Clinical characteristics and response to tyrosine kinase inhibitors of patients with non-small cell lung cancer harboring uncommon epidermal growth factor receptor mutations

Yan Zhang[1*], Zheng Wang[2*], Xuezhi Hao[1], Xingsheng Hu[1], Hongyu Wang[1], Yan Wang[1], Jianming Ying[3]

[1]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China; [2]Department of Pathology, Beijing Hospital, National Center of Gerontology, Beijing 100730, China; [3]Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China

*These authors contributed equally to this work.

Correspondence to: Yan Wang. Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China. Email: wangyanyifu@126.com; Jianming Ying. Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China. Email: jmying@hotmail.com.

Abstract

Objective: To investigate the clinical features of patients with non-small cell lung cancer (NSCLC) harboring uncommon epidermal growth factor receptor (EGFR) mutations, and the treatment outcomes of EGFR tyrosine kinase inhibitors (TKIs) in these patients.

Methods: We retrospectively analyzed the data of 128 NSCLC patients pathologically diagnosed with uncommon EGFR mutation in the Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and Beijing Hospital from January 2010 to December 2015, including 40 advanced patients who received EGFR-TKI.

Results: Among the total 128 patients, 11 patients were non-adenocarcinoma, including squamous carcinoma (3.9%), adenosquamous carcinoma (2.3%), large cell carcinoma (0.8%), and composite neuroendocrine carcinoma (1.6%). Single mutations accounted for 75.0% (96/128), including G719X (29.7%), S768I (18.0%), 20 exon insertion (13.3%), L861Q (12.5%), *De novo* T790M (0.8%), and T725 (0.8%). Thirty-two patients harbored complex mutations. Forty advanced patients received EGFR-TKI, the objective response rate (ORR) was 20.0%, the disease control rate (DCR) was 85.0%, and the progression-free survival (PFS) was 6.4 [95% confidence interval (95% CI), 4.8–7.9] months. The exploratory analysis of tumor response and PFS in 33 patients with G719X/S768I/L861Q subtypes showed that ORR was 21.2% (7/33), the DCR was 93.9% (31/33), and PFS was 7.6 (95% CI, 5.8–9.4) months. Patients with exon 20 insertion mutation and *De novo* T790M experienced rapid disease progression with PFS no more than 2.7 months.

Conclusions: Uncommon EGFR-mutant NSCLCs are heterogeneous, EGFR-TKIs can have different efficacy in this specific subtype, and thus further individual assessment is required for each case.

Keywords: Non-small cell lung cancer; EGFR; uncommon mutation; target therapy

Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death [1,2]. The traditional therapy was based on cancer histology. However, since the identification of epidermal growth factor receptor (EGFR) in 2004, therapy paradigm has been changed toward molecularly driven strategy based on driver mutations in genes and specific inhibitors of these pathways. EGFR is the product of oncogene *C-erbB-1* (*HER-1*). It is not created equally in different races, with higher mutation incidence in Asian than in Caucasian (30%–60% *vs*. 10%–20%) [3-5]. EGFR mutation is an effective factor of EGFR tyrosine kinase inhibitors (TKIs) treatment response in NSCLC, of which short in-frame deletion in exon 19 (19 del) and L858R substitution account for 90%. These common EGFR mutations are associated with good efficacy of EGFR-TKI, and the objective response rate (ORR) and progression-free survival (PFS) are approximately 70% and 10–11 months, respectively [3-6].

The remaining 10% of EGFR mutations are generally called uncommon mutation, including a heterogeneous group of molecular alterations within exon 18–21. The clinical characteristics and therapeutic effects of EGFR-TKIs on NSCLC with uncommon EGFR mutation subtypes remain unclear. Here we summarized the clinical data of patients who harbored uncommon EGFR mutations in order to perform a retrospective analysis of NSCLC patients with uncommon EGFR mutations and to reveal their association with treatment outcomes after TKI therapy.

