5, $p = 0.002$), non-dramatic progression (hazard ratio [HR] 4.9, 2.1-11.3, $p = 0.000$) and long-term duration of continued EGFR-TKIs (hazard ratio [HR] 1.9, 1.2-3.3, $p = 0.042$) were associated with the longer survival (Table IV).

Discussion

This retrospective clinical study was designed for elderly patients with advanced NSCLC harboring EGFR and acquired resistance to EGFR-TKIs. We determined that the median PFS1 and median OS of the whole group of patients were 11.8 months and 24.1 months respectively, which was in accordance with several large clinical studies for continued EGFR-TKIs treatment (median PFS: 10.5 months in NEG002 and 13.7 months in OPTIMAL; median OS: 27.7 months in NEG002 and 22.7 months[4,17]. This confirmed the accuracy of our results.

Kenichi et al[8] retrospectively analyzed a group of Japanese patients who either continued EGFR-TKI or switched to chemotherapy beyond PD. Continued EGFR-TKIs was associated with better survival based on multivariate analyses (HR 0.42, 95%CI 0.21-0.83, $p = 0.103$). Chaft et al[6] evaluated 61 EGFR-mutant NSCLC patients with acquired resistance; these patients mandated EGFR-TKIs discontinuation before administration of other treatment. Then 14 patients performed disease flare-ups, occurring at 8th day after EGFR-TKIs discontinuation. Faehling et al[18] reported that long-term erlotinib administration for treatment of NSCLC patients beyond PD leading to prolonged OS. These studies all suggested that clinical benefit might be still sus-

