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Research Paper

Continuation of Tyrosine Kinase Inhibitor is Associated with Survival Benefit in NSCLC Patients with Exon 19 Deletion after Solitary Progression

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Abstract

Introduction: The benefit and selection criteria of continuing tyrosine kinase inhibitor (TKI) after secondary resistance in non-small cell lung cancers (NSCLCs) with epidermal growth factor receptor (*EGFR*) mutation remain largely unknown. This study was designed to investigate the role and predictive factors of TKI continuation in patients with solitary progression.

Methods: We retrospectively analyzed NSCLCs treated with first generation of TKI from June 2009 to October 2014 in our cancer center. Number of progressive lesions upon first progression was recorded per RECIST v1.1.

Results: Sixty-one of 144 (42.4%) patients progressed with one lesion. Postprogression TKI use information was available in 58 patients. No brain metastases and stable disease compared to immediate prior scans were associated continued TKI. In the whole cohort, TKI as the first line treatment was found to be associated with longer postprogression survival, but TKI continuation was not. In patients with exon 19 deletion, TKI continuation compared to discontinuation was significantly associated with longer postprogression survival (32.0 months, 95% CI: 20.8 - 43.3 vs. 15.6 months, 95% CI: 7.3 - 23.8, p=0.013). This difference was not observed in L858R mutation. Exon 19 deletion patients had longer time to TKI cessation after progression (13.7 months, 95% CI: 4.5-22.9 vs. 5.6 months in L858R, 95% CI: 0.0-11.9, p = 0.047).

Conclusions: TKI continuation may prolong survival of NSCLCs with exon 19 deletion rather than L858R. Further studies are required to validate this finding.

Key words: *EGFR* mutation; exon 19 deletion; L858R; TKI continuation.

Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) has revolutionized the treatment of non-small cell lung cancer (NSCLC) with *EGFR* mutation and has become the standard of care in such patients[1]. However, almost all patients eventually develop resistance [2].

It has been suggested that a subgroup of patients may benefit from TKI continuation despite objective progression, but the criteria of patient selection remain largely unknown. Three clinical resistant modes were proposed based on a cohort of Chinese patients – dramatic, progressive, and local

progression[3]. Of great interest, longer postprogression survival was found in patients who had received postprogression TKI compared to chemotherapy. A large single arm trial in Asia showed remarkable second progression-free survival (PFS) of 14 months in patients who continued erlotinib after first progression. In this study, choice of erlotinib continuation was not standardized, but was based on decisions of treating physicians, so it remains unclear who would benefit.

T790M mutation is responsible for the majority of resistance[4-6]. It was found to be heterogeneous even among different tumor foci in an individual patient, indicating that some tumors may be still sensitive to first generation of TKI after another population of tumor cells have developed resistance[7].

However, a recently published randomized phase III trial demonstrated no benefit of continuing gefitinib after objective progression, highlighting the role of correct patient selection in making a decision on continuation or not[8].

National Comprehensive Cancer Network guideline recently included continuation of first generation of TKI after solitary progression in conjunction with local therapy as one of the treatment options if symptomatic[9]. In this study, we aimed to investigate the benefit of continuing first generation of TKI in patients with solitary progression and to explore factors that may assist patient selection.

Material and Methods

The Institutional Review Board of West China Hospital reviewed and approved this study. Written informed consent was obtained from all participants involved in the study. Medical records of TKI-naïve metastatic NSCLC patients with common *EGFR* mutation (exon 19 deletion and L858R) treated with first generation of EGFR-TKIs between June 2009 to October 2012 were retrospectively reviewed. Imaging workup at baseline typically involved chest and abdominal computed tomography (CT) and brain magnetic resonance imaging (MRI). Patients were followed typically every two months with routine chest and abdominal CT. Follow-up brain MRI was performed if clinically indicated. We reviewed images according to RECIST 1.1 and recorded the number of progressive lesions[10]. *EGFR* mutation was determined by ADx-ARMS *EGFR* Mutations Detection Kit (Amoy Diagnostics, Xiamen, China).

PFS was defined from first TKI initiation till objective progression and/or death. Longer PFS was defined as a PFS longer than the median PFS of patients with solitary progression. Change of scanning at the time of progression compared to immediate preceding scan was recorded as stable disease (SD) or progressive disease (PD) per RECIST 1.1 and was considered a surrogate clinical index of tumor growth rate. The followings were considered as definitive local therapy after progression: 1) surgical resection; 2) conventional fractionated radiotherapy with a total dose >= 50 Gy; 3) stereotactic body radiotherapy with a biological equivalent dose >=100 Gy; and 4) stereotactic radiosurgery to brain metastases. Solitary progression was defined as only a single lesion progress and the rest of lesions were stable in patients with multisite lesions.

