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Original Article

Continuous epidermal growth factor receptor-tyrosine kinase inhibitor administration in primary lung adenocarcinoma patients harboring favorable mutations with controlled target lung tumors dose not hinder survival benefit despite small new lesions

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ABSTRACT

Background: In this study, we investigated the efficacy of continuous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) administration in lung adenocarcinoma patients harboring favorable mutations regarding the progressive disease (PD) status with appearance of indolent new lesions.

Methods: From June 2010 to October 2012, 102 patients with lung adenocarcinoma, harboring favorable EGFR mutations and treated with EGFR-TKI were analyzed. Definite new lesions were detected during EGFR-TKI therapy, even though the primary target tumors were controlled.

Results: Of the 102 patients, 57 continued and 45 discontinued EGFR-TKI therapy. The median overall survival was 529 days for the discontinuation group and 791 days for the continuation group ($p = 0.0197$). Median survival time after the discontinuation of EGFR-TKI was 181 days and 115 days in the discontinuation and continuation groups, respectively ($p = 0.1776$), whereas median survival time after the appearance of indolent new lesions was 204 days and 262 days, respectively ($p = 0.0237$).

Conclusion: Continuous EGFR-TKI administration in favorable EGFR-mutative lung adenocarcinoma patients with controlled primary tumors did not hinder the survival benefit, despite the appearance of new lesions.

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At a glance commentary

Scientific background of the subject

Some advance lung adenocarcinoma patients, harboring favorable epidermal growth factor receptor mutation, who were receiving epidermal growth factor receptor-tyrosine kinase inhibitor, were detected with small new lesions in the follow-up images, which defined progressive disease by RECIST criteria. However, these patients had controlled primary target lesions with stable clinical condition.

What this study adds to the field

For advance lung adenocarcinoma patients, harboring favorable epidermal growth factor receptor mutation, even the appearance of small new lesions while receiving EGFR-TKI. Continuous EGFR-TKI administration did not hinder the overall survival and survival time after the occurrence of new lesions in patients with controlled primary target lesions.

Lung cancer is a leading cause of cancer-related deaths in both male and female patients worldwide [1]. Nonsmall cell lung cancer (NSCLC) accounts for approximately 85% of primary lung cancers and approximately 40% are adenocarcinoma [2,3]. The prognosis of the most nonresectable lung cancers (approximately 80% of NSCLCs) is poor, with a mean survival of 8–14 months [4]. Anti-epidermal growth factor receptor (EGFR) agents have been developed as a treatment for NSCLC and as an alternative to conventional chemotherapy [5–8]. A subset of patients harboring favorable EGFR mutations, such as an exon 19 deletion and L858R, benefit from EGFR targeted therapy [9,10]. However, most patients eventually develop the progressive disease (PD) because of acquired resistance, which might be related to a second-site EGFR mutation, MET amplification, or other factors [11].

Previous reports have only described the progression of local lesions without the representation of systemic resistance; therefore, the clinical definition of acquired resistance for NSCLC is unclear [12–16]. Our preliminary data showed that lung adenocarcinoma patients treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and who had progression-free survival (PFS) of more than 6 months, developed new lesions, but remained clinically stable when EGFR-TKI was continued [17]. However, these patients were selected based only on the clinical efficacy of EGFR-TKI treatment with more than 6 months of PFS and they did not undergo analysis of the EGFR mutation because gene analysis was not performed routinely in clinical practice in our institute before 2009. New lesions are considered when a lesion is identified through follow-up imaging of an anatomic location without lesions at baseline [18]. The appearance of one or more new lesions is defined as PD by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.0, published in 2000) [19].

However, according to the revised RECIST 1.1 guidelines (2009), the first appearance of new lesions might not definitively indicate PD. If new lesions cannot be identified initially, treatment can be continued until the next scheduled assessment. Nonetheless, follow-up imaging that confirms the development of new lesions should also confirm PD [18], after which therapeutic agents should be altered. However, acute deterioration of disease after EGFR-TKI withdrawal has been reported in EGFR-mutant lung cancer patients with acquired resistance [14]. Furthermore, in clinical practice, some patients with a first appearance of new malignant lesions and PD have been observed to regain disease stability when the original EGFR-TKI treatment is continued [17].

The present study was intended to determine whether the survival of a subset of patients with EGFR mutative lung adenocarcinoma, with controlled target lesions, and new malignant lesions could be affected by discontinuing EGFR-TKI based on the appearance of new lesions, which are defined by RECIST, a PD status.