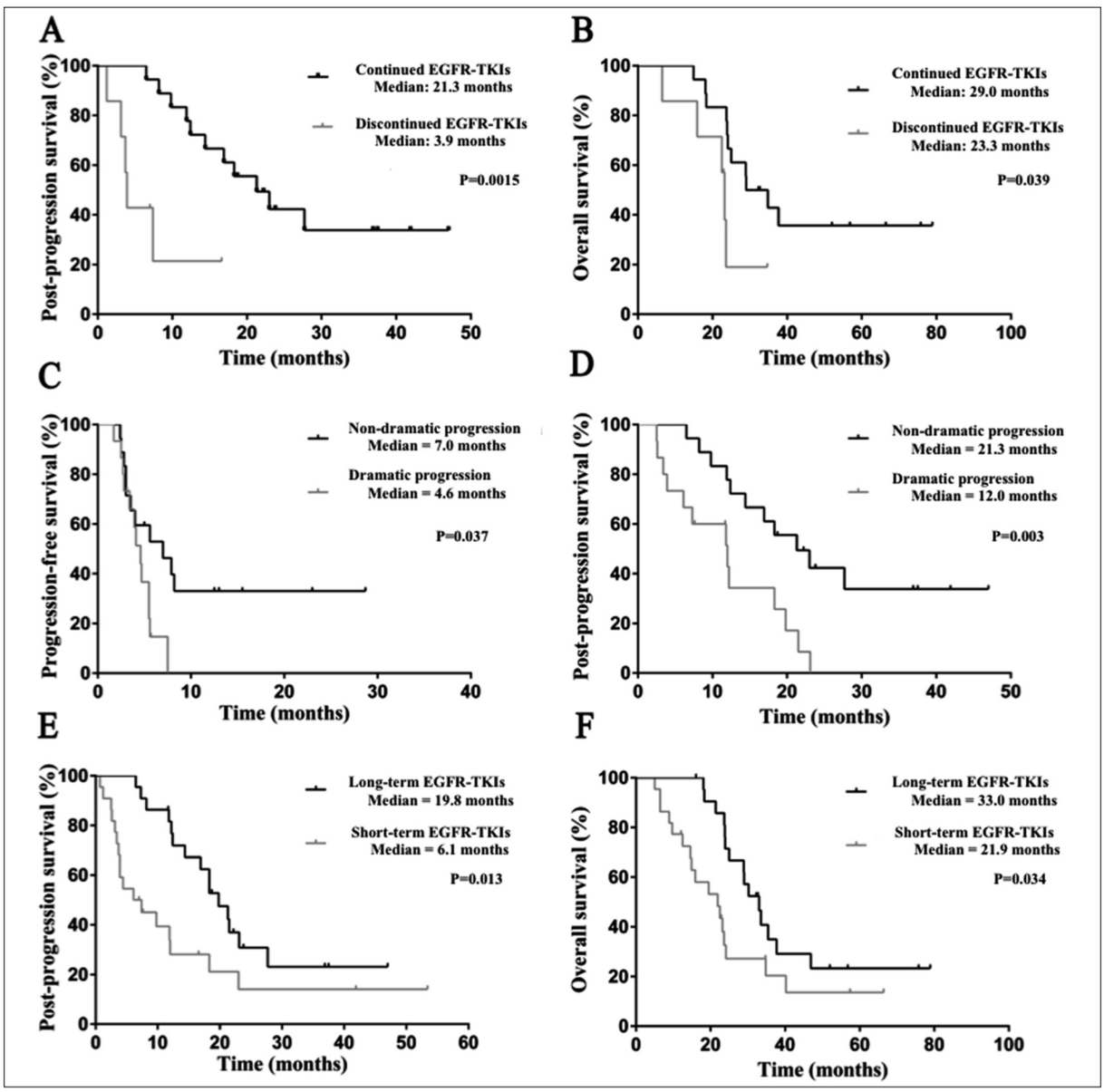

Figure 3. ***A,*** Subgroup analyses. ***A-B,*** Kaplan-Meier curve for PPS and OS in the non-dramatic progressed population compared with patients who continued EGFR-TKIs and those who did not. ***C-D,*** Kaplan-Meier curve for PFS2 and PPS in the continued EGFR-TKIs population by different types of progression of PFS1. ***E-F,*** Kaplan-Meier curve for PPS and OS by median duration of EGFR-TKIs treatment beyond PD.

tained by continued EGFR-TKIs treatment. Oxnard et al[19] explained this phenomenon *in vitro* using EGFR-mutant NSCLC cell lines. They indicated that resistant tumors are likely a mixed population of EGFR-TKIs-sensitive and resistant cells. Then continued EGFR-TKIs treatment along with chemotherapy after PD may target both cell populations more effectively than chemotherapy alone.

However, at the 2014 ESMO conference, a phase III double-blind IMPRESS study evaluated the efficacy of continued gefitinib plus cisplatin/pemetrexed *vs.* placebo plus the same chemotherapy regimen in patients with acquired resistance to first-line gefitinib. Results showed that continued gefitinib along with chemotherapy did not promote better OS than the doublet chemotherapy alone group, and might lead to worse OS.

Table III. Univariate analysis for OS for different characteristics of patients.

Characteristics	Variables	Patients (n)	Median OS (months)	95% CI	*p*
Sex	Male	40	23.9	22.1-25.8	0.475
	Female	4	28.9	3.9-53.9	
Age	< 80	12	29	22.8-34.6	0.022
	≥ 80	32	24.1	21.8-26.4	
Smoking	Never	18	29	12.6-45.4	0.062
	Current/EX	26	23.8	18.1-29.5	
ECOG PS	0-2	25	33.5	26.5-40.5	0.004
	> 2	19	23.7	22.0-25.4	
Histology	Adenocarcinoma	36	29	18.4-39.7	0
	Non-adeno	8	14.9	10.2-19.6	
Stage	Recurrence	19	33.5	27.4-39.6	0.095
	IIIb/IV	25	23.6	21.8-25.4	
EGFR-TKIs response	PR	16	30.2	17.1-43.3	0.077
	SD	28	23.6	21.3-25.9	
Continued EGFR-TKIs after 1st PD	Yes	33	28.9	29.6-37.1	0.462
	No	11	23.2	12.4-32.6	
Dramatic progression	Yes	18	21.9	16.6-27.2	0.018
	No	26	28.9	21.0-36.8	
Duration of continued EGFR-TKIs after 1st PD	Short-term group	22	21.9	12.2-31.6	0.034
	Long-term group	22	33	27.0-39.9	