Three first generation EGFR-TKIs have been approved in China: gefitinib, erlotinib, and icotinib. Patients who switched to another TKI after objective progression were still considered as TKI continuation. TKI continuation was defined as no cessation of TKI use for more than one month after progression. Age, gender, smoking history, line of TKI, ECOG performance status, new/original site progression, presence of brain metastasis, and chemotherapy use were also collected. Chemotherapy given within 2 month postprogression was considered as immediate.

Postprogression survival was defined as from first objective TKI progression till any causes of death. Chi-square or Fisher's exact test was used to analyze factors associated with TKI continuation. Survival was estimated by Kaplan-Meier method and compared by logrank test. Multivariate analyses of factors associated with postprogression survival was performed by Cox regression test with forward conditional method. All statistical analyses were performed by IBM SPSS Statistics v22.

Results

61 of 144 (42.4%) patients progressed with one lesion after a median PFS of 11.9 months (95% CI: 9.9 -13.9). Median postprogression survival was 21.1 months (95% CI: 12.2 - 30.1). Postprogression TKI use information was available in 58 of the 61 patients. Median time of follow-up from progression was 14.4 months (range, 0.6 - 59.8).

Patient characteristics and association with TKI continuation

Patient characteristics were summarized in Table 1. Demographical distribution of smoking history and histology is consistent with the previous reports of patients with *EGFR* mutation. EGFR-TKI was the first line of systemic treatment in 43 (74.1%) patients. 41 (70.7%) patients progressed in an original site and 39 (67.2%) had stable disease compared to preceding scan. 12 (20.7%) patients received definitive local therapy either to primary or metastatic lesions after progression, but none received both. All definitive metastatic local therapies were stereotactic

radiosurgery to brain lesions. 5 of 32 patients with exon 19 deletion received definitive local therapy; while 6 of 26 L858R received. No patient received radiofrequency ablation after progression. One patient received AZD9291, but no other patients received third generation of TKI.

Table 1. Patient Characteristics Stratified by Tyrosine Kinase Inhibitor (TKI) Continuation

	TKI Discontinuation		TKI Continuation		P value
	Number	%	Number	%	
Total	21		37		
Age (y)					0.729
<65	18	85.7%	29	78.4%	
Sex					0.702
Female	13	61.9%	21	56.8%	
Smoker					0.741
Non-smoker	16	76.2%	30	81.1%	
ECOG performance status					
0-1	21	100.0%	37	100.0%	
Histology					0.743
Adenocarcinoma	20	95.2%	34	91.9%	
Squamous carcinoma	1	4.8%	2	5.4%	
Adenosquamous carcinoma	0	0.0%	1	2.7%	
Mutation Type					0.437
Exon 19 deletion	13	61.9%	19	51.4%	
L858R	8	38.1%	18	48.6%	
Line of TKI					0.788
1	16	76.2%	27	73.0%	
>=2	5	23.8%	10	27.0%	
Brain metastases					<0.001
Yes	19	90.5%	5	13.5%	
Number of Extracranial Lesions					1.000
<=6	17	81.0%	30	81.1%	
Scan comparison with immediate prior scan					0.016
Progressive Disease	11	52.4%	8	21.6%	
Stable Disease	10	47.6%	29	78.4%	
Progressive site					0.268
Original Site	13	61.9%	28	75.7%	
New Site	8	38.1%	9	24.3%	
Prior progression-free survival (months)					0.585
Long	9	42.9%	20	54.1%	
Short	12	57.1%	17	45.9%	
Treatment after progression					
Immediate Chemotherapy					0.040
Yes	10	47.6%	8	21.6%	
Chemotherapy at any time postprogression					0.760
Yes	15	71.4%	25	67.6%	
Definitive primary local therapy					0.402
Yes	1	4.8%	5	13.5%	
Definitive metastatic local therapy					0.148
Yes	0	0.0%	5	13.5%	
Definitive local therapy to any site					0.036
Yes	1	4.8%	10	27.0%	

Patient treatment characteristics stratified by TKI Continuation were summarized in Table 4. 15 (71.43%) patients in TKI continuation group received chemotherapy, and 12(57.14%) patients received platinum-based regimen (doublet) treatment; in TKI continuation group, 25(67.57%) patients received chemotherapy including 15(40.54%) platinum-based regimen (doublet) and 10(27.03%) single-drug cytotoxic. Use of SBRT or CRT radiotherapy after postprogression of the study radiotherapy was greater in TKI continuation group than in TKI discontinuation group. In TKI continuation group 2(5.4%) patients received SBRT, the strategy was 50Gy/10f and 40Gy/8f respectively; 8 (21.62%) patients underwent CRT which total dosage ranged from 30Gy to 66Gy, and all the radiotherapy were confined to the area of the solitary progression lesion. In TKI discontinuation group, there was only one patient received CRT with 40Gy total dose.

