Association between EGFR exon 19 or exon 21 mutations and survival rates after first-line EGFR-TKI treatment in patients with non-small cell lung cancer

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Abstract. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC) who have an EGFR mutation. However, little has been reported about the association between EGFR exon 19 deletions or an exon 21 mutation (specifically the L858R point mutation) and survival rates following first-line EGFR-TKI treatment in patients with NSCLC. As a retrospective study, 72 patients with stage IIIB/IV NSCLC carrying EGFR mutations (exon 19 deletions or an exon 21 mutation) were enrolled between 1 January 2008 and 31 December 2013, and all of the patients received first-line EGFR-TKI treatment. The associations between EGFR mutation status or clinical characteristics and response rate (ORR), progression-free survival (PFS) or overall survival (OS) were analyzed. Patients with exon 19 deletions (37 cases) had a higher ORR (75.7 vs. 51.4%; P=0.032), disease control rate (DCR; 89.2 vs. 68.6%; P=0.031), modified median PFS (13.2 vs. 10.8 months; P=0.030) and OS (30.2 vs. 25.6 months; P=0.030) compared with those with an exon 21 mutation (35 cases). Cox multivariate analysis indicated that sex, histological type and smoking history were key factors that affected PFS and OS. Mutations status was associated with PFS, but not OS. Following EGFR-TKI therapy, a better ORR, DCR, PFS and OS was observed in patients with EGFR deletions in exon 19 compared with those with an exon 21 mutation. The EGFR mutation status of patients with non-small cell lung cancer may therefore predict the efficacy and prognosis of EGFR-TKI.

Introduction

Lung cancer is the most common malignant tumor worldwide, with increasing annual incidence and mortality trends (1). Non-small-cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers (2). People diagnosed with NSCLC have a low 5-year survival rate (<15%) (3) and 30-40% patients with locally advanced or metastatic cancer are not eligible for radical operation (4).

Epidermal growth factor receptor (EGFR) gene mutations frequently occur in exons 18-21, while deletions in exon 19 and a mutation in exon 21 (specifically the L858R point mutation) occur during EGFR-tyrosine kinase inhibitor (TKI) treatment (5). Among the non-selective Chinese patients with NSCLC, the total rate of EGFR mutations is ~30% (6). In the patients with adenocarcinoma, the total rate of EGFR mutations is 50% and, in non-smoking patients with adenocarcinoma, it was 60-70% (6). EGFR-TKI, a small molecule drug that is in competition with ATP, binds to the tyrosine kinase of EGFRs on the cell membrane. Consequently, EGFR-TKI can prevent tyrosine phosphorylation and inhibit a series of signaling pathways associated with the formation, proliferation and apoptosis of malignant cells, so as to inhibit the proliferation of tumor cells (7).

The existing literature revealed that the EGFR mutation status (deletions in exon 19 and an exon 21 mutation) was an important index for predicting the effectiveness of the EGFR-TKI in the treatment of NSCLC, which is the current standard first-line treatment (8,9). However, there are only a small number of reports on the association between the two different mutation statuses and the response and survival rates following treatment (10).

The aim of the present study was to demonstrate that, NSCLC patients with EGFR exon deletions survive longer following EGFR-TKI treatment than those with exon 21 mutitions.

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Abbreviations: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate

Materials and methods

Eligibility criteria. The eligibility criteria were the following: i) Outpatients and inpatients diagnosed with advanced NSCLC (stage IIIB or IV) who had EGFR mutations (confirmed using second generation sequencing or the amplification refractory mutation system method) were enrolled in the Xuzhou Cancer Hospital (Xuzhou, China) between 1 January 2008 and 31 December 2013 [cancer classification was done according to the American Joint Committee on Cancer lung cancer staging criteria (Seventh Edition)] and were treated with the first-line EGFR-TKI treatment (11); ii) Aged between 18 and 75 years old; iii) A Eastern Cooperative Oncology Group performance status (PS) score of ≤2 (12). All the patients were screened for EGFR gene expression using second generation sequencing or the amplification refractory mutation system method. The samples were analyzed using histological approach and iv) The presence of ≤1 measurable lesion, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines, which was defined as the target lesions measurement (13).