Materials and methods

Patients

From January 2010 to December 2015, patients with histologically diagnosed uncommon EGFR mutation by amplification refractory mutation system (ARMS) or direct sequencing in the Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and Beijing Hospital were enrolled. Uncommon EGFR mutations were defined as all mutations except 19 del, L858R point mutation or acquired T790M mutation. Pathological diagnosis was based on specimens from surgery, percutaneous transthoracic biopsy, transbronchial biopsy, lymph node biopsy, or metastatic tumor biopsy. Patients were eligible for TKI efficacy analysis if they had

stage IIIB/IV (American Joint Committee on Cancer AJCC TNM Staging system, 7th edition) NSCLC with uncommon EGFR mutation and had been treated with EGFR-TKIs (gefitinib, erlotinib or icotinib) for more than one month. The type of EGFR TKIs depended on the physicians' discretion. Patients were given 250 mg of gefitinib daily or 150 mg of erlotinib daily, whereas patients who were treated with nicotine received 125 mg three times daily. Patients received TKI as adjuvant therapy or with other concomitant anticancer therapy were excluded.

Follow-up and effectiveness evaluation of TKI

All enrolled patients were under regular clinical follow-up exams including a physical examination, chest enhanced computed tomography (CT) (including liver and adrenal glands) and routine laboratory test one month after initial treatment and then every 2 months thereafter to evaluate the response to treatment. Baseline assessments were carried out before treatment. The responses were defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to the criteria of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). The treatment response and PFS were determined by review of CT by one chief physician and one attending doctor, and sometimes another one chief physician was needed when different evaluation results occurred. Disease control status comprised CR, PR and SD. The cutoff date was December 31, 2015. PFS was measured from the first day of EGFR-TKI treatment until the clinical sign of disease progression or death or cutoff date.

Ethics

This retrospective study was approved by the Institutional Ethics Review Board of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. Informed consent was exempted by the board due to the retrospective nature of this research. Patient records were anonymized and de-identified prior to analysis.

Statistical analysis

All analyses were carried out by SPSS software (Version 13.0; SPSS Inc., Chicago, IL, USA). Demographic and clinical data were summarized as medians with ranges for continuous variables, and categorical variables were

expressed as the means of absolute and percentage numbers. PFS after EGFR-TKI treatment was estimated by the Kaplan-Meier method to assess the time to death or progression.

Results

Characteristics of NSCLC patients with uncommon EGFR

From January 2010 to December 2015, excluding 19 del, L858R point mutation or acquired T790M mutation, 128 patients with driver oncogene detection were enrolled. Among these patients, 59.4% were women, 62.5% were never smokers, and the median age was 58 years old. Eleven patients were non-adenocarcinoma, including squamous carcinoma (3.9%), adenosquamous carcinoma (2.3%), large cell carcinoma (0.8%), and composite neuroendocrine carcinoma (1.6%) (*Table 1*).

Table 1 Clinicopathological features of patients with NSCLC (N=128)

Characteristics	Case No.	%
Age (year)		
Median (range)	58 (31–83)	
Gender		
Female	76	59.4
Male	52	40.6
Smoking		
Never	80	62.5
Ever	48	37.5
Histology		
Adenocarcinoma	117	91.4
Squamous carcinoma	5	3.9
Adenosquamous carcinoma	3	2.3
Composite neuroendocrine carcinoma	2	1.6
Large cell carcinoma	1	0.8
TNM staging		
I	26	20.3
II	14	10.9
III	9	7.0
IV	79	61.7
EGFR mutation testing		
ARMS	113	88.3
Direct sequencing	15	11.7

NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis; EGFR, epidermal growth factor receptor; ARMS, amplification refractory mutation system.

Types of EGFR uncommon mutation

Of all 128 patients, single mutations account for 75.0% (96/128), including G719X (29.7%), S768I (18.0%), 20 exon insertion (13.3%), L861Q (12.5%), *De novo* T790M (0.8%), and T725 (0.8%). Complex mutations were detected in 32 patients: L858R + 19 del in 2 patients, L858R/19 del + uncommon mutation in 15 patients, and uncommon + uncommon mutation in 15 patients (*Table 2*).