Methods

Study population

From June 2010 to October 2012, 486 patients diagnosed with stage IIIB or IV primary lung adenocarcinoma were tested for EGFR mutation status and were screened. All the patients were enrolled in the NHI program of Taiwan and received comprehensive and updated therapy for NSCLC. The patients were evaluated to determine the stage of the disease before the start of treatment, at regular intervals, and for disease progression or relapse. The disease stage was determined according to a complete medical history; physical examination; imaging survey, including chest X-ray (CXR) and computed tomography (CT) of the chest and abdomen; and additional staging procedures such as magnetic resonance imaging (MRI) of the head, bone scintigraphy, and fluorodeoxyglucose positron-emission tomography (FDG-PET). Tumor response was assessed during therapy, based on RECIST Version 1.0 or 1.1, depending on the respective year. Patient's lung cancer-related symptoms such as dyspnea, cough, hemoptysis, chest pain, and metastatic-lesion-related symptoms were recorded at each clinical visit or hospitalization. Clinical information was prospectively recorded following the Chang Gung Memorial Hospital (CGMH) lung cancer protocol and retrieved from the Cancer Registry System of the Cancer Center of CGMH.

Patient selection

The inclusion criteria were: (1) Patients with EGFR mutations that were sensitive to EGFR-TKI; (2) patients who had received EGFR-TKI therapy; (3) patients who were receiving EGFR-TKI therapy with controlled target primary lung tumors and preexisting metastatic tumors; (4) appearance of small new lesions in the follow-up images during EGFR-TKI therapy, defined as PD by RECIST; (5) patients who were asymptomatic or exhibited stable preexisting symptoms or mild symptoms

that did not deteriorate general condition or performance status. The exclusion criteria were: (1) Patients with wild-type EGFR or a mutation that was resistant to EGFR-TKI; (2) patients who had never received EGFR-TKI; (3) patients who were receiving EGFR-TKI treatment without PD status; (4) patients who had PD related to primary lung tumors or preexisting metastatic tumors; (5) patients who exhibited deterioration of preexisting symptoms or new symptoms that in turn deteriorated the general condition or performance status. The way of patient selection was summarized in Fig. 1.

Data for 102 patients with a mean age of 61.7 ± 13.0 years, favorable mutations of EGFR and exhibiting new lesions with controlled primary target lung, and preexisting metastatic lesions meeting the enrolled criteria were retrieved from the prospective recording and registry system. The retrospectively analyzed data included demographics (age and sex), initial lung cancer stage, performance status, smoking status, line of EGFR-TKI treatment and duration, PFS, overall survival (OS), survival before administration and after the discontinuation of EGFR-TKI, survival after the occurrence of new lesions (RECIST-defined PD), and site of the new lesions. The EGFR mutations were detected using direct sequencing and ARMS-Scorpion methods, which have been firmly established in the Central Molecular Lab of the Department of Pathology at CGMH, a College of American Pathologists-accredited laboratory.

Treatment after the appearance of small new lesions

All the patients received considerably close follow-up with CXR every 1–4 weeks and CT every 1–2 months for pulmonary tumors or other new lesions and MRI for bone or brain lesions to evaluate the treatment response and tumor progression. Pulmonary oncologists integrated information from the radiographic images and the speed of progression in the interval between the imaging studies to determine optimal therapy after re-staging. EGFR-TKI in the continuation group was used until PD of the primary target lung lesions, persistent progression of new lesions, or deterioration of related symptoms. In the continuation group, EGFR-TKI was continued for more than 1 month after the appearance of new lesions, and clinicians continued EGFR-TKI based on the principle of intent to treat, the patients' requests, and consideration of the benefits and tolerance of switching to chemotherapy. For the discontinuation group patients, EGFR-TKI was discontinued within 1-month of the appearance of new lesions with or without switching to another treatment.

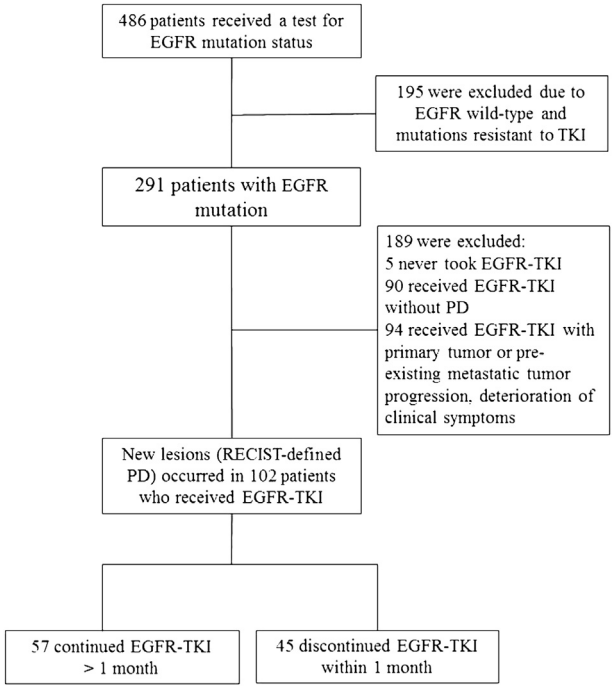

Fig. 1 – Patient selection flow chart.