The detection of EGFR mutation by ARMS-PCR was performed as follows: Tissues were paraffin embedded and sliced into 10 μm thick sections. Biopsy samples were stored for a maximum of 3 years. A microscope was utilized to observe the sections and to determine the tumor tissue content, the location of which was then marked. Tumor cells were then enriched to remove the effect of normal cells on the test results. Subsequently, commercial kits were utilized to extract human genomic DNA. Extracted DNA was then determined using a UV spectrophotometer. The optical density (OD) and concentration of DNA OD260/OD280 was required to be in the range of 1.8-2.0 and 3-300 ng/μl, respectively. Samples with a quality out of these ranges were discarded. Extracted DNA was then immediately tested or stored below -20°C for <6 months. The negative and positive controls were then set. The positive control was required to exhibit a typical amplification curve. According to the Ct value of different fluorescent signal channels, the sample test results were analyzed to determine whether or not the EGFR mutation was present.

Medical records and efficacy evaluation
Treatment plan. A total of 72 patients with advanced NSCLC (IIIB/IV) who had EGFR mutations (exon 19 deletions or a mutation in exon 21) were subjected to first-line EGFR-TKI treatment. This treatment consisted 250 mg/day gefitinib or 150 mg/day erlotinib administered orally.

Efficacy evaluation. To evaluate the curative effect, the type of response [either complete response (CR), partial response (PR), stable disease (SD) or progression disease (PD)], the objective response rate (ORR) of CR and PR patients, and the disease control rate (DCR) of CR, PR and SD patients were determined 3 months after treatment. These criteria were examined according to the RECIST 1.1 guidelines. Progression-free survival (PFS) was defined as the duration between treatment initiation and the start of disease progression or mortality (all-cause). Overall survival (OS) was defined as the interval between the initiation of medication and mortality (all-cause)

or the end of the follow-up period. Adverse drug reactions were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (14). Other characteristics assessed were as follows: Sex, age, histological type, clinical stage, PS score, smoking history, name of EGFR-TKI administered, whether the patients received subsequent surgical treatment or chemotherapy. Non-smokers were defined as patient who smoked ≤100 cigarettes during their lifetime. During the first two months of EGFR-TKI therapy, all patients underwent imaging examinations as detailed below, every 8±1 weeks. Patients underwent chest, abdomen and pelvic computer tomography scans, and brain magnetic resonance imaging every 3 months until disease progression.

Follow-up. All the patients were regularly followed up by the telephone every 3 months. The last follow-up was performed 18 months after the last recruitment date.

Statistical analysis. SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Categorical variables were reported as numbers and percentages, and continuous variables were reported as the mean ± standard deviation. Categorical variables were compared using a chi-square test. The association between EGFR mutation status, clinical characteristics and the effect of EGFR-TKI was tested by χ^2; PFS and OS were analyzed with the log-rank test and Cox regression analysis. P<0.05 was considered to indicate a statistically significant difference.

Results

Patients with deletions in exon 19 have similar clinical characteristics as patients with a mutation in exon 21. From a total of 72 patients, 37 cases were subjected to first-line oral gefitinib treatment and 35 to erlotinib; 20 cases were males and 52 cases were females (Table I). Among these cases, patients ≥70 years old accounted for ~51.4%. In addition, 61 cases were diagnosed with adenocarcinoma and 11 with squamous cell carcinoma. A total of 33 cases were in the IIIB stage and 39 in the IV stage; 31 cases had PS scores of 0 or 1 and 41 had PS scores of 2. There were a total of 15 smokers and 57 non-smokers. No statistical differences in these characteristics were identified between the exon 19 deletions and exon 21 mutation groups.

