

Effectiveness of tyrosine kinase inhibitors on uncommon E709X epidermal growth factor receptor mutations in non-small-cell lung cancer

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Background: Clinical features of epidermal growth factor receptor (EGFR) mutations: L858R, deletions in exon 19, T790M, insertions in exon 20, G719X, and L861X in non-small-cell lung cancer (NSCLC) are well-known. The clinical significance of other uncommon *EGFR* mutations, such as E709X, is not well understood. This study aimed to improve the understanding of E709X, and the clinical response to tyrosine kinase inhibitors (TKIs) of NSCLC patients with such an uncommon mutation.

Methods: Specimens from 3,146 patients were tested for *EGFR* mutations. We surveyed the clinical data and the effectiveness of TKI treatment in NSCLC patients with *EGFR* mutations E709X.

Results: Of the 3,146 patients, 1,689 (53.7%) had *EGFR* mutations. This included 726 patients with deletions in exon 19, 733 patients with L858R, and 230 (13.6%) patients with other *EGFR* mutations. In the 230 patients who had mutations other than single deletion in exon 19 or single L858R in exon 21, 25 (1.5%) patients had the uncommon E709X mutations. Twenty patients had complex E709X mutations and five had single E709X mutation: delE709-T710insD. Of these 25 patients, 18 received either gefitinib or erlotinib treatment. The response rate of TKIs treatment was 50.0%, and the median progression-free survival was 6.2 months. All 5 patients who had delE709-T710insD were non-responders to TKI treatments.

Conclusion: E709X *EGFR* mutations constituted a small part of the whole group of *EGFR* mutations. Most patients had complex mutations. The mutation delE709-T710insD was a single mutation and was not associated with good response to TKI treatment.

Keywords: EGFR, erlotinib, gefitinib, lung cancer, mutations

Introduction

Mutations of the epidermal growth factor receptor (EGFR) have influenced the treatment decisions in patients with non-small-cell lung cancer (NSCLC) in the recent years.¹ *EGFR* mutations were found in 30% to 60% of Asian patients and in 10% to 20% of Caucasian patients with NSCLC.²⁻⁴ Apart from their association with ethnicity, *EGFR* mutations occur more frequently in NSCLC of never smokers, females, and adenocarcinoma cell type.^{5,6} The EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib or gefitinib, are highly active against advanced NSCLC with *EGFR* mutations.^{7,8}

EGFR mutations exist in exons 18 to 21, and the two major *EGFR* mutations are deletions in exon 19 and L858R in exon 21^{9,10} which constitute about 80% to 90% of total *EGFR* mutations.^{2-4,11,12} In addition to deletions in exon 19 and L858R, other categories of *EGFR* mutations, which are also well-known, are T790M,^{13,14} insertions (or in-frame duplications) in exon 20,^{15,16} G719X and L861X.¹⁷ T790M can be

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a primary mutation,^{18,19} or a secondary mutation acquired after treatment with EGFR TKIs.^{13,14} Both insertions (or in-frame duplications) in exon 20 or T790M (also in exon 20) give rise to resistance to EGFR TKIs. Besides, amino acid substitutions at G719 (G719X) and L861 (L861X) are *EGFR* mutations that were associated with favorable effectiveness of EGFR TKIs.¹⁷

These *EGFR* mutations, including deletions in exon 19, L858R, G719X, L861X, T790M and insertions in exon 20, have documented clinical significance and are well clarified. In the present study, we focused on another category of *EGFR* mutation which is constituted of amino acid substitutions or deletions in E709 (E709X). E709X was only reported in small case numbers in the literature, and their influences on the effectiveness of EGFR TKIs have not been fully understood.^{17,20,21} On the contrary, the effectiveness of TKIs in NSCLC patients who harbored *EGFR* mutations beyond the rare mutation variant E709X has been documented. For example, in patients with deletions in exon 19 and L858R treated with TKIs, the response rate (37.5% to 82.7%),^{3,5,7,8} progression-free survival (PFS) (7.5 months to 12.6 months),^{3,4} and overall survival (16.1 months to 27.0 months)^{3,4} are favorable. In order to increase the understanding to the entire spectrum of *EGFR* mutations, we investigated the clinical features of these E709X *EGFR* mutations in the present study.

