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ORIGINAL ARTICLE

Investigation of therapeutic modalities of G719X, an uncommon mutation in the EGFR gene in non-small cell lung cancer

Hua Zheng, Yuan Gao (Co-first author), Zan Liu (Co-first author), Zhe Qian, Tongmei Zhang, Jie Li, Hongmei Zhang, Qunhui Wang, Fanbin Hu (✉), Baolan Li (✉)

Department of Medical Oncology, Beijing Chest Hospital, Capital Medical University, Beijing 101149, China

Abstract

Objective G719X is the most frequently seen uncommon mutation of the epidermal growth factor receptor (EGFR) gene, which is a point mutation at exon 18 with three common subtypes, G719A/G719C/G719S. This study explored the clinicopathological characteristics of the G719X mutation and investigated the efficacy of EGFR-tyrosine kinase inhibitor (TKI) treatment and chemotherapy in patients with the G719X mutation; the survival rate after these different treatment modalities were then analyzed in order to provide evidence for clinical treatment.

Methods Clinical data of 41 patients with the G719X mutation admitted in the Beijing Chest Hospital, Capital Medical University from September 2014 to July 2018, were collected and the EGFR mutations were detected by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). The clinicopathological characteristics of the G719X mutation were analyzed, and the relationship among the G719X mutation, the efficacy of different treatment modalities, and the progression-free survival (PFS) was analyzed.

Results Of the 41 cases, 24 (58.5%) were G719X single mutations and 17 (41.5%) were compound mutations, including G719X/S768I, G719X/L861Q, G719X/19del, and G719X/c-Met compound mutation. The objective response rate (ORR) of first-line EGFR-TKI therapy was 50% (6/12), the disease control rate (DCR) was 83.3% (10/12), and the median PFS (mPFS) was 9 months. After resistance to EGFR-TKI in the previous treatment, the ORR (71.4%, 5/7) and DCR (100%, 7/7) were still high following EGFR-TKIs, by an mPFS of 8 months. The ORR of chemotherapy was 33.3% (2/6), the DCR was 100% (6/6), and the mPFS was 6 months.

Conclusion G719X is an uncommon mutation of the EGFR gene and is sensitive to many EGFR-TKIs. It can be treated with the second- or third-generation EGFR-TKIs after resistance to the first-generation EGFR-TKIs. G719X mutation also showed favorable effect to chemotherapy.

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Key words: lung neoplasms; EGFR; uncommon mutation; G719X; target therapy

Epidermal growth factor receptor (EGFR) is the product of the proto-oncogene C-erbB1 (HER-1). It is a glycoprotein receptor on the surface of the cell membrane. It is over-expressed in many cancers and participates in the proliferation, invasion, and metastasis of cancers. Blocking EGFR-mediated signal transduction pathway can inhibit cancer growth. At present, EGFR-tyrosine kinase inhibitors (TKIs), which are drugs that target the intracellular tyrosine kinase region of EGFRs, have been widely used in non-small cell lung cancer (NSCLC), with a response rate of 70%–80%, and progression free survival (PFS) reaching 10–12 months [1–3], far exceeding the response rates and PFS associated with chemotherapy. Since the mutation status of EGFR gene can predict the efficacy of EGFR-TKIs, they have been approved for the first-line treatment of non-small cell lung cancer (NSCLC) with EGFR sensitive mutation, which significantly prolonged the survival of NSCLC patients with EGFR gene sensitive mutation. Along with the wide application of EGFR-TKIs and the development of mutation detection technology, researchers have found the diversity of EGFR gene mutations. More than

✉ Correspondence to: Fanbin Hu. Email: hufanbin@sina.com
Baolan Li. Email: libaolan1109@163.com

250 EGFR mutations have been reported [4], and not all patients with EGFR mutations benefit from EGFR-TKIs. Patients with a deletion in exon 19 and L858R mutation, called sensitive mutation, which accounts for about 80%–90% of the total EGFR mutations showed a good response to the first-generation EGFR-TKIs [5–6], while mutations in exon 20, like T790M showed resistance to the first-generation EGFR-TKIs. The third-generation EGFR-TKI (osimertinib) showed a good response to the T790M mutation whereas other mutations, the so called uncommon mutations, account for about 10-20% of the total mutations [5–6]. The response of EGFR-TKIs to these uncommon mutations is not consistent in the literature, and most of them were reported in case reports.