Table 2 Types of EGFR uncommon mutation (N=128)

Uncommon EGFR mutation	Case No.	%
Single mutation	96	75.0
G719X	38	29.7
S768I	23	18.0
Exon 20 insertion	17	13.3
L861Q	16	12.5
T790M (primary mutation)	1	0.8
T725T synonymous mutation	1	0.8
Complex mutation	32	25.0
Sensitive+sensitive mutation	2	1.6
L858R + 19 del	2	1.6
Sensitive + uncommon mutation	15	11.7
L858R + *De novo* T790M	7	5.5
L858R + S768I	4	3.1
L858R + L861Q	1	0.8
19 del + G719X	1	0.8
19 del + *De novo* T790M	1	0.8
19 del + L861Q	1	0.8
Uncommon + uncommon mutation	15	11.7
G719X + S768I	9	7.0
G719X + *De novo* T790M	3	2.3
G719X + E709A	2	1.6
G719X + L861Q	1	0.8

EGFR, epidermal growth factor receptor; 19 del, exon 19 deletion.

EGFR TKI effectiveness and survival in patients with uncommon EGFR mutation

Forty advanced patients receiving EGFR TKI treatment were eligible for TKI effectiveness analysis. Gefitinib was administered in 26 patients, and erlotinib and icotinib were administered in 7 patients respectively. EGFR TKIs were used as first-line treatment for 21 patients, second line for 15, and third or later lines for 4 patients. By the time of cutoff date, 8 patients still had cancer remained controlled.

The ORR in those 40 patients was 20.0%, the disease control rate (DCR) was 85.0% and the PFS was 6.4 [95% confidence interval (95% CI), 4.8–7.9] months (*Figure 1*).
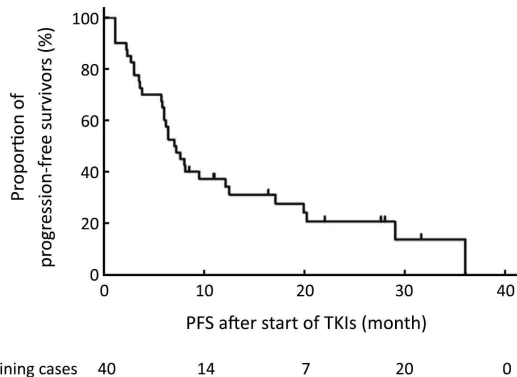

Figure 1 The PFS analysis of patients with EGFR uncommon mutations treated with EGFR-TKIs. PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

In the subset analysis, 2 patients with L858R + 19 del achieved PR, and PFS was 6.0 months and 6.2 months, respectively. Two patients with 20 exon insertion mutation experienced rapid disease progression after one-month treatment. *De novo* T790M occurred concurrently with sensitive mutations, L858R (2/3) or exon 19 deletion (1/2). Two patients with *De novo* T790M + L858R mutation had rather limited benefit from EGFR-TKI, with one having progressed disease after one month of TKI therapy and the other one suffering SD with PFS only 2.7 months. However, the PFS of the patient with *De novo* T790M + 19 del reached as long as 8.1 months. The exploratory analysis of tumor response and PFS in 33 patients with G719X/S768I/L861Q subtypes showed the DCR was 93.9% (31/33), ORR was 21.2% (7/33), and PFS was 7.6 (95% CI, 5.8–9.4) months. The subset analysis of G719X/S768I/L861Q subtype is demonstrated in *Table 3*.

Remarkably, a 64-year-old Chinese male, with 20 pack-years smoking history, was detected with S768I mutation. Nicotine was given 125 mg three times a day as second-line therapy. The tumor still maintained SD at the time of cutoff date, totally 31 months of TKI treatment.