37 (63.8%) patients continued EGFR-TKI after objective progression. No significant difference of prior PFS was observed in patients who continued TKI (11.7 months, 95% CI: 8.6 - 14.8) versus those who discontinued (12.7 months, 95% CI: 7.4 - 18.1). Patients without brain metastases (94.1% continued vs. 20.8% in those with, p<0.001) and stable disease compared to immediate prior scan (74.4% continued vs. 42.1% in those with PD, p=0.016) were significantly associated with TKI continuation. Patients who continued TKI (27.0% vs. 4.8% in those discontinued) were more likely to have receive definitive local therapy to either primary or metastatic site (p=0.036) after progression. Immediate chemotherapy was more common in TKI discontinuation group (47.6% vs. 21.6%, p=0.040).

Postprogression survival in the whole cohort

Patients who continued TKI did not have a significantly longer postprogression survival (p=0.28, Figure 1A). On multivariate analyses, only TKI used in the first line setting (hazard ratio: 0.43, 95% CI: 0.16 - 0.83) was significantly associated with longer postprogression survival (Table 2). In subgroup analysis, exon 19 deletion (hazard ratio: 0.31, 95% CI: 0.06-0.67) and long prior PFS (hazard ratio: 0.34, 95% CI: 0.46-0.82) significantly favored TKI continuation (Figure 2).

Postprogression survival stratified by mutation type

In patients with exon 19 deletion mutation, TKI continuation was associated with significantly longer postprogression survival (32.0 months, 95% CI: 20.8 - 43.3 vs. 15.6 months, 95% CI: 7.3 - 23.8, p=0.013). Among other factors, line of TKI was also significant (Table 3). On multivariate analyses, only TKI continuation remained significant (p=0.023). However, in patients with L858R mutation, no benefit of continuing TKI was observed. SD compared to immediate prior scan, original site failure and no brain metastases were associated with longer postprogression survival on multivariate analyses in L858R mutation patients.