The most frequently seen uncommon mutation is the G719X mutation, which occurs in about 3% of the Asian and Caucasian populations [7–10]. The G719X mutation refers to a point mutation at exon 18 of the EGFR gene, where glycine at position 719 is replaced by other amino acids, mainly by alanine (G719A), cysteine (G719C), or serine (G719S). In addition, G719X mutation often exists as compound mutations, mostly with S768I [11–12], but also with other gene mutations, such as KRAS, BRAF, and PIK3CA [11]. The efficacy of EGFR-TKIs and chemotherapy against G719X mutation is yet to be ascertained. This study retrospectively analyzed 41 cases of non-small cell lung cancer with G719X mutation, their treatment modalities, and response, so as to provide evidence for clinical treatment.

Materials and methods

Patients

The medical information of the NSCLC patients, with detected EGFR gene mutations, in Beijing Chest Hospital, Capital Medical University were collected from September 2014 to July 2018. Diagnosis of NSCLC in all patients was confirmed by pathological biopsy. Amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) was used for the detection of the EGFR mutations. All the specimens were obtained before treatment, and the clinical data of the patients with G719X mutation were analyzed retrospectively.

Detection by ARMS

All samples were fixed in 10% formalin and sealed in paraffin. The EGFR mutations were analyzed by fluorescence quantitative ARMS-PCR (Xiamen Ailing human EGFR gene mutation detection kit), including 19 exon deletion; 21 exon L858R, T790M; 20 exon insertion, G719X, S768I, and L861Q mutation.

Treatments and follow-up

Patients receiving first-line treatment should have at least one measurable lesion, at stage IIIB/IV, availing standard treatment of gefitinib, erlotinib, icotinib, afatinib, or osimertinib for at least 30 days or two cycles of chemotherapy, and the first computed tomography (CT) examination should be performed after one month of EGFR-TKIs treatment, or two cycles of chemotherapy. According to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, efficacy was evaluated and divided into the complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) was reported as the proportion of patients with complete or partial response, and the disease control rate (DCR) was calculated as the proportion of patients with an objective response or stable disease (for at least 6 weeks). Progression-free survival (PFS) was calculated as the time from the first day of treatment until progression of disease or date of death (from any cause). Patients who were alive at the cutoff date (December 31, 2018) or failed to attend the follow-up were censored at the last date of follow-up.

Statistical analysis

All data were analyzed using the statistical software SPSS 22.0 (SPSS Inc., Chicago, IL). Survival analysis was performed using the Kaplan-Meier curve, and differences were compared using the Log-rank test. A two-sided P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Among the 41 patients, 26 (63.4%) were females, and 15 (36.6%) were males with a median age of 67 years (42-81 years). Nine (22.0%) cases were current or former smokers, and 32 (78%) cases never smoked. The pathological types included adenocarcinoma (40 cases, 97.6%) and NSCLC (1 case, 2.4%); the TNM stages were stage I (12 cases, 29.3%), stage II (1 case, 2.4%), stage III (6 cases, 14.6%), and stage IV (20 cases, 48.8%) (Table 1).

Frequency of EGFR mutation

From September 2014 to July 2018, 3136 NSCLC patients were tested in our hospital for the presence of EGFR gene mutations. Among them, 1425 (45.4%) harbored EGFR mutations, of which 1321 (92.7%) had deletion in exon 19, L858R, and T790M mutation, 30 (2.1%) had insertion in exon 20, 74 (5.2%) had uncommon mutation, and 41 (2.9%) had G719X mutation. Among the 41 G719X mutations, 24 (58.5%) were G719X single mutations, 17 (41.5%) were compound mutations, such as G719X/S768I mutations (11, 26.8%), G719X/L861Q mutations (4, 9.8%), G719X/19del mutation (1, 2.4%),

and G719X/c-Met mutation (1, 2.4%).