Discussion

As the efficacy of EGFR TKIs for the treatment of patients

Table 3 Tumor response and PFS in G719X/S768I/L861Q subtypes

EGFR mutation	n (%)		PFS [median (range)] (month)
	DCR	ORR	
G719X (N=22)	20 (90.9)	5 (22.7)	7.6 (4.9–10.4)
G719X (n=14)			
G719X + S768I (n=5)			
G719X + L858R (n=2)			
G719X + E709A (n=1)			
S768I (N=11)	10 (90.9)	3 (27.3)	8.0 (4.3–11.8)
S768I (n=4)			
S768I + G719X (n=5)			
S768I + L858R (n=2)			
L861Q (N=5)	5 (100)	0 (0)	5.7 (1.6–9.8)
L861Q (n=4)			
L861Q + L858R (n=1)			

EGFR, epidermal growth factor receptor; DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival.

with uncommon mutations has not yet been fully elucidated, more research and data should be encouraged to share for clinical practice. In this study, we reported the clinical data of 128 NSCLC patients with uncommon EGFR mutations diagnosed in the Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and Beijing Hospital. We observed that uncommon EGFR mutations were harbored not only in adenocarcinoma, but also in squamous carcinoma, adenosquamous carcinoma, large cell carcinoma and carcinoid. Forty patients received EGFR-TKIs, the ORR was 20.0% and the PFS was 6.4 (95% CI, 4.8–7.9) months. Both results were inferior to the patients with common EGFR mutations in previous reports (5,6).

Mutations on G719X/S768I/L861Q constituted a major part of uncommon EGFR mutations, accounting for nearly 6% of EGFR mutations (7). One hundred and sixty-one patients with stage IIIB/IV lung adenocarcinoma bearing G719X/S768I/L861Q mutations were enrolled in a study from Taiwan, China. After receiving EGFR-TKI treatment, patients with those uncommon mutations exhibited a significantly inferior tumor response rate (41.6% *vs.* 66.5%; P<0.001) and PFS (median, 7.7 *vs.* 11.4 months; P<0.001) than patients with common mutations in the controlled group (8). The exploratory analysis of G719X/S768I/L861Q subtypes in our study showed that

the PFS was 7.6 (95%CI, 5.8–9.4) months, which was consistent with the previous research.

G719X in exon 18 was found with the highest incidence in our cohort. The frequency of exon 18 mutations was about 5%, among which G719X accounted for the majority. An *in vitro* study had indicated that the affinity of G719X mutation with ATP was lower than that of L858R but higher than that of wild type (9). A six-fold higher concentration of gefitinib was required to inhibit the growth of cells expressing G719X compared with cells expressing L858R (10). A previous study reported patients with G719X single mutation or compound mutations had a median PFS of 8.1 months and a median OS of 16.4 months (11). After receiving EGFR-TKI treatment in our study, patients with G719X single mutation or compound ones exhibited an ORR of 22.7% and a median PFS of 7.6 months. Therefore, first-generation EGFR-TKIs were active in G719X mutations though less effective than in common mutations. However, a preclinical and clinical study demonstrated that second-generation EGFR-TKI afatinib may be an optimal choice for G719X mutations, with a median PFS of 13.8 months (12). Additionally, E709X, S720P, V689M and insertion mutations in 18 exon were also rarely reported in previous studies. In our study, one of two patients with G719X + E709A received EGFR-TKI and experienced a PFS of 6.3 months. It was less effective than single G719X mutation due to E709A reducing the sensitivity of G719X to EGFR-TKI as demonstrated in an *in vitro* study (13,14).