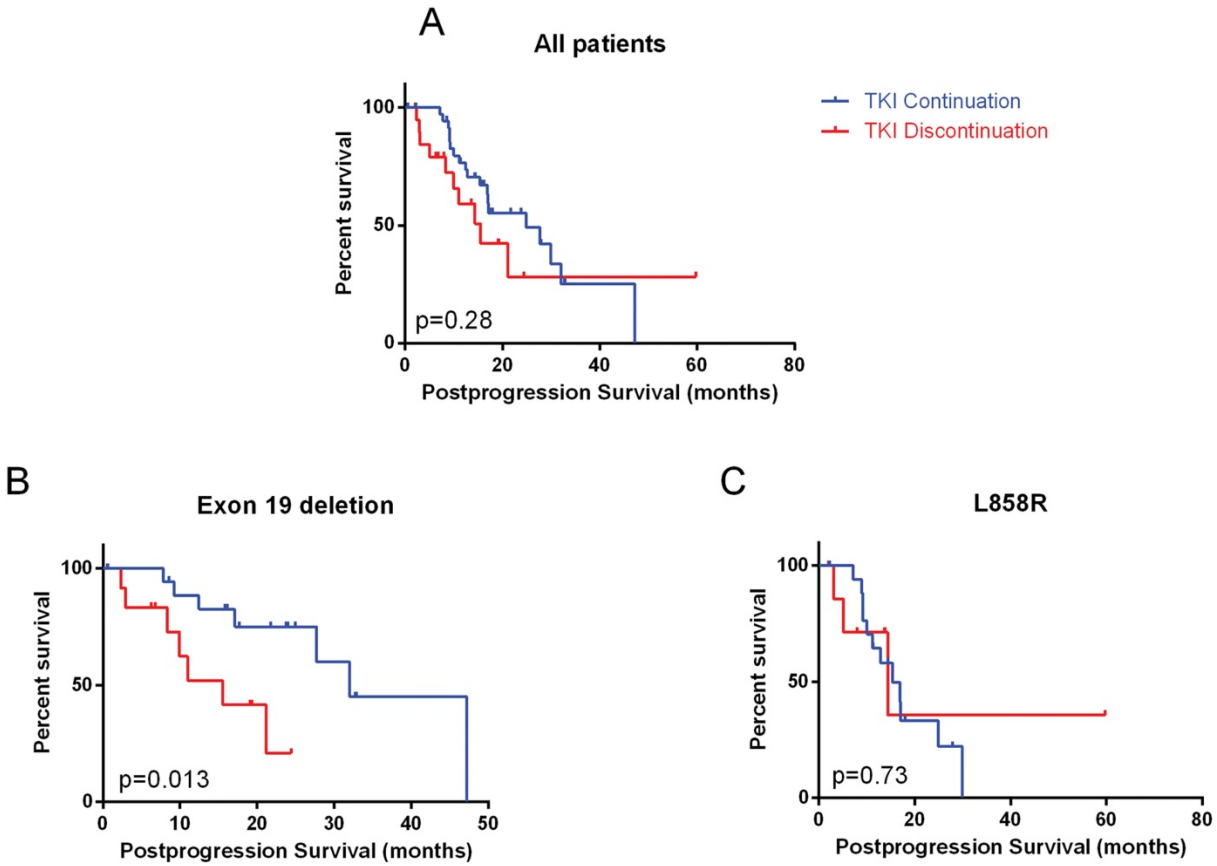

Figure 1. Postprogression survival in A) whole cohort; B) exon 19 deletion mutation; C) L858R mutation

In patients who continued TKI, exon 19 deletion was significantly associated with longer postprogression time to TKI cessation (13.7 months, 95% CI: 4.5-22.9 vs. 5.6 months in L858R, 95% CI: 0.0-11.9, p = 0.047, Figure 3).

Discussion

This study showed that in unselected *EGFR* mutant patients with solitary progression after TKI treatment, TKI continuation was not associated with longer postprogression survival. Interestingly, subgroup analysis showed that patients with exon 19 deletion rather than L858R mutation may benefit from TKI continuation, evidenced by longer postprogression survival and longer time to TKI cessation. To the best of our knowledge, this is the first study investigating difference of postprogression TKI continuation between the two common *EGFR* mutation in patients with solitary progression.

Although both are common, exon 19 deletion and L858R have been considered to be different in its biology and treatment response to TKI. A pooled analysis of LUNX-LUNG 3 and 6 demonstrated overall survival benefit of afatinib, an EGFR-TKI in exon 19 deletion patients, but not in L858R over chemotherapy[11]. A meta-analysis of 7 randomized trials also found 50% greater PFS benefit of exon 19 deletion compared to patients with L858R. This efficacy difference may be explained by a greater degree of EGFR phosphorylation inhibition by gefitinib in a preclinical study[12]. However, whether this difference exists in patients who continues TKI after progression has been largely unknown.

Table 2. Factors associated with postprogression survival

	Univariate P value	Multivariate P value
Age >= 65 (year)	0.027	0.117
Gender	0.255	
Smoking	0.911	
Line of tyrosine kinase inhibitor	0.018	0.022
Tumor growth rate (PD or SD)	0.474	
Mutation type	0.165	
Number of extracranial lesions	0.307	
Brain metastases	0.654	
Immediate chemotherapy	0.156	
Progressive site	0.023	0.114
Definitive local therapy to metastatic site(s)	0.111	
Definitive local therapy to primary site(s)	0.343	
Definitive local therapy to any site(s)	0.053	
Continuation of tyrosine kinase inhibitor	0.283	
Longer progression-free survival	0.602	