Treatment response

Seventeen cases underwent first-line treatment, such as targeted therapy (12 cases), chemotherapy (4 cases), and immunotherapy (1 case). Sixteen patients had received targeted therapy during the whole treatment period, with gefitinib (4 patients), erlotinib (2 patients), icotinib (8 patients), afatinib (6 patients), and osimertinib (2 patients); 6 patients received two or more kinds of EGFR-TKIs, and 1 patient received three kinds of EGFR-TKIs. The ORR of the first-line targeted therapy was 6/12 (50%), DCR was 10/12 (83.3%), 2 patients showed disease progression after 1 month of EGFR-TKI treatment (2/12, 16.6%), and the median PFS (mPFS) was 9 months. It is worth mentioning that, after showing resistance to the previous EGFR-TKIs, the patients (6 cases) receiving other kinds of EGFR-TKIs demonstrated good ORR (5/7, 71.4%), DCR (7/7, 100%), and mPFS (8 months). Patients can receive different types of EGFR-TKIs consecutively; mostly afatinib or osimertinib is chosen after gefitinib/erlotinib/icotinib. Combining all EGFR-TKI treatments, the total ORR was 12/22 (54.5%), DCR was 20/22 (90.9%), and mPFS was 9 months, regardless of the treatment lines. The mean PFS of single G719X mutation (8 cases) was 7.0 months compared to 11.2 months for compound G719X mutation (8 cases), and the mPFS was 3 months compared to 12 months for EGFR-TKI treatment given for the first time (P = 0.08).

Six patients received chemotherapy, including first, second and third treatment lines. The chemotherapy regimen included pemetrexed or paclitaxel with platinum, either alone or in combination with antivascular therapy (bevacizumab/endostatin). The ORR was 2/6 (33.3%), DCR was 6/6 (100%), and mPFS was 6 months. A patient received second-line chemotherapy combined with EGFR-TKI had achieved the partial response (PR) as the best response; PFS reached 12 months (Table 2).

Table 1 Clinicopathological features of 41 patients with EGFR gene G719X mutation in NSCLC

Clinical characteristics	No. of patients (n = 41)	Proportion (%)
Age (years)		
Median	67	
Range	42-81	
< 60	11	26.8
≥ 60	30	73.2
Gender		
Male	15	36.6
Female	26	63.4
Smoking status		
Never	32	78.0
Ever	9	22.0
Histology		
Adenocarcinoma	40	97.6
NSCLC	1	2.4
TNM staging		
I	12	29.3
II	1	2.4
III	6	14.6
IV	20	48.8
Unknown	2	4.9
Mutation type		
Single mutation	24	58.5
Compound mutation	17	41.5

Discussion

In this study, we analyzed 41 NSCLC patients with the uncommon mutation G719X of the EGFR gene and found that G719X is a sensitive mutation to EGFR-TKIs, and could be treated with consecutive EGFR-TKIs, i.e., the second- or third-generation EGFR-TKIs can be used after resistance to the first-generation EGFR-TKIs. The G719X showed a favorable response to chemotherapy.

The G719X mutation was reported first by Lynch *et al* in 2004 [13], where a patient with the G719C mutation had shown a good response to gefitinib. The best response was PR and the overall survival time was 17.9 months. It is known that G719X is a point mutation located in exon 18 of the EGFR gene, i.e., glycine at position 719 is substituted by other amino acids, generally by alanine (G719A), cysteine (G719C), or serine (G719S) [14]. It is the most frequently seen uncommon mutation, accounting for about 3% of the EGFR mutations. It is reported that rare mutations, which are different from common mutations, are more common in males [15–16], and are related to smoking history [15–16]. In this study, 63.4% are females, and 22% are smokers, which is inconsistent with the previous reports. It may refer to the heterogeneity of uncommon mutations, which means not all uncommon mutations are related to males or smoking history. It is still not clear whether G719X mutation is related to males and smoking history and more cases are needed to make a conclusion.

The G719X often exists in the form of compound mutations [8, 15, 17–19]. In this study, 24 cases (58.5%) were single G719X mutations, and 17 cases (41.5%) were G719X compound mutations, including G719/S768I, G719X/L861Q, G719/19del, and G719X/c-Met. Studies consider that the formation of complex mutations occur because a single G719X mutation is not enough to drive tumorigenesis, making it necessary to work with other mutations to initiate tumorigenesis [14]. It has been found that the autophosphorylation level of G719S is relatively low, suggesting that the tumorigenicity of G719S is weaker than the other two uncommon mutations [20–21]. Compared to a single G719X mutation, the sensitivity of a complex mutation to EGFR-TKIs is still obscure.