Our results showed that median OS and median PPS were not significantly different between the continued and discontinued EGFR-TKIs group. This may indicate that not all patients should continue EGFR-TKIs beyond PD. Physicians need to determine which patients should continue EGFR-TKIs or what kind of patients would benefit the most from continued EGFR-TKIs treatment. Yang et al[20] classified different types of EGFR-TKIs failure modes in NSCLC. Results showed that median PFS and OS differed significantly among these grouping models. In the gradual progression group, continued EGFR-TKIs promoted longer OS than switching to chemotherapy (39.4 months *vs.* 17.8 months; $p = 0.02$). In the current study, results showed that patients with non-dramatic progression can achieve better OS and PPS by continued EGFR-TKIs treatment, but this was not the case in the dramatic progression group. Patients with non-dramatic progression continued to benefit from EGFR-TKIs treatment, perhaps because tumor cells retain certain sensitivity to EGFR-TKIs. EGFR-TKIs can still control the cloning of this part of cells. Dramatic progression demonstrated higher tumor burden and more secondary mutant tumor cells, which caused resistance to EGFR-TKIs.

The present study had performed that too few individuals were found to have received subsequent chemotherapy. Only 3 patients switched to chemotherapy after PD. It was not then possible to further compare the survival results of continued EGFR-TKIs with those of switching to chemotherapy. The main reason for this may be the fast deterioration of general physical condi-

Table IV. Multivariate analysis for OS.

Variables		HR	RR 95% CI	*p*-value
PS score	0-2	1	2.5-18.4	0
	> 3	6.8		
Adenocarcinoma	Yes	1	1.7-9.5	0.002
	No	3.9		
Non-dramatic progression	Yes	1	2.1-11.3	0
	No	4.9		
Duration of continued EGFR-TKIs after 1st PD	Long-term	1	1.2-3.3	0.042
	Short-term	1.9		

tion. The ECOG PS score quickly dropped to 3-4 when PD took place. Under these circumstances, the elderly patients were unable to tolerate cytotoxic chemotherapy and most of them had to choose best supportive care. The other reason, more common, is the patients' own decisions. Most of them were reluctant to switch from the relatively comfortable EGFR-TKIs to chemotherapy.

Of 33 patients who continued EGFR-TKIs beyond PD, median PFS1 was not significantly different between the non-dramatic and dramatic progression groups (14.3 months *vs.* 11.2 months, $p = 0.227$). This may indicate that tumor cells initially performed sensitivity with little difference to EGFR-TKIs. Despite this, with anti-tumor treatment, tumor cells tended to respond differently to continued EGFR-TKIs, thus, leading to different rates of progression. As a result of that, median PFS2 and median PPS were both significantly different between patients of non-dramatic and dramatic progression group. The disadvantage of dramatic progression transformed into poor survival outcome, which further indicated that continued EGFR-TKIs is not a suitable option for this group of patients.

ASPIRATION study had showed that continued Erlotinib beyond PD is feasible, and the median duration of continued EGFR-TKIs beyond PD was 3.7 mouths. Asami et al[21,22] set a period of 3 months after PD as the median duration of gefitinib treatment and this value was found to be suitable for analysis in terms of survival time. Here, the patients were divided into 2 groups by median duration of continued EGFR-TKIs beyond PD (5.9 months). This period is much longer than that used in the aspiration or Asami's studies, probably because the participants in the current study were all elderly patients, who were prone to EGFR-TKIs treatment, rather than switching to other treatment. Results showed that both OS and PPS were significantly longer in the long-term group than in the short-term group. Long-term EGFR-TKIs treatment was also a good independent prognostic factor with the multivariate analysis.

The current study has some limitations. The number of patients is little. And the identification for non-dramatic group and dramatic group was still depended on the determination of tumor progression with sudden worsening of symptoms by professor, which should be further investigated to find biomarkers. Then, the non-dramatic group or dramatic group was not further subdivided in survival analysis. The mechanism of acquired resistance has been studied intensively and reports indicating that half the relapsed patients had a T790M, and approximately 20% patients experienced MET amplification[23]. Unfortunately, in the current study, screening of molecular information was performed in only a very few cases and no one underwent a re-biopsy after PD.

Conclusions

Continuation of EGFR-TKIs beyond PD may be a good option for elderly patients who do not experience dramatic progression. However, further investigation of treatment after the failure of EGFR-TKIs is needed to determine and novel drugs should be developed to overcome the resistance to EGFR-TKIs.