Materials and methods

Patient characteristics

NSCLC patients diagnosed at the National Taiwan University Hospital between January 2000 and December 2014 were included in the study. Complete cancer staging, including bronchoscopy, computed tomography (CT) of the head, chest, and abdomen, and whole-body bone scintigraphy, was performed for all patients in the hospital. The patients' clinical data were reviewed. Never smokers were defined as those who had smoked <100 cigarettes in their lifetime. Lung cancer histology was defined on the basis of the World Health Organization pathology classification.²² Date of diagnosis, treatments received, and responsiveness to treatments were recorded. Clinical staging was decided according to the sixth edition of TNM classification of NSCLC. Tumor specimens obtained by either surgical or needle biopsy/aspiration procedures, from primary lung tumors, other distant metastases, and malignant effusion cell blocks, were sequenced for mutational analysis. This study was approved by the National Taiwan University Hospital's Institutional Review Board. Written informed consent for use of tissue in molecular analysis was acquired from patients at the procurement of tumor specimens.

Efficacy evaluation of EGFR TKIs

We identified the treatments of TKIs (gefitinib or erlotinib) for stage IIIB or stage IV NSCLC from the records of the hospital's Department of Pharmacy. The timing of different EGFR TKIs depended on the physicians' discretion. Baseline assessments were performed before treatment. Chest radiography was routinely carried out and assessed every 2–4 weeks to evaluate the response to treatment, while a chest CT scan (including liver and adrenal glands) was performed every 2–3 months to evaluate treatment response and disease progression.

According to the criteria of the response evaluation criteria in solid tumors (RECIST) group, treatment responses were stratified as complete response, partial response, stable disease, and progressive disease.²³ Responders to anti-tumor therapy were defined as patients with partial or complete response, and the rest were classed as non-responders. Disease control status comprised complete response, partial response, and stable disease.²⁴ Disease control rate was defined as the patient number with disease control status divided by the total patient number. The cut-off date for data collection was January 10, 2016. PFS with erlotinib or gefitinib was measured from the first day of gefitinib or erlotinib treatment until the first objective or clinical sign of disease progression or death. Overall survival was measured from the first day of gefitinib or erlotinib treatment to the cut-off date or the day of death.

Mutational analysis of EGFR

Tumor specimens, including paraffin blocks or frozen tissues of surgical specimens, fine needle biopsies, and pleural effusions, were obtained for mutational analysis. Acquisition of tumor specimens for testing for *EGFR* mutations was performed before EGFR TKI treatments. Tissue sections were examined for adequacy by microscopy with hematoxylin and eosin staining and macrodissection was used. Some of the materials have been examined previously, and reported in studies regarding *EGFR* mutations.^{6,15,25–29}

The mutational analysis of *EGFR* genes was performed as previously reported.^{6,26,30} In summary, DNA was derived from tumors embedded in paraffin blocks by using a QIAmp DNA Mini Kit (Qiagen, Valencia, CA, USA). The exons 18, 19, 20 and 21 of *EGFR* were amplified, while independent polymerase chain reaction (PCR) amplifications were purified and analyzed by direct dideoxynucleotide sequencing with an automatic ABI Prism 3100 or 3700 DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

Frozen lung cancer tissues were procured at surgery, immediately snap frozen in liquid nitrogen, and stored until use. Malignant pleural effusion fluid was centrifuged

at 250× *g* for 10 min, and the cell pellets were frozen in RNAlater (Qiagen).

Total mRNA was extracted from frozen cancer tissue or cell pellets from pleural effusion using TRI reagent (Molecular Research Center, Cincinnati, OH, USA) and an RNA extraction kit (RNeasy Mini Kit; Qiagen). The four exons (exons 18–21) of the *EGFR* gene were amplified by reverse transcription-PCR (RT-PCR) using a Qiagen One-Step RT-PCR Kit (Qiagen). The primers and RT-PCR conditions have been reported previously.^{26,30} The cDNA amplicons were purified and sequenced. Both the forward and reverse sequences obtained were analyzed.