Table 2 Clinicopathological and treatment information of 17 advanced NSCLC patients with G719X mutation

PT ID	Sex	Age	Smoking	Stage	Histology	EGFR mutation	Treatment	Treatment line	Best response	PFS (month)	PD or not
1	M	42	N	IV	ADC	G719X	Afatinib	1st line	PR	6	N
2	M	66	N	IV	ADC	G719X/S768I	Afatinib	1st line	PR	6	NA
3	F	55	N	IV	ADC	G719X/S768I	PN	1st line	SD	6	Y
							TC + icotinib	2nd line	PR	12	Y
4	F	53	N	IV	NSCLC	G719X/L861Q	Gefitinib	1st line	SD	5	Y
5	M	64	N	IA→IV	ADC	G719X/L861Q	Erlotinib	1st line	PR	9	Y
							Afatinib	2nd line	PR	8	Y
6	F	42	N	IV	ADC	G719X/c-Met	Icotinib	1st line	SD	4	Y
							Icotinib + crizotinib	2nd line	SD	10	Y
							PN + Bev + PBmaint	3rd line	PR	9	NA
7	F	68	N	IV	ADC	G719X	PC + Bev	1st line	1st line	3	Y
							Erlotinib	2nd line	2nd line	3	Y
							Afatinib	3rd line	3rd line	7	N
8	F	62	N	IIIA→IV	ADC	G719X/S768I	Icotinib	1st line	PR	4	N
9	F	77	N	IV	ADC	G719X/L861Q	Gefitinib	1st line	SD	5	NA
10	F	52	N	IV	ADC	G719X	Gefitinib	1st line	PD	1	Y
							TC + Bev + Bmaint	2nd line	PR	12	Y
							Osimertinib	3rd line	SD	2	Y
11	F	64	N	IV	ADC	G719X	PN + endostatin	1st line	SD	4	N
12	F	73	N	IV	ADC	G719X	Icotinib	1st line	PR	12	Y
13	M	63	Y	IV	ADC	G719X/S768I	Afatinib	1st line	PR	14	N
14	M	48	Y	IV	ADC	G719X	TP	1st line	SD	7	Y
							Icotinib	2nd line	SD	4	NA
15	M	70	Y	IV	ADC	G719X	Icotinib	1st line	PD	1	Y
							Apatinib	2nd line	SD	4	NA
16	F	63	N	IV	ADC	G719X	Pembrolizumab	1st line	SD	7	Y
							Gefitinib	2nd line	PR	1	N (DILI)
							Icotinib	3rd line	PR	7	Y
							Afatinib	4th line	SD	4	N
17	M	72	Y	IIIA→IV	ADC	G719X	Icotinib	1st line	SD	3	Y
						G719X/T790M	Osimertinib	2nd line	PR	9	Y

Pt: patient; M: male; F: female; Y: Yes; N: No; ADC: adenocarcinoma; NSCLC: non-small cell lung cancer; PR: partial remission; SD: stable disease; PD, progressive disease NA: not available; PC: pemetrexed and carboplatin; PN: pemetrexed and nedaplatin; TC: taxol and carboplatin; TP: taxol and cisplatin; Bev: bevacizumab; PBmaint: pemetrexed and bevacizumab maintenance therapy; Bmaint: bevacizumab maintenance therapy; DILI: drug-induced liver injury

The PFS for a compound mutation was reported to be significantly shorter compared to a single mutation (5.7 vs 12.3 months; $P = 0.02$), and inefficient to EGFR-TKIs (38% vs 89%; $P < 0.001$) [22]. However, only 1 of the 8 compound mutations reported in the study was related to G719X (G719S/S768I), the best response was PR, and PFS reached 13.1 months. All the other mutations were common sensitive mutations, combined with PIK3CA or exon 20–21 mutations. Similar results were shown in another study (mPFS 3.0 months vs 12.3 months, $P = 0.03$), but all of them were EGFR mutations in combination with another mutation, such as TP53, KRAS, CTNB1, PIK3CA, SMAD4, and MET. In our study, 16 patients were treated with EGFR-TKIs, PFS was not significantly different between a single G719X mutation and a G719X compound mutation ($P = 0.08$), but G719X compound mutation had a tendency to have longer PFS than single G719X mutation, similar to a study by Chiu *et al* [23]. Chiu *et al* reported a significant difference in the PFS between a single and compound G719X/L816Q/S768I EGFR mutation, and patients with compound mutations had a longer PFS and OS than those with a single mutation [23]. Therefore, there is heterogeneity among the different compound mutations in their response to EGFR-TKIs. We assumed that G719X might have a good response in combination with other mutations within the EGFR gene, such as G719X/L861Q and G719X/S768I. However, if G719X is combined with mutations outside the EGFR gene, such as KRAS, TP53, or PIK3CA, it may affect the efficacy of EGFR-TKIs.