PD: progressive disease; SD: stable disease

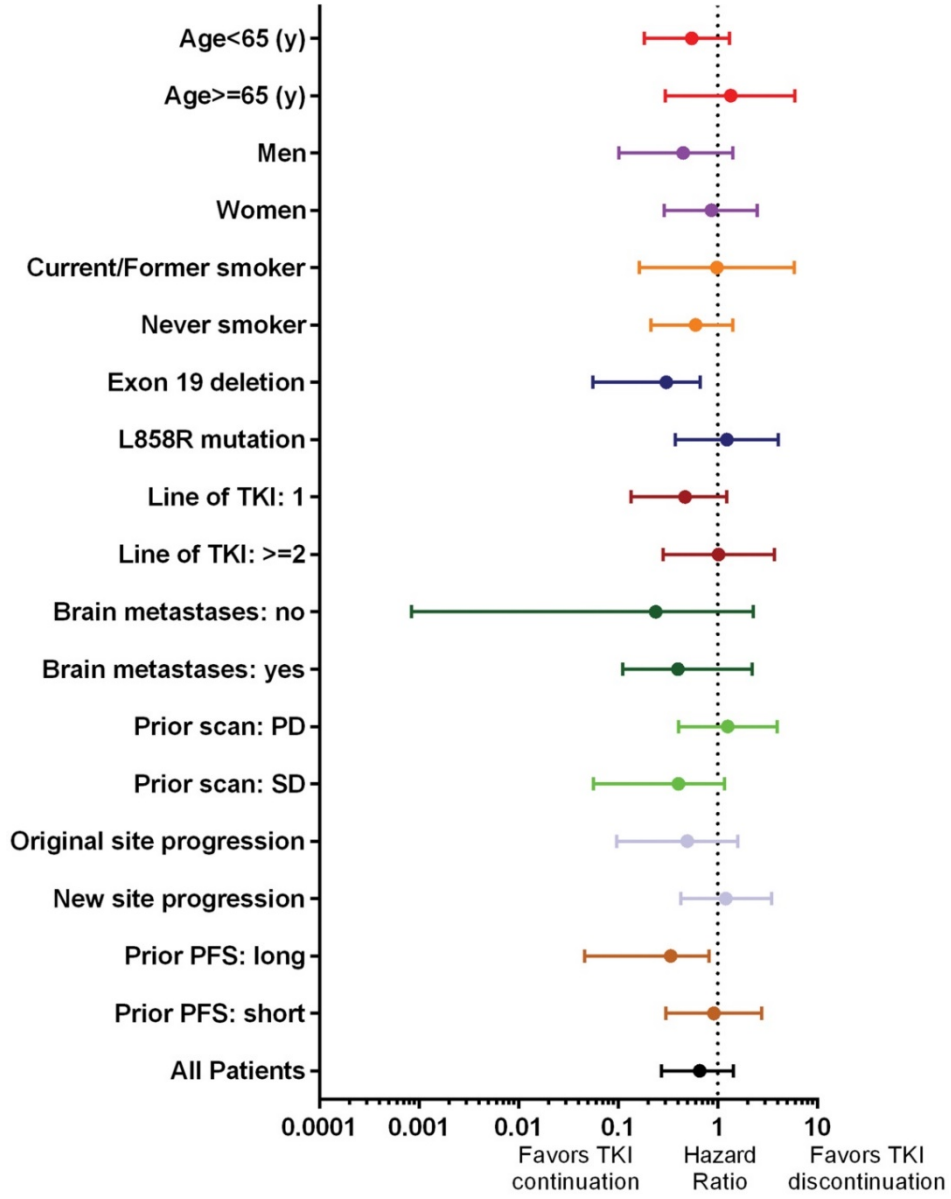

Figure 2. Forest plot of postprogression survival subgroup analyses. Only 11 patients received definitive local therapy and analysis was not possible. TKI: tyrosine kinase inhibitor; PD: progressive disease; SD: stable disease; PFS: progression-free survival

Table 3. Factors associated with postprogression survival stratified by mutation type

	Exon 19 deletion		L858R	
	Univariate p value	Multivariate p value	Univariate p value	Multivariate p value
Age (>=65y)	0.824		0.200	
Female	0.743		0.214	
Non-smoker	0.673		0.310	
Line of tyrosine kinase inhibitor	0.038	0.081	0.235	
Slow tumor growth (stable disease)	0.300		0.876	0.007
Original site progression	0.681		0.006	<0.001
Number of extracranial lesions	0.812		0.300	
Brain metastases	0.111		0.641	0.032
Immediate chemotherapy	0.476		0.559	
Any definitive local therapy	0.166		0.110	
Tyrosine kinase inhibitor continuation	0.013	0.023	0.733	
Longer progression-free survival	0.720		0.336	

Table 4. Treatment Characteristics Stratified by Tyrosine Kinase Inhibitor (TKI) Continuation

	TKI Discontinuation		TKI Continuation	
	Number	%	Number	%
Patient who received chemotherapy				
Platinum alone*	0	0	1	2.70%
Platinum-based regimen (doublets)	12	57.14%	15	40.54%
Other single-drug**	3	14.29%	10	27.03%
Patient who received radiotherapy				
SBRT	0	0	2	5.40%
CRT	1	4.70%	8	21.62%