Statistical analyses

All categorical variables were analyzed with chi-square tests or Fisher's exact test. For multivariate analysis, logistic regression, using the stepwise method, was implemented. Overall survival and PFS after gefitinib or erlotinib treatment were analyzed with the Kaplan–Meier method to assess the time to death or progression. Cox-regression was used for multivariate survival analysis. A log-rank test was employed to compare cumulative survival in different groups. All *P*-values were two-sided and a *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS software (version 13.0; SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

Tumor specimens (996 surgical specimens, 1,002 fine-needle biopsies, and 1,148 pleural effusions) from a total of

3,146 NSCLC patients were examined for mutations of the *EGFR* tyrosine kinase domain. Of the total 3,146 patients, 696 were smokers and 2,450 were never smokers. There were 2,636 adenocarcinomas and 510 non-adenocarcinomas.

Sixteen hundred and eighty nine (53.7%) patients had *EGFR* mutations, and 1,457 patients had wild type *EGFR* (Table 1). The mutations were more frequent in never smokers than smokers (61.6% vs 26.0%, *P*<0.001), in adenocarcinomas than non-adenocarcinomas (61.1% vs 15.3%, *P*<0.001), and in females than males (63.9% vs 43.7%, *P*<0.001).

Of the 1,689 patients with *EGFR* mutations, 733 (43.4%) patients had single L858R in exon 21, 726 (43.0%) patients had single deletions in exon 19, and 230 patients had other *EGFR* mutations (13.6%). In the 230 patients who had mutations other than single deletion in exon 19 or single L858R in exon 21, 25 (1.5%) patients had uncommon E709X mutations. The demographics of all the patients with and without *EGFR* mutations, and patients with E709X mutations are listed in Table 1.

In the 25 patients with *EGFR* E709X mutations, 5 patients had single mutation DelE709-T710insD, and the other 20 patients had complex mutations (one E709X mutation and another *EGFR* mutation) (Tables 2 and 3). Some of these patients had been reported in previously published studies (case 8, 10, 12, 13, 18, 19, 20, 24, 25).^{4,17}

EGFR TKI treatment in patients with E709X mutations

Medical records from all 25 patients with these E709X *EGFR* mutations were reviewed in detail. Of the 25 patients,

Table 1 Demographics of patients screened for *EGFR* mutations

	All patients screened for <i>EGFR</i> mutations	Patients with <i>EGFR</i> mutations	Patients with wild type <i>EGFR</i>	<i>P</i> -value ^a	Patients with E709X <i>EGFR</i> mutations
Patient number	3,146	1,689	1,457		25
Median age (year, range)	66 (25–102)	65 (27–96)	67 (25–102)		64 (48–85)
Gender				<0.001	
Male	1,590	695	895		13
Female	1,556	994	562		12
Smoking				<0.001	
Smoker	696	181	515		8
Never smoker	2,450	1,508	942		17
Histology				<0.001	
Adenocarcinoma	2,636	1,611	1,025		22
Non-adenocarcinoma	510	78	432		1
EGFR mutation					
Deletion in exon 19		726			
L858R		733			
Others		230			

Note:^aComparison between patients with *EGFR* mutation and patients with wild type *EGFR*.

Abbreviation: EGFR, epidermal growth factor receptor.