In our study, 17 patients received first-line treatment, and 16 patients received EGFR-TKIs during the course of treatment. Targeted medicine included first-generation, second-generation, and third-generation EGFR-TKIs, including gefitinib, erlotinib, icotinib, afatinib, and osimertinib. The mPFS of the first-line targeted therapy

was 9 months, which was similar to and slightly longer than the previous reports; Shi *et al* (27 cases) reported that mPFS of first-line targeted therapy to G719X was 8.2 months [16], Zhang *et al* (22 cases) reported 7.6 months [24], Pilotto *et al* (6 cases) reported 8.38 months [4], and Wu *et al.* (15 cases) reported 8.1 months [25]. The length of PFS may be related to the type of EGFR-TKIs used. All patients in the above studies received first-generation EGFR-TKIs, including gefitinib, erlotinib, or icotinib. However, in our study, patients received first-generation (gefitinib, erlotinib, or icotinib) and second-generation EGFR-TKIs (afatinib) as the first-line treatment. Preclinical and clinical studies have also confirmed that the sensitivity of different EGFR-TKIs to G719X mutation is different. An in vitro study showed that gefitinib had a lower affinity to uncommon mutations than to common mutations [26]. Compared to L858R mutated cells, the concentration of gefitinib needed for G719X mutated cells to inhibit cell growth was 6 times more [27]. Jiang *et al* found that gefitinib could inhibit G719X autophosphorylation in a dose-dependent manner, and G719S needs a higher concentration of gefitinib than L858R mutated cells [28]. Some researchers compared the sensitivity of erlotinib and gefitinib to G719X mutation and found that erlotinib was more sensitive than gefitinib. Compared to erlotinib, irreversible EGFR-TKI (WZ-4002) could inhibit the growth of G719X cells at low concentrations [29]. Some in vitro studies have suggested that afatinib is sensitive to G719S and L861Q mutations [30]. Preclinical studies have also shown that neratinib is more sensitive to G719S and L861Q mutations than erlotinib [31]. Neratinib showed considerable efficacy in G719X mutations in a phase-II clinical study. Three of the 4 patients achieved PR with tumors shrinking by more than 50%, 1 achieved stable disease (SD) with a response rate of 75% and a disease control rate of 100% and this state was maintained for 40 weeks [32]. In addition, in the Lux-Lung 3 and 6 studies, Yang et al. reported that the second-generation EGFR-TKI, afatinib, showed a good therapeutic effect on G719X, with an effective rate of 77.8% (14/18), mPFS of 13.8, and OS 26.9 months, which was significantly better than that the first-generation EGFR-TKIs having ORR of 35.1% (47/134) [14] and mPFS 7.6~8.38 months [4, 16, 24–25] (Table 3). Based on the above results, we can roughly sort the sensitivity of different EGFR-TKIs to G719X as gefitinib < erlotinib < afatinib / neratinib / WA-4002. Therefore, in our study, we can see that the patients can still benefit from EGFR-TKIs after being resistant to the previous EGFR-TKIs. The mPFS is 8 months, and the order of drug used is in line with the above sensitivity; thus, after resistance to gefitinib/erlotinib/icotinib, afatinib/osimertinib can be used. However, it is still unknown which modality can result in longer survival: second- or third-generation EGFR-TKIs should be directly chosen as the first-line therapy, or used after resistance to the first-generation EGFR-TKIs. More cases or prospective clinical trials are needed to make a conclusion.