Statistical analysis

Data are presented as means ± standard deviation except where otherwise mentioned. Because the data did not approximate a Gaussian distribution, a nonparametric statistical analysis, the Mann–Whitney U-test was performed for unpaired data to assess the significance of the difference between the two groups. Frequency distributions between the two groups were tested using the Chi-square or Fisher's exact probability tests. Survival rates were calculated using the Kaplan–Meier method, and a comparison of survival curves was based on the log rank test and hazard ratio (HR) was produced via Cox proportional hazards model. All the tests were two-sided and $p < 0.05$ was considered as statistically significant. GraphPad Prism (Version 5.0; GraphPad Software, San Diego, CA, USA) was used for all the statistical analyses.

Results

A representative patient with continued epidermal growth factor receptor-tyrosine kinase inhibitors after the appearance of indolent new lesions

A representative patient with metastatic lung adenocarcinoma was treated with cisplatin and paclitaxel for 6 cycles as first-line therapy. After 185 days of disease control, the tumor progressed [Fig. 2A]. An EGFR mutation test was conducted and a mutation of exon 19 deletion was detected. Therefore, gefitinib was administrated as the subsequent second-line treatment. After the administration of EGFR-TKI for 660 days, new brain lesions were detected in a follow-up brain MRI that was performed based on the complaints of mild dizziness. Because this patient had no other newly developing neural symptoms and the primary lung tumor was being controlled by EGFR-TKI treatment, the treatment was continued without switching or additional therapy such as brain irradiation. These brain lesions exhibited a stable disease status without progression, with the continuation of EGFR-TKI treatment. New lung lesions after 793 days of EGFR-TKI were detected in regular follow-up chest CT with controlled targeted lesions, but without alterations in clinical manifestations. The new lung nodules were stationary after the continuation of EGFR-TKI to 879 days [Fig. 2B–F]. Gefitinib was discontinued at day 935 because additional new lung lesions were appeared and the primary target lung tumor was

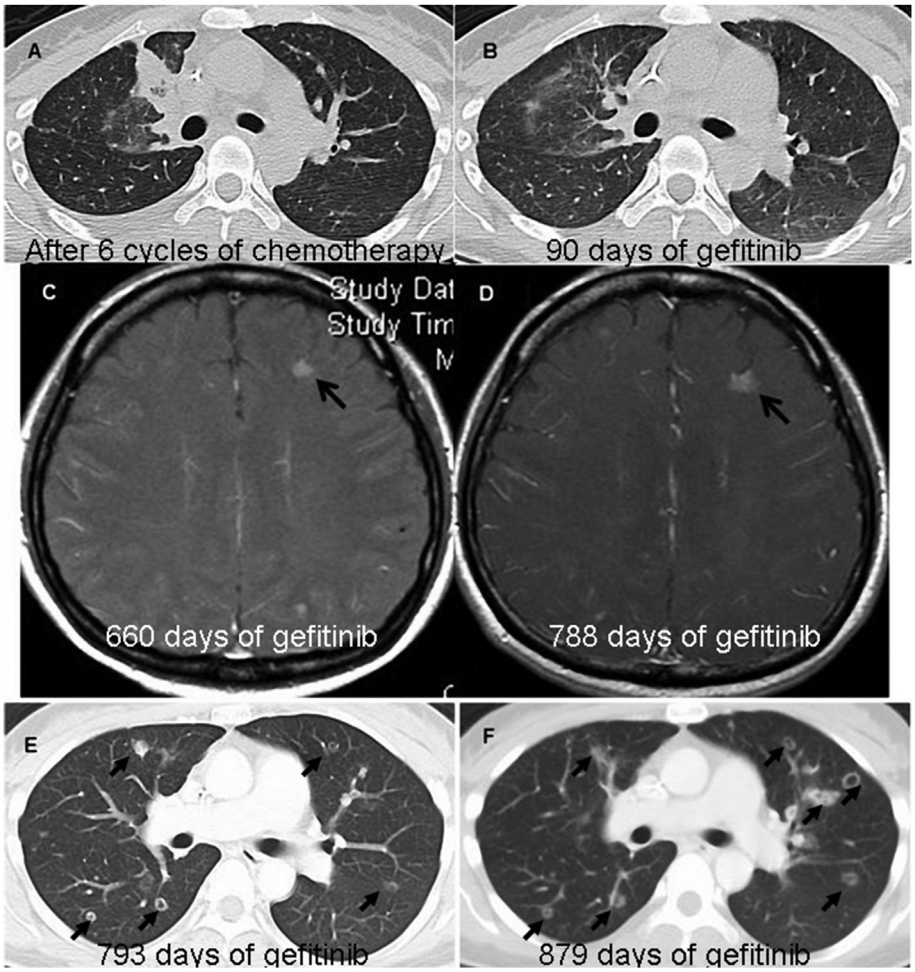

Fig. 2 – A patient with metastatic lung adenocarcinoma received 6 cycles of cisplatin plus paclitaxel as first-line chemotherapy. The primary lung tumor then enlarged with disease progression. The epidermal growth factor receptor mutation test revealed an exon 19 deletion mutation, and the patient then received gefitinib as subsequent second-line therapy. (A) Primary right upper lobe (RUL) lung tumor before second-line gefitinib treatment was administered. (B) Regression of the targeted RUL lung tumor after 90 days of gefitinib treatment. (C) First appearance of new brain lesions after 660 days of gefitinib treatment. (D) Stationary brain lesions after 788 days of gefitinib treatment. (E) First appearance of new, minute, nodular lung lesions after 793 days of gefitinib treatment. (F) More new, minute, and stationary nodular lung lesions after 879 days of gefitinib treatment.