Table 2 Summary of clinical information of patients treated with EGFR TKIs

Patient no	Gender	Age (y)	Smoking	Stage	Cell	EGFR mutations	TKI	TKI response	Outcome	PFS (m)	OS (m)
1	F	61	No	IV	AD	DelE709-T710insD	Gefitinib	SD	Alive	5.1	79.0
2	M	65	Yes	IV	AD	DelE709-T710insD	Gefitinib	PD	Dead	0.9	11.1
3	F	57	No	IV	AD	DelE709-T710insD	Gefitinib	PD	Dead	0.6	24.1
4	M	79	Yes	IV	AD	DelE709-T710insD	Gefitinib	SD	Alive	6.2	6.2
5	M	68	Yes	IV	AD	DelE709-T710insD	Gefitinib	PD	Alive	2.3	29.5
6	F	59	No	IV	AD	E709A + G719C	Gefitinib	SD	Alive	7.3	12.1
7	F	58	No	IV	AD	E709A + G719C	Erlotinib	PR	Dead	14.9	29.3
8	M	76	No	IV	AD	E709A + L858R	Erlotinib	SD	Dead	3.9	5.4
9	F	48	No	IV	AD	E709A + L858R	Gefitinib	PR	Dead	13.6	32.0
10	M	69	No	IV	AD	E709G + G719C	Erlotinib	PD	Dead	1.4	8.3
11	F	57	No	IV	AD	E709G + Del exon 19	Gefitinib	PR	Dead	77.4	104.6
12	M	85	Yes	IIIB	AD	E709G + L858R	Erlotinib	PR	Dead	8.6	13.2
13	F	48	No	IV	AD	E709G + L858R	Gefitinib	PD	Dead	2.4	6.8
14	F	55	No	IV	AD	E709G + L858R	Gefitinib	PR	Dead	18.4	75.3
15	F	64	No	IV	AD	E709K + G719S	Gefitinib	PR	Alive	11.1	11.1
16	M	71	No	IV	AD	E709K + L858R	Gefitinib	PR	Alive	6.5	6.5
17	M	69	Yes	IV	AD	E709K + L858R	Gefitinib	PR	Alive	8.6	8.6
18	M	66	Yes	IV	AD	E709V + L858R	Gefitinib	PR	Dead	9.2	9.5

Abbreviations: EGFR, epidermal growth factor receptor; AD, adenocarcinoma; TKI, tyrosine kinase inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; F, female; M, male.

18 had received EGFR TKI treatment (Table 2). Gefitinib was administered to 14 patients and the other 4 received erlotinib. EGFR TKIs as first-line treatment was used for 15 patients, 2 as second-line, and 1 as third-line or later lines treatment. At the start of EGFR TKI treatment, 1 was stage IIIB with malignant pleural effusion and the other 17 were stage IV.

The response rate to EGFR TKIs in patients with E709X was 50.0% (9/18), and the disease control rate was 72.2% (13/18). Median follow-up was 13 months (range, 5.4 to 104.6). The median PFS of EGFR TKIs was 6.2 months

(range 0.6–77.4). The median overall survival after start of EGFR TKIs was 29.3 months (range 5.4–104.6 months).

To evaluate the effectiveness of EGFR TKI treatment in patients with uncommon *EGFR* mutation E709X, we compared these patients with those patients with classical *EGFR* mutations (L858R in exon 21 and deletions in exon 19) and patients with wild type EGFR in our previously published study with updated survival follow-up.¹⁷ These 18 patients with *EGFR* E709X mutation, who received TKI treatments, were compared with 278 patients with classical mutations

Table 3 Predictive factors associated with clinical response to TKIs

Variables	No patients, N=296	Responder	Response rates (%)	Univariate analysis, P-value ^a	Multivariate analysis, P-value ^b
Type of mutation				0.026	0.035
E709X	18	9	50.0		
Classical	278	206	74.1		
Gender				0.508	0.611
Female	188	139	73.9		
Male	108	76	70.4		
Age				0.626	0.637
≤65 years	153	113	73.9		
>65 years	143	102	71.3		
Smoking status				0.312	0.388
Smoker	65	44	67.7		
Non-smoker	231	171	74.0		

Notes: ^aChi-square test; ^blogistic regression test (all 4 variables included for analysis).

Abbreviation: TKIs, tyrosine kinase inhibitors.

Table 4 Association between clinical factors and survivals after TKI treatment

Variables	No patients, N=296	PFS (months)	Univariate analysis, P-value ^a	Multivariate analysis, P-value ^b	OS (months)	Univariate analysis, P-value ^a	Multivariate analysis, P-value ^b
Type of mutation			0.782	0.783		0.370	0.370
E709X	18	6.2			29.3		
Classical	278	9.1			19.1		
Gender			0.394	0.396		0.093	0.093
Female	188	8.4			21.6		
Male	108	9.8			17.7		
Age			0.675	0.677		0.934	0.935
≤65 years	153	8.8			20.3		
>65 years	143	9.0			17.7		
Smoking status			0.099	0.101		0.877	0.877
Smoker	65	10.7			18.2		
Non-smoker	231	8.2			19.9		

Notes: ^aKaplan–Meier method; ^bCox-regression method (all 4 variables included for analysis).