A large number of clinical trials have confirmed that the efficacy of EGFR-TKIs is much better than systemic chemotherapy in the patients harboring common sensitive mutations [1-3]. However, there was no significant difference in the efficacy and survival between chemotherapy and EGFR-TKIs in uncommon mutations. In a study, among 70 patients with uncommon mutations, 30 patients were treated with EGFR-TKIs, and 40 patients underwent platinum-based chemotherapy [16]. The results showed that there was no difference between EGFR-TKIs compared with chemotherapy (ORR, 23.3% *vs* 27.5%, P = 0.693; DCR, 93.3% *vs* 82.5%, P = 0.5. 328; mPFS, 7.1 *vs* 6.1 months, P = 0.893). Arrieta *et al.* [34] also reported similar results. In patients with uncommon mutations, the response rate of platinum-based chemotherapy was 49.6%, and mPFS was 6.0 months (95% CI, 5.1–6.6), and there was no difference in ORR and PFS between chemotherapy and EGFR-TKIs. Therefore, the authors suggested that platinum-based chemotherapy could be the first-line treatment for patients with uncommon mutations. In our study, 6 patients had received chemotherapy during the course of the disease, including first-, second-, or third-line chemotherapy. The regimens were pemetrexed or paclitaxel combined with platinum, and with or without anti-vascular therapy (bevacizumab/endostatin). The ORR was 33.3% (2/6), DCR 100% (6/6), and mPFS 6 months. Patients can benefit from

Table 3 Response and survival to EGFR-TKIs in patients with the G719X mutation

Reference number	Year of publishing	Case number	ORR	DCR	PFS	OS	EGFR-TKI
33	2015	18	77.8	NA	13.8	26.9	Afatinib
14	2017	134	35.1	NA	NA	NA	G/E/I
4	2018	6	0.0	66.7	8.38	17.0	G/E
16	2017	27	NA	NA	8.2	NA	G/E/I
24	2017	22	22.7	90.0	7.6	NA	G/E/I
25	2011	15	55.3	NA	8.1	16.4	G/E

ORR: overall response rate; DCR: disease control rate; PFS: progression free survival; OS: overall survival; EGFR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor; G: gefitinib; E: erlotinib; I: icotinib; NA: not available

chemotherapy regardless of the treatment lines (PFS 3-12 months). Hence, we suggest that patients with G719X mutation should receive both EGFR-TKIs and chemotherapy during the course of treatment, so that they can survive longer than those who only receive EGFR-TKIs or chemotherapy.

Another feasible choice is to combine EGFR-TKI treatment with chemotherapy. A phase-III clinical trial, NEJ009, comparing gefitinib monotherapy with gefitinib combined with pemetrexed and platinum, showed that the OS of gefitinib combined with chemotherapy was significantly longer than that of gefitinib monotherapy (OS 52.2 *vs* 38.8 months, $P = 0.013$) [35]. This study assumed that the OS of a patient depends more on the efficacy of the initial treatment. The higher the remission rate of the initial treatment, the longer is the remission time, and the longer the patient will live. Therefore, the most effective treatment should be used at the first-line. Some patients in the single drug group developed rapid disease progression and died after gefitinib resistance, losing the opportunity to receive second-line treatment, resulting in a significantly shortened OS. In addition, the higher the remission rate of the initial treatment, the lower the residual tumor burden. It will reduce the diversity of the cancer cells and slower the rate of drug resistance of the cancer cells, i.e., lower the drug-resistant tumor burden and reduce the risk of death caused by disease progression, so that patients can have the opportunity to receive the next generation treatment. In this study, one patient received TC plus icotinib as the second-line treatment, and the PFS lasted for 12 months; whereas the PFS was 6 months with PN regimen in the first-line treatment. The survival of the patient was prolonged, which was longer than the first-line PFS. Therefore, EGFR-TKI combined with chemotherapy is a good choice for the patients with good performance status.

The limitation of this study is that the case number is small, and it is a retrospective study. The conclusions drawn from the study are preliminary, and more cases and prospective studies are needed to confirm the results. However, the advantage of this study is that we focused on a single mutation, G719X, and thereby avoided the diverse sensitivity of different uncommon mutations, making the results relatively credible.

Conclusion

The G719X is a sensitive mutation of the EGFR gene. It is sensitive to many kinds of EGFR-TKIs. It can be treated with consecutive EGFR-TKIs treatments. After resistance to the first-generation EGFR-TKIs, the second- or third-generation EGFR-TKIs can be used. The G719X mutation in NSCLC also showed a favorable response to chemotherapy. Combination treatment using EGFR-TKIs and chemotherapy is another alternative.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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