enlarged, indicating PD deterioration. The treatment was switched to chemotherapy with pemetrexed, which was administered for 12 cycles as third-line therapy. Survival time after discontinuing EGFR-TKI was 336 days. In summary, this patient regained a stable clinical condition after continuing EGFR-TKI, even though new nodular lung and brain lesions were waxed and waned [Fig. 2].

Characteristics of patients with new lesions receiving epidermal growth factor receptor-tyrosine kinase inhibitors treatment

A total of 102 patients with advanced and metastatic lung adenocarcinoma, with sensitive mutations, and receiving EGFR-TKI treatment were analyzed [Table 1]. Eight patients (7.8%) were stage IIIB and 94 (92.2%) were stage IV. Forty-five patients discontinued EGFR-TKI treatment and received further management, whereas 57 patients continued EGFR-TKI treatment for more than 1 month after the appearance of new indolent lesions. Thirty-seven (75%) patients in the discontinuation group received EGFR-TKI treatment as first-line therapy, whereas 34 (59.6%) in the continuation group. Forty-three patients received gefitinib initially in the continuation group, among who continued gefitinib at the first appearance of new lesions and 2 switched to erlotinib for personal insurance reasons. The other 14 patients in the continuation group, who received erlotinib initially, continued the same targeted therapy. No significant difference was observed in the performance status between the continuation and discontinuation groups, after the occurrence of new lesions.

Among the 57 patients with continuous EGFR-TKI therapy, 17 had new lesions in the lung and 40 had extra-pulmonary new lesions. For the 45 patients in the discontinuation

Table 1 – Patient characteristics.

Characteristics	Total	EGFR-TKI		p
		Discontinued	Continued	
Number of patients	102	45	57	
Age (year)	61.7 ± 13.0	63.2 ± 11.7	60.5 ± 14.0	0.2431
Gender (male/female)	46/56	19/26	27/30	0.6040
Smoking (never/former + current)	76/26	34/11	42/15	0.4148
Stage (IIIB/IV)	8/94	3/42	5/52	0.4965
PS (0–1/2–4) at diagnosis	79/23	33/12	46/11	0.2586
PS (0–1/2–4) after new lesion	59/43	26/19	33/24	0.5748
EGFR mutation				
Exon 21 L858R	46	22	24	0.4942
Exon 19 deletion	50	21	29	0.6947
Other sensitive but rare mutations[a]	6	2	4	0.6917
Duration of EGFR-TKI treatment (days)	427 ± 236	358 ± 186	500 ± 264	0.0076
Duration of EGFR-TKI treatment after definite new lesions (days)	88 ± 110	14 ± 6	167 ± 112	0.0001
Progression-free survival with EGFR-TKI (median days)	263	279	254	0.6437
Overall survival (median days)	650	529	791	0.0197
Initial EGFR-TKI (gefitinib/erlotinib)	82/20	39/6	43/14	0.1210
Lines of EGFR-TKI				0.0527[b]
1st	71	37	34	0.0173
2nd	25	7	18	0.0687
3rd	6	1	5	0.2246
Overall survival of first-line EGFR-TKI patients (median days)	628 ($n = 71$)	518 ($n = 37$)	657 ($n = 34$)	0.0532
Overall survival of non-first-line EGFR-TKI patients (median days)	806 ($n = 31$)	865 ($n = 8$)	806 ($n = 23$)	0.9761
Time prior to EGFR-TKI use (median days)	25	19	32	0.2242
Survival time after the discontinuation of EGFR-TKI (median days)	163	181	115	0.1776
Survival time after definite new lesions (median days)	248	204	262	0.0237
Location of new lesions				
Lung lesions	23	6	17	0.0582
Nonlung lesions	79	39	40	0.0582
Number of organs with metastasis (mean, 95% CI)	1.67 ± 0.95	1.62 ± 0.91	1.70 ± 0.98	0.5695
Overall survival of lung new lesion patients (median days)	544 ($n = 23$)	732 ($n = 6$)	544 ($n = 17$)	0.7581
Overall survival of nonlung new lesion patients (median days)	644 ($n = 79$)	528 ($n = 39$)	748 ($n = 40$)	0.0080

Abbreviations: SD: Standard deviation; PS: Performance status; EGFR: Epidermal growth factor receptor; EGFR-TKI: Epidermal growth factor receptor-tyrosine kinase inhibitors; CI: Confidence interval.