Abbreviations: TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival.

who also received TKI treatments. Similar TKI courses were noted in these 278 patients, with most patients receiving TKI treatments as first-line therapy (158 as first-line, 52 as second-line, and 68 as third or later lines treatments). The response rate to EGFR TKIs was significantly higher in individuals with the classical *EGFR* mutations than in those with E709X mutations (74.1% vs 50.0%, $P<0.026$). Clinical factors (gender, age, smoking, and mutation type) were included for multivariate analysis by logistic regression. The mutation type was independently associated with clinical response to TKI treatment ($P=0.032$) (Table 3).

On the cut-off date, 16 patients (88.9%) with E709X mutations had completed follow-up, and 2 were lost to follow-up. In 278 patients with classical mutations, 243 patients (87.4%) had completed follow-up. The median PFS (9.1 months vs 6.2 months, $P=0.782$) and median overall survival after start of EGFR TKIs (19.1 months vs 29.3 months, $P=0.370$) were not statistically different between patients with classical *EGFR* mutations and patients with E709X mutations. We included clinical factors (gender, age, smoking, and mutation type) and performed multivariate survival analysis by Cox-regression. The mutation type was not associated with difference in survivals after TKI treatment in the multivariate analysis (Table 4).

When compared with patients with wild type EGFR, patients with E709X mutations had a better response rate to EGFR TKIs than those with wild type EGFR (50.0% vs 16.5%, $P<0.001$). And the median PFS (6.2 months vs 2.0 months, $P=0.003$) and overall survival after start of EGFR TKIs (29.3 months vs 11.8 months, $P=0.010$) were also better in patients with E709X mutations than patients with wild type EGFR.

Subtypes of E709X mutations

Of the 25 patients who had uncommon E709X mutations, 20 patients had E709X complex mutations (one E709X mutation and another *EGFR* mutation). Thirteen out of the 20 patients received TKI treatments, and 9 of them (9/13) were responders to TKI treatment.

Out of the 25 patients who had uncommon E709X mutations, 5 patients had single *EGFR* mutation: DelE709-T710insD. All of the 5 patients, who had single DelE709-T710insD, received TKI treatments, and all were non-responders to TKI (2 had stable disease and 3 had progressive disease). Median PFS after TKI treatment of the 5 patients was only 2.3 months, which was significantly shorter than that of patients with E709 complex mutations (13.6 months, $P=0.004$) (Figure 1). However, the median overall survival of those patients was 24.1 months, which was not different from that of E709 complex mutation group (29.3 months, $P=0.384$) (Figure 1).

Patients who did not receive EGFR TKI treatment

Of the 25 patients who had uncommon *EGFR* E709X mutation, 7 did not receive TKIs in their treatment course (Table 5). One patient received treatment in another hospital after a diagnosis of cancer (case 19). Two patients (case 20 and 21) were in stage IIIA when lung cancer was diagnosed. Two patients (cases 22 and 23) had been diagnosed in early stage, and received an operation without subsequent recurrence. They underwent operation and adjuvant chemotherapy. One patient (case 24) received supportive care after her disease was diagnosed at an advanced stage. One patient received chemotherapy for his lung cancer (case 25). On the