In our current study, another uncommon mutation with high incidence was S768I. The frequency of mutation in exon 20 differed in diverse population, ranging from 1% to 17% (15-17). The efficacy of EGFR-TKI in S768I mutation was controversial. Kancha *et al.* showed in preclinical study that the IC_{50} value of gefitinib or erlotinib in S768I was higher than that of G719X and L861Q. In other words, S768I may be resistant to EGFR-TKI (10). However, a clinical study demonstrated similar response in S768I compared with 719X and L861Q (8). In our population, S768I mutation had favorable response (ORR, 27.3%; DCR, 90.9%) and survival (PFS, 8 months). Additionally, one patient harbored S768I with icotinib treatment as second-line therapy experienced 31 months of TKI treatment at the time of cutoff date and still maintained SD. Similarly, Masago *et al.* also reported the case of a patient harboring S768I with gefitinib as second-line therapy had a PFS as long as 15 months. Although National Comprehensive Cancer Network (NCCN)

Guidelines have not recommended it as drug-sensitive mutation, S768I indeed seemed to be sensitive to EGFR-TKIs (18,19).

The mutation of L861Q accounted for approximately 2% of EGFR mutations (20). The response of L861Q to EGFR-TKI in previous reports was inconsistent. A number of studies demonstrated that first-generation EGFR-TKI was active in patients with L861Q mutations though less effective than in those with common mutations, with a PFS of 8.9 months and an OS up to 21.98 months (7,10,21). Therefore, L861Q was recommended as TKI-sensitive mutation in NCCN Guidelines. However, there was a study elucidated first-generation EGFR-TKIs might be an ineffective treatment option for this patient population (22). In current study, the PFS of patients with L86IQ was 5.7 (95%CI, 1.6–9.8) months. Thus, cancers with L861Q mutation were probably heterogeneous and associated with different EGFR TKIs treatment responses.

EGFR exon 20 insertion mutation (approximate 10% of all EGFR mutations) was generally associated with insensitivity to available TKIs (23). Consistent with the previous study, patients with exon 20 insertion in our cohort suffered progressed disease one month after TKI therapy. However, it was reported that the effectiveness of EGFR-TKI in exon 20 insertion mutation depended on the type and location of the insertion, for instance, the specific EGFR-A763 Y764ins alteration was associated with a high DCR (13). Therefore, EGFR-TKI was not recommended as the first-line therapy for EGFR exon 20 insertion mutation in clinical practice.

EGFR T790M was considered as the most common mechanism of resistance to first-generation EGFR-TKIs. But before exposure to EGFR TKIs, patients with baseline EGFR T790M were detected by standard molecular analysis in our study. The incidence of primary T790M ranged from 1% to 25% depending on the detection method and the population tested (24). Generally, *De novo* T790M occurred concurrently with sensitive mutations as observed in our research (25). Proved by previous and current studies, *De novo* EGFR T790M mutations had limited benefit from EGFR-TKIs and reduced the sensitivity of classical active mutations (24).

According to previous studies, 3.19%–15% of patients with EGFR mutations had complex mutations (26,27). In this study, most complex mutations contained the 19 del or L858R mutations, and the result suggested that the concomitant occurrence of 19 del and L858R might be a strong predictive factor in terms of the efficacy of EGFR

TKIs. Earlier studies showed that patients with 19 del + L858R mutations had a median PFS of 9.53–16.5 months after TKI treatment (21,28). Furthermore, 19 del or L858R + rare mutations also seemed to be strong predictors of sensitivity. In current study, 2 patients with L858R + 19 del achieved PR and PFS of 6.0 months and 6.2 months, respectively. Consistent with previous studies, patients in our study who had a T790M mutation in addition to an L858R or 19 del mutation failed to demonstrate a superior response to EGFR TKI therapy, although contained an L858R or 19 del mutation. Therefore, first-generation TKIs such as erlotinib, gefitinib and icotinib maybe the optimal choice of therapy for patients with complex mutations containing 19 del or L858R mutations but not T790M.

The major limitation of this study is its retrospective design. Besides, uncommon EGFR mutations are heterogeneous and should be analyzed separately. However, due to its low incidence, the sample size in each subgroup is rather small. We therefore had to integrate the diverse mutations into one group and made conclusions combining with previous literature.

Conclusions

Uncommon EGFR-mutant NSCLC is a group of rare diseases with heterogeneity, and EGFR-TKIs can have different efficacy in specific subtypes. Thus, further individual assessment is required for each case.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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