[a] Other sensitive mutations: Exon 18 G719A (2), exon 19 E746G (1) exon 19 L747P (1), exon 20 S768I (1), exon 20 R776H (1), exon 21 L861Q (2). Two patients had double mutations and both were in the discontinuation group.

[b] Multiple contingency table analyses.

group, 6 had pulmonary new lesions and the other 39 had extra-pulmonary new lesions. The locations and characteristics of the new lesions are summarized in Supplementary Table 1.

Thirty patients were noted to have new lesion-related symptoms, which are summarized in Supplementary Table 2. No significant difference in these symptoms was observed among the groups. The median OS in the patients with new lesion-related symptoms was 650 days for the discontinuation group and 791 for the continuation group (HR: 1.311, 95% confidence interval [CI]: 0.5508–3.120, $p = 0.5407$) [Supplementary Table 2].

Progression-free survival and overall survival

The median time from diagnosis to the 1st time use of EGFR-TKI therapy was 19 days and 32 days for the discontinuation and continuation groups, respectively (HR: 1.294, 95% CI: 0.8540–1.294, $p = 0.2242$) [Fig. 3A]. PFS with EGFR-TKI therapy was 279 days for the discontinuation group and 254 days for the continuation group (HR: 1.028, 95% CI: 0.6404–1.65; $p = 0.6437$) [Fig. 3B]. The median OS was 529 days and 791 days for the discontinuation and continuation groups, respectively (HR: 1.839, 95% CI: 1.102–3.070, $p = 0.0197$) [Fig. 3C]. The median survival time after the discontinuation of EGFR-TKI was 181 days for the discontinuation group and 115 days for the continuation group (HR: 0.7106, 95% CI: 0.4332–1.166, $p = 0.1776$) [Fig. 3D]. Survival time after the appearance of definite new lesions (RECIST-defined PD) was 204 days and 262 days for the discontinuation and continuation groups, respectively (HR: 1.516, 95% CI: 0.9201–2.498, $p = 0.0237$) [Fig. 3E]. The PFS of first subsequent new treatment after EGFR-TKI was 125 and 92 days for the discontinuation and continuation groups, respectively (HR: 1.009, 95% CI: 0.6192–1.643, $p = 0.9724$) [Fig. 3F]. Particular subsets of patients in both groups were also analyzed [Table 1]. For patients receiving EGFR-TKI as first-line therapy, the median OS was 518 days for the discontinuation group and 657 days for continuation group (HR: 0.5455, 95% CI: 0.2952–1.0084, $p = 0.0532$). For patients with lung new lesions, the median OS was 732 days for discontinuation group and 544 days for the continuation group (HR: 1.204, 95% CI: 0.3692–3.927, $p = 0.7581$). For patients with nonlung new lesions, the median OS was 528 days for the discontinuation group and 748 days