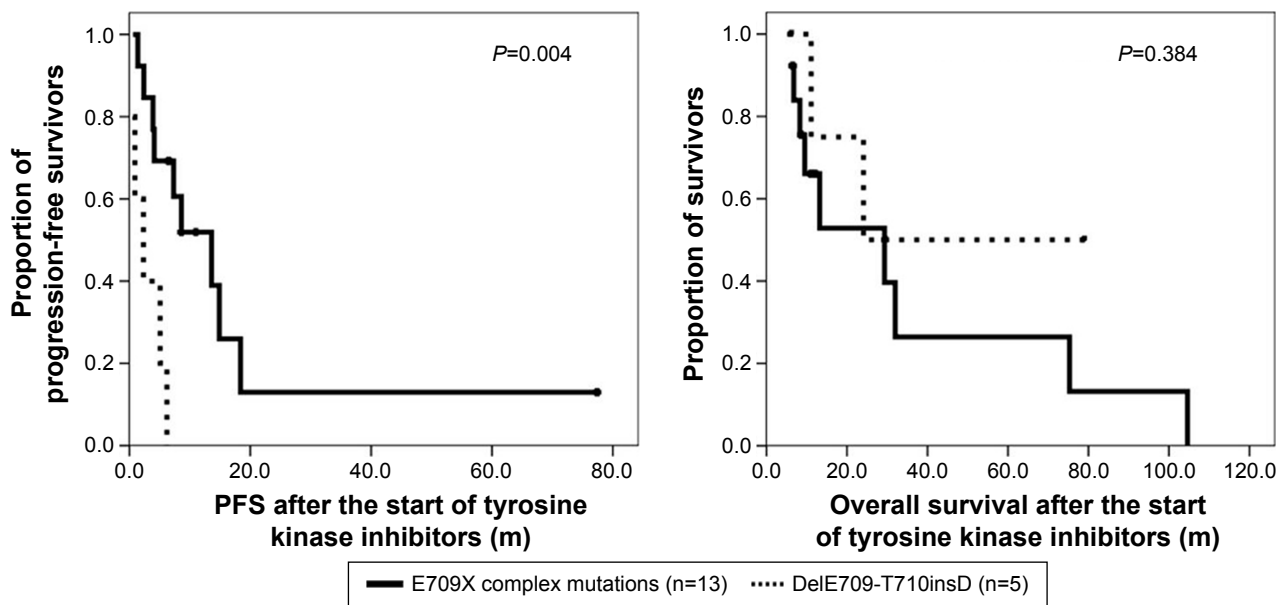


Figure 1 Progression-free survival (PFS) and overall survival after the start of EGFR TKIs in patients with single DelE709-T710insD, or E709X complex mutations. **Abbreviations:** EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

cut-off date, 4 patients were alive and the other 3 patients had expired (Table 5).

Discussion

EGFR exon 18 mutations compose a minor group of the whole EGFR mutations of lung cancer. G719X mutations, which are activating mutations, are most common exon 18 EGFR mutations. E709X mutations are second common exon 18 mutations, but the proportion of E709X was much smaller than G719X, not to mention classical mutations (deletions in exon 19 or L858R in exon 21).²⁰ This study included a large group of patients who underwent testing for EGFR mutations, and presented patients with uncommon E709X EGFR mutations. These E709X EGFR mutations comprised 1.48% of the entire EGFR mutations, and exist in 0.79% (25/3146) of the whole NSCLC patient cohort. Generally, patients with E709X mutations who received EGFR TKI treatment had lower response

rate compared to patients with deletions in exon 19 or L858R in exon 21. On the contrary, their outcomes (response rate, PFS and overall survival) were better than those with wild type EGFR. Moreover, the response of E709 mutations to EGFR TKI can be divided into two subtypes: delE709-T710insD is a unique E709X mutation, which conferred worse response and shorter PFS to TKI treatments than E709X complex mutations. To our knowledge, this study presented the largest group of E709X mutations in the literature.²⁰

In the present study, the EGFR mutation developed at E709 is either a deletion-insertion (delE709-T710insD) or an amino acid substitution. All the amino acid substitution E709X mutations are complex mutations (combination of one E709X and another mutation). Most E709X mutations reported in the literature are complex mutations (doublets),^{20,31} similar to those in our study (Table 6). Even rarer exceptions are scantily reported. For example, the study of Pao et al

Table 5 Summary of clinical information of patients who did not receive EGFR TKIs

Patient no	Gender	Age (years)	Smoking	Stage	Cell	EGFR mutations	Outcome
19	F	65	No	IV	AD	E709A + G719A	Alive
20	M	48	No	IIIA	AD	E709K + G719A	Alive
21	M	61	No	IIIA	AD	E709G + L858R	Alive
22	M	61	Yes	IB	AD	E709G + L858R	Dead
23	F	81	No	IIA	AD	E709K + L858R	Alive
24	F	72	No	IV	SQ	E709V + L858R	Dead
25	M	57	Yes	IV	AD	E709V + L858R	Dead

Abbreviations: EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; AD, adenocarcinoma; SQ, squamous cell carcinoma; F, female; M, male.