Acknowledgements

We thank the financial support from Chinese People's Liberation Army General Hospital.

Ethical Approval

We thank the financial support from Chinese People's Liberation Army General Hospital.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Ohashi K, Maruvka YE, Michor F, Pao W. Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. J Clin Oncol 2013; 31: 1070-1080.

2) Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E,

Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. 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: 239-246.

3) Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M; West Japan Oncology Group. 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: 121-128.

4) Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Yiping, Xiu Q, Ma J, Zhang L, You C. 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: 735-742.

5) Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, Iafrate AJ, Mino-Kenudson M, Engelman JA. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011; 3: 75ra26.

6) 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: 6298-6303.

7) Riely GJ, Kris MG, Zhao B, Akhurst T, Milton DT, Moore E, Tyson L, Pao W, Rizvi NA, Schwartz LH, Miller VA. 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: 5150-5155.

8) Nishie K, Kawaguchi T, Tamiya A, Mimori T, Takeuchi N, Matsuda Y, Omachi N, Asami K, Okishio K, Atagi S, Okuma T, Kubo A, Maruyama Y, Kudoh S, Takada M. Epidermal growth factor receptor tyrosine kinase inhibitors beyond progressive disease: a retrospective analysis for Japanese patients with activating EGFR mutations. J Thorac Oncol 2012; 7: 1722-1727.

9) Liang Y, Lu P. Health-related quality of life and the adaptation of residents to harsh post-earthquake conditions in China. Disaster Med Public 2014; 8: 390-396.

10) Kanda S, Horinouchi H, Fujiwara Y, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Kubota K, Tamura T, Ohe Y. Cytotoxic chemotherapy may overcome the development of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. Lung Cancer 2015; 89: 287-293.

11) Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends-an update. Cancer Epidem Biomar 2016; 25: 16-27.

12) Zhu J, Sharma DB, Gray SW, Chen AB, Weeks JC, Schrag D. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA 2012; 307: 1593-1601.

13) Chen YM, Tsai CM, Fan WC, Shih JF, Liu SH, Wu CH, Chou TY, Lee YC, Perng RP, Whang-Peng J. Phase II randomized trial of erlotinib or vinorelbine in chemonaive, advanced, non-small cell lung cancer patients aged 70 years or older. J Thorac Oncol 2012; 7: 412-418.

14) Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics 2014. CA Cancer J Clin 2014; 64: 9-29.

15) Liang Y, Cao R. Employment assistance policies of Chinese government play positive roles. The impact of post-earthquake employment assistance policies on the health-related quality of life of Chinese earthquake populations. Soc Indic Res 2015; 120: 835-857.

16) DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, Alteri R, Robbins AS, Jemal A. Cancer treatment and survivorship statistics, 2014. Ca Cancer J Clin 2014; 64: 252-271.

17) Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-2388.

18) Faehling M, Eckertb R, Kampb T, Kuoma S, Griesec U, Sträterd J, Ottc G, Spenglere W. EGFR-tyrosine kinase inhibitor treatment beyond progression in long-term Caucasian responders to erlotinib in advanced non-small cell lung cancer: a case-control study of overall survival. Lung Cancer 2013; 80: 306-312.

19) Oxnard GR, Arcila ME, Chmielecki J, Ladanyi M, Miller VA, Pao W. New strategies in overcoming acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in lung cancer. Clin Cancer Res 2011; 17: 5530-5537.

20) Yang JJ, Chen HJ, Yan HH, Zhang XC, Zhou Q, Su J, Wang Z, Xu CR, Huang YS, Wang BC, Yang XN,

Zhong WZ, Nie Q, Liao RQ, Jiang BY, Dong S, Wu YL. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. Lung Cancer 2013; 79: 33-39.

21) Asami K, Okuma T, Hirashima T, Kawahara M, Atagi S, Kawaguchi T, Okishio K, Omachi N, Takeuchi N. Continued treatment with gefitinib beyond progressive disease benefits patients with activating EGFR mutations. Lung Cancer 2013; 79: 276-282.

22) Liang Y, Wang P. Influence of prudential value on the subjective well-being of Chinese urban-rural residents. Soc Indic Res 2014; 118: 1249-1267.

23) Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Jänne PA. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007; 316: 1039-1043.