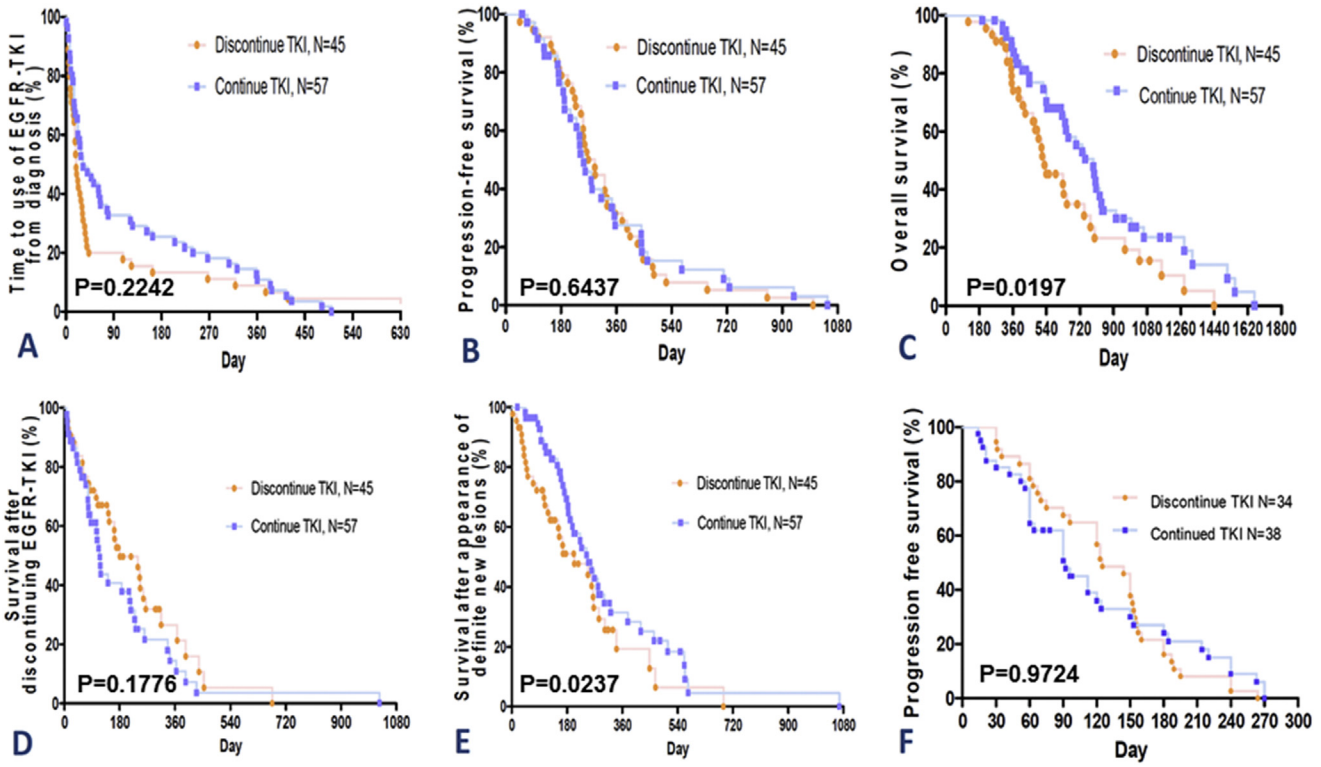

Fig. 3 – Survival proportion traced using the Kaplan–Meier method. (A) Median time to the use of epidermal growth factor receptor-tyrosine kinase inhibitors between the discontinuation and continuation groups was 19 versus 32 days (hazard ratio: 1.294, 95% confidence interval: 0.8540–1.294; $p = 0.2242$). (B) Median progression-free survival with epidermal growth factor receptor-tyrosine kinase inhibitors for the discontinuation and continuation groups: 279 and 254 days, respectively (hazard ratio: 1.028, 95% confidence interval: 0.6404–1.65; $p = 0.6437$). (C) Median OS for the discontinuation and continuation groups was 529 and 791 days, respectively (hazard ratio: 1.839, 95% confidence interval: 1.102–3.070; $p = 0.0197$). (D) Median survival time after the discontinuation of epidermal growth factor receptor-tyrosine kinase inhibitors for the discontinuation and continuation groups was 181 and 115 days, respectively (hazard ratio: 0.7106, 95% confidence interval: 0.4332–1.166; $p = 0.1776$). (E) Median survival time after the appearance of new lesions for the discontinuation and continuation groups was 204 and 262 days, respectively (hazard ratio: 1.516, 95% confidence interval: 0.9201–2.498, $p = 0.0237$). (F) The median progression-free survival of first-subsequent new treatment after epidermal growth factor receptor-tyrosine kinase inhibitors was 125 and 92 days for the discontinuation and continuation groups, respectively (hazard ratio: 1.009, 95% confidence interval: 0.6192–1.643, $p = 0.9724$).

for the continuation group (HR: 0.4537, 95% CI: 0.2528–0.8137, $p = 0.0080$).

Further management of new lesions and subsequent therapy after epidermal growth factor receptor-tyrosine kinase inhibitors treatment

The management at the appearance of new lesions and subsequent treatment are summarized in Table 2. After the appearance of the new lesions, 11 patients received additional radiation therapy and 46 continued with EGFR-TKI alone in the continuation group. Among the 45 patients, who discontinued EGFR-TKI therapy, treatment was switched from EGFR-TKI to chemotherapy alone in 25 patients, 16 received radiation therapy, 12 underwent chemotherapy accompanied with radiation therapy, and 2 received radiation therapy alone for the treatment of brain and bone lesions [Table 2].

Among the 57 patients in the EGFR-TKI continuation group, 38 received subsequent chemotherapy after EGFR-TKI was discontinued. Twenty-three patients in the continuation group were re-treated with EGFR-TKI after chemotherapy and 22 were re-treated with EGFR-TKI in the discontinuation group. Twenty-four (23.5%) patients received best supportive care after EGFR-TKI [Table 2].

Discussion

In clinical practice, indolent new lesions with controlled primary target lung lesions are observed in the follow-up images of patients who have lung adenocarcinoma harboring sensitive EGFR mutations and are receiving EGFR-TKI treatment. Some patients have been observed to have uncommonly long survival time and clinical stability when they received continuing EGFR-TKI treatment, even after the first appearance of new lesions. In the present study, further analysis of the patients with lung adenocarcinoma harboring sensitive EGFR mutations and receiving EGFR-TKI therapy showed that

Table 2 – Management after the appearance of new lesions and subsequent therapy after EGFR-TKI.