Table 6 Response of TKI in patients with E709X EGFR mutations in the study and in literature

Mutations	Exon	Total cases	Responder to TKI	Non-responder to TKI
DelE709-T710	18	1		1 (32)
DelE709-T710insD	18	6	1 (21)	5 (this study)
E709Q	18	1	1 (13)	
E709A + G719C	18	5	1 (this study), 1 (33), 1 (34)	1 (this study), 1 (35)
E709A + G719S	18	1	1 (36)	
E709A + L858R	18+21	2	1 (this study)	1 (this study)
E709A + L861G	18+21	1	1 (36)	
E709G + G719C	18	1		1 (this study)
E709G + Del exon19	18+19	1	1 (this study)	
E709G + L858R	18+21	6	2 (this study), 2 (37)	1 (this study), 1 (37)
E709H + G719C	18	1		1 (5)
E709K + G719A	18	1	1 (38)	
E709K + G719C	18	1	1 (20)	
E709K + G719S	18	1	1 (this study)	
E709K + L858R	18+21	4	2 (this study), 1 (12), 1 (20)	
E709V + L858R	18+21	1	1 (this study)	

Note: Number (reference number).

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

reported a single mutation E709Q, which conferred good response to TKI treatment.¹³ The study of Beau-Faller et al reported a patient with delE709-T710 (without amino acid insertion), and this patient did not have a favorable response to erlotinib therapy.³²

Five patients had the mutation delE709-T710insD in our study. DelE709-T710insD is a rare EGFR mutation (existing in 0.16% of all 3,146 patients in our cohort), and its clinical characteristics and sensitivity to TKI treatment are not clear. All 5 of the patients in this study received gefitinib treatment for pulmonary adenocarcinoma, and all were non-responders to gefitinib. The PFS after gefitinib was 2.3 months. The study of Ackerman et al also reported an NSCLC patient who had the EGFR mutation delE709-T710insD and received gefitinib treatment. Partial response was noted in this patient.²¹ More clinical data and in vitro studies are needed to increase the understanding of the EGFR mutation delE709-T710insD.

In our study, we divided the E709X mutations into two groups: DelE709-T710insD and E709X complex mutations. In the E709X complex mutation group, we may postulate the E709X is simply a passenger mutation, and is possibly insignificant. The other mutation in the complex is the driver mutation. For example, response rate to TKI treatments was 77.8% (7/9) while the E709X mutation existed with a classical mutation (L858R in exon 21 or deletions in exon 19). One can simply ignore the E709X mutation in this group, and the TKI response rate for this group is totally in line with the published data on oncogenic EGFR mutations. On the contrary, DelE709-T710insD is a significant mutation, which was associated with poor response to EGFR TKI treatment.

The major limitation of this report is its retrospective nature. In addition, although the number of patients with uncommon E709X EGFR mutations in this study was relatively large compared with other studies, more clinical experience in the treatment of patients with these EGFR mutations is needed.

In conclusion, we reported on a large group of lung cancer patients with uncommon EGFR E709X mutations and their association with treatment of EGFR TKIs. These EGFR mutations comprised a small but distinct proportion of the total EGFR mutations population, and are worthy of notice. Mutations of amino acid substitutions on E709 frequently exist with another EGFR mutation, while the delE709-T710insD developed solely. Complex mutations with one E709X mutation are sensitive EGFR mutations to EGFR TKI treatment. On the contrary, delE709-T710insD conferred poor response to TKI treatment. Our report may help to guide choices for therapy in NSCLC patients.

Abbreviations

EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

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Disclosure

The authors report no conflicts of interest in this work.

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