*Carboplatin, cisplatin, or nedaplatin.
**Docetaxel, paclitaxel, pemetrexed, gemcitabine, or vinorelbine.
SBRT: Stereotactic Body Radiation Therapy CRT: Conventional Radiation Therapy

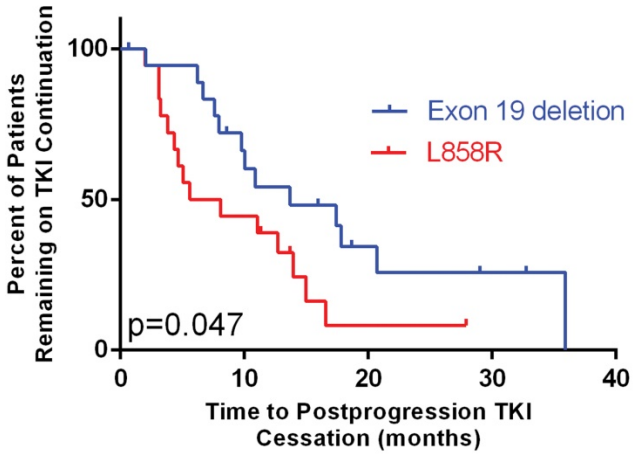

Figure 3. Time to tyrosine kinase inhibitor (TKI) cessation after progression stratified by mutation type

The benefit of TKI continuation after progression has not been confirmed. Neither consensus on patient selection criteria has been reached. The IMPRESS study demonstrated no benefit of gefitinib continuation in unselected patients[8]. The post-resistance PFS was 5.4 months, identical between patients with or without gefitinib continuation. Interestingly, its subgroup analysis showed a trend toward a longer second PFS in patients with exon 19 deletion over L858R mutation, but overall survival result has not been reported. The ASPIRATION study, a single-arm phase II trial showed that in patients selected by treating physicians, the postprogression PFS by erlotinib continuation was 14.1 months, which was even numerically longer than the first PFS (11.0 months)[13]. The discrepancy between IMPRESS and ASPIRATION studies suggests that with the right selection, TKI may still be beneficial in a subgroup of patients. However, the selection criteria remain largely unknown. Subgroup analysis of this study showed that patients with exon 19 deletion and long prior PFS benefited from TKI continuation (Figure 2). Because of the objective nature of mutation type, we therefore chose exon 19 deletion for further analysis.

Salvage local therapy has been used increasingly in selected asymptomatic patients with limited number of progressive lesions, good performance status, and small number of total metastatic burdens. A retrospective analysis from a single institution showed that oligometastatic and solitary progressive *EGFR* mutant patients achieved an impressive 10 months of median time to progression after local therapy[14]. They also reported the median time until a subsequent change in systemic therapy was 22 months. The benefit of local therapy has been reported by other studies as well[15, 16]. The latest NCCN guideline included local therapy beyond focal progression as a treatment option[9]. However, it is hard to determine the benefit of local therapy in this cohort of patients, because of the small number of patients who received definitive local therapy.

With the advent of third generation of TKI, continuation of first generation of TKI appears to be less appealing[17-19]. However, new resistances to those novel drugs have emerged after a certain time of treatment as in the first generation drugs[20, 21]. On the other hand, the mechanism of TKI resistance is complex, except the presence of new mutations in EGFR gene, such as T790M and C797S[20], PI3K mutation or MET amplification and pathological transformation also play an important role in acquired resistance to EGFR-TKI[22, 23]. Therefore, continuation of first generation of TKI seems to be reasonable as long as patient can still benefit, considering the cost and inevitable subsequent resistance from the newer drugs.

This study has the typical limitations of retrospective studies and is small in patient numbers. The postprogression treatment is also heterogeneous, including concurrent chemotherapy + TKI, TKI alone, chemotherapy alone, etc. Therefore, we grouped patients into TKI continuation and discontinuation and used postprogression survival as the outcome endpoint instead of postprogression PFS. Besides, as the patient's characteristics between the TKI discontinuation group and TKI continuation group were not balanced, so the interpretation of the postprogression survival subgroup analyses forest plot needs to be more careful.

In conclusion, this study showed that in *EGFR*-mutant patients with solitary progression, EGFR TKI continuation compared to discontinuation was associated with longer postprogression survival in exon 19 deletion patients, but not in L858R and unselected patients. Time to TKI cessation was also significantly longer in patients with exon 19 deletion.

This result should be validated in larger and prospective studies.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Competing Interests

The authors have declared that no competing interest exists.

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