Management of new lesions	EGFR-TKI		p
	Discontinued	Continued	
Number of patients	45	57	
Radiation therapy	16	11	0.0744
Radiation therapy to brain	6	5	0.6794
Radiation therapy to bone	10	6	0.6974
EGFR-TKI alone	0	46	<0.0001
Systemic chemotherapy alone	25	0	<0.0001
EGFR-TKI combined radiation therapy	0	11	0.0021
Chemotherapy combined with radiation therapy	12	0	<0.0001
Subsequent therapy after EGFR-TKI			
Radiation therapy	16	12	0.1032
Chemotherapy	37	38	0.0770
Platinum-base doublet chemotherapy	21	23	0.7403
1 subsequent chemotherapy	22	20	0.5515
≥2 subsequent chemotherapies	15	18	0.5515
Re-treated with EGFR-TKI	20	23	0.6776
BSC	10	14	0.7821
Median PFS of subsequent new treatment			
Median PFS (days)	125	92	0.9724

Abbreviations: EGFR-TKI: Epidermal growth factor receptor-tyrosine kinase inhibitors; PFS: Progression-free survival; BSC: Best supportive care.

OS and survival after the occurrence of definite new lesions in patients receiving continued EGFR-TKI therapy were not inferior to those of the discontinuation group. These results suggested a possible dynamic balance between tumor growth and cell death on the continuation of reversible EGFR-TKI therapy, as indicated by the central attenuated nodules and waxing and waning tumor size in the patients. Differences in the histological growth patterns and molecular characteristics of lung adenocarcinoma may influence the clinical outcome [20]. Some tumor cells can remain sensitive to EGFR-TKI after the occurrence of new lesions, which can complicate the decision-making, regarding the selection of therapeutic agents when new lesions or PD occurs [18].

Most patients with EGFR-mutant lung adenocarcinoma, receiving EGFR-TKI treatment, develop PD after a median time of 10–16 months [21]. Acquired resistance to EGFR-TKI may involve a reversible "drug-tolerant" state, the mechanism of which must be established; furthermore, the contributions of specific resistance-conferring mutational and nonmutational mechanisms and the role of tumor cell subpopulations to drug resistance remain unclear [22]. A previous study reported that in NSCLC patients, who were initially responded, but later developed acquired resistance to EGFR-TKI, gefitinib, or erlotinib, discontinuing EGFR-TKI, resulted in symptomatic progression and increased tumor size [13]. Symptoms were improved and tumor size was decreased after restarting EGFR-TKI, suggesting that a proportion of cells in a resistant tumor cell population remain sensitive to EGFR and that EGFR-TKI may be beneficial even after the RECIST-defined PD [13]. A recent study also showed that EGFR-TKI re-treatment can be effective after failure of initial gefitinib treatment [16], and some EGFR-mutant lung cancer patients with PD experienced disease flare after discontinuing EGFR-TKI and after initially benefiting from erlotinib or gefitinib [14].

Re-treatment with erlotinib can be helpful even for NSCLC patients who initially get benefit from previous EGFR-TKI treatment and progress after standard cytotoxic chemotherapy [15]. Another recent study showed the possible benefit of continuous EGFR-TKI administration following radiotherapy after PD in isolated CNS metastasis [12]. Yang et al. [23] reported that the continuation of EGFR-TKI yielded longer OS in a certain subgroup of NSCLC patients who had already failed EGFR-TKI. For patients who had mild symptoms or were asymptomatic with a slow increment of tumor burden, continuing EGFR-TKI alone was recommended. In the present study, the patients in the EGFR-TKI continuation group had significantly longer survival rate after the appearance of new lesions than had those in the discontinuation group. Moreover, patients who received continuous EGFR-TKI after the appearance of new lesions had the same opportunity to receive subsequent treatment after discontinuing EGFR-TKI as those in the discontinuation group did. In addition, no significant difference was observed in the PFS of subsequent post-EGFR-TKI treatment between the two groups. Although the survival after discontinuing EGFR-TKI seemed longer in the discontinuation group than in the continuation group, our data suggested that continuing EGFR-TKI after the appearance of new lesions can maintain clinical stability for a period and dose not hinder OS. Continuous EGFR-TKI treatment can remain as an effective option for therapy when new lesions occur. Additional, prospectively designed studies are critical for determining the appropriate management of NSCLC patients with EGFR-sensitive mutations receiving TKI therapy and with the appearance of local or indolent disease progression.

Response to additional local therapy in patients receiving prolonged EGFR-TKI therapy after the occurrence of new lesions might also suggest a favorable outcome, which is consistent with previous reports [12,24]. Local intervention such as radiation therapy for new lesions has been recommended by the aforementioned studies. The local intervention can be withheld and administered electively, if patients exhibit clinical stability after EGFR-TKI therapy, asymptomatic extra-pulmonary lesions, or only mild symptoms that can be controlled and do not deteriorate the patients' general clinical condition. Several studies have indicated the safety of systemic chemotherapy and EGFR-TKI without radiation therapy for NSCLC patients with brain metastasis [25–27]. Accordingly, some patients in this study did not receive extra-pulmonary local therapy based on the clinical stability of the patients and the consideration of adverse effects from therapy.

According to the Iressa Pan-Asia Study and other similar reports [6,8,28], the efficacy of EGFR-TKI regarding OS is similar to first- and second-line use. Our survival analysis showed that patients who received EGFR-TKI treatment continuously after the first appearance of definite new lesions had a significantly longer median OS. The PFS of EGFR-TKI did

not differ among the groups, nor did the survival time after discontinuing EGFR-TKI. Nevertheless, survival time was longer for patients with continuous EGFR-TKI after the appearance of new lesions compared with that of the discontinuation group. Hence, the data in this study suggest the possible survival benefits of the individualized extension of EGFR-TKI therapy for patients with lung adenocarcinoma harboring sensitive EGFR mutations and controlled target lung tumors, despite the appearance of new lesions.

A review of the characteristics of new lesions in patients with continuous EGFR-TKI therapy revealed that a smaller size and number of lesions and nodular patterns with central low-attenuation in radiographic images suggesting tumor necrosis might predict possible benefits of continuous EGFR-TKI. Therefore, the prolongation of EGFR-TKI therapy can be considered as a factor contributing to the survival benefit in the present study. Patients in the continuation group received EGFR-TKI until progression of the primary target lung lesions or the appearance of new lesions with overall disease deterioration. Definite new lesions are typically considered as PD and a change in regimen is always suggested in clinical practice. However, both previous reports and the present study indicate that continuous EGFR-TKI might still be effective for a particular subset of patients although the characteristics of such patients and the mechanism require further investigation.

If FDG-PET is not performed at baseline, the interpretation of new lesions depends on a comparison among the follow-up CT images [18]. Thus, the first appearance of new lesions might not definitively indicate PD. FDG-PET and low-dose high-resolution CT can help evaluate tumor volume and the increase in the speed of volume. In the present study, some new lesions were remained stable or regained responsiveness to continuous EGFR-TKI, and OS was not hindered. This suggests that for patients receiving EGFR-TKI therapy and with controlled primary target lesions, the policy of changing medication on the appearance of definite new lesions warrants further evaluation. Moreover, a practical adjunct test to evaluate the systemic acquired resistance and tumor progression more thoroughly than by using the anatomic definition should be developed.

This study had several limitations. Because Taiwan's NHI program has covered the first and second lines of TKI treatment for only a few years, the number of patients with a completed therapeutic course and adequate follow-up time retrieved from the Cancer Registry System of our hospital was limited. Therefore, only a small number of patients were enrolled, which made subset analysis difficult. Although conditional or subset survival analysis can be used in the evaluation of difference for a heterogeneous group in a clinical study [2], the small number of patients in this study, hindered further survival risk analysis based on the sensitive mutation subtypes or the patterns of imaging studies for newly developed lesions, and significant predictors for continuing or discontinuing EGFR-TKI without bias or with a clear pathogenetic basis could not be determined. In our study, differences were observed in some baseline characteristics among the groups such as the proportion of first-line therapy with EGFR-TKI and pulmonary or nonpulmonary new lesions. However, the median OS analyzed for these subgroups had a similar trend as that of overall patients. In addition, because this was a retrospective study, the treatments were determined according to the clinical decisions of the physicians, caring for the patients under the principle of intent to treat. The patients were not randomized into each subsequent treatment group and selection bias might have existed, which might have influenced the PFS and OS. Although all of the patients in the present study were evaluated for lesions by using chest radiographs, CT, MRI, bone scintigraphy or PET, according to the predetermined management protocols set by our cancer center, the intervals among the evaluations were not as uniform as those in a prospective trial. A prospective study with a larger patient population is required to validate and apply our findings in clinical practice.

Conclusion

Continuous EGFR-TKI did not hinder OS and survival time after the occurrence of new lesions in patients with lung adenocarcinoma harboring sensitive mutations of EGFR and with controlled primary target lung lesions. A prospective study with a larger number of patients is warranted to characterize the predictive factors for the benefit of continuous TKI and to establish a therapeutic strategy for patients fulfilling these criteria.

Ethics statement

This study was conducted in accordance with the Guide for the Use of Clinical Information and the Regulations for Retrieving Clinical Information from the Patient Registry Center and Patient Database of CGMH, as promulgated by the Medical Research Council of CGMH. The lung cancer patients enrolled in the present study were covered by the National Health Insurance (NHI) program of Taiwan. In accordance with the policies of the NHI program established by the Bureau of National Health Insurance, all the key clinical information related to the diagnosis, management, and outcome of cancer patients are registered and stored in the hospital database and submitted to the bureau. The hospital's Institutional Review Board approved the retrieval and retrospective analysis of the information in the database (CGMH IRB No. 100-3723B) and waived the requirement for personal informed consent.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bj.2015.07.002.

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