Patients with deletions in exon 19 exhibit an improved response and survival rate compared with patients that possess a mutation in exon 21. The curative effect among 72 patients was evaluated; there were 2 cases of CR, 44 cases of PR, 11 cases of SD and 15 cases of PD, with an ORR of 44% and DCR of 72% (Table II). Furthermore, the patients with deletions in exon 19 of EGFR included 1 case of CR, 27 cases of PR, 5 cases of SD, 4 cases of PD and an ORR of 75.7%, while patients with a mutation in exon 21 of EGFR included 1 case of CR, 17 cases of PR, 6 cases of SD, 11 cases of PD and an ORR of 51.4%. The ORR of patients with deletions in exon 19 was significantly higher compared with the patients with a mutation in exon 21 (χ^2=4.583; P=0.032). The patients with deletions in exon 19 had a DCR of 89.2%, while those with a mutation in exon 21 had a DCR of 68.6%. The DCR of patients with deletions in

Table I. Clinical characteristics of 72 patients with advanced non-small cell lung cancer carrying EGFR mutation.

Clinical characteristics	Exon 19 deletions (n=37)	An exon 21 mutation (n=35)	P-value
Sex			0.884
Male	10 (27.0)	10 (28.6)	
Female	27 (73.0)	25 (71.4)	
Age (years)			0.995
<70	18 (48.6)	17 (48.6)	
≥70	19 (51.4)	18 (51.4)	
Histological type			0.820
Adenocacinoma	31 (83.8)	30 (85.7)	
Squamous	6 (16.2)	5 (14.3)	
Clinical stage			0.984
IIIB	17 (45.9)	16 (45.7)	
IV	20 (54.1)	19 (54.3)	
PS score			0.974
0 or 1	16 (43.2)	15 (42.9)	
2	21 (56.8)	20 (57.1)	
Smoking history			0.866
Smoker	8 (21.6)	7 (20.0)	
Non-smoker	29 (78.4)	28 (80.0)	
EGFR-TKI			0.642
Gefitinib	20 (54.1)	17 (48.6)	
Erlotinib	17 (45.9)	18 (51.4)	
Sequential surgery			0.968
Surgery	1	1	
Non-surgery	36	34	
Sequential chemotherapy			0.925
Chemotherapy	5	32	
Non-chemotherapy	5	30	

Data are presented as n or n (%). EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PS, performance status

Table II. Efficacy of EGFR-TKI treatment.

Group	CR	PR	SD	PD	ORR (%)	P-value	DCR (%)	P-value
Exon 19 deletions	1	27	5	4	75.7	0.032	89.2	0.031
An exon 21 mutation	1	17	6	11	51.4		68.6	

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

exon 19 was significantly higher compared with the patients with a mutation in exon 21 (χ^2=4.686; P=0.031).

Following EGFR-TKI treatment, the modified median PFS in the patients with NSCLC who have deletions in exon 19 was 13.2 months, while it was 10.8 months in patients with a mutation in exon 21 (Fig. 1). The difference between the two groups' PFS was statistically significant (χ^2=4.700; P=0.030). Furthermore, significant differences in the PFS were observed between the sexes, patients with adenocacinoma or squamous, smoking and non-smoking patients, and patients with mutations in exons 19 and 21 of EGFR (Table III). The results revealed that the median PFS in females (P=0.009), patients with deletions in exon 19 (P<0.001), patients with adenocarcinoma (P=0.004) and non-smoking patients (P=0.046) were significantly higher compared with the median PFS in males, patients with a mutation in exon 21, patients with squamous cell carcinoma and smoking patients, respectively. No statistically significant differences in PFS were observed in relation to the patients' age, tumor stage, PS score and whether the patient had received gefitinib or erlotinib.
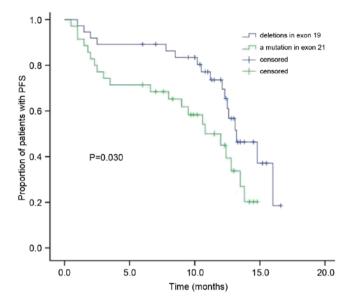
Figure 1. The Kaplan-Meier curve of PFS between the two groups. PFS, progression-free survival.

Figure 2. The Kaplan-Meier curve of OS between the two groups. OS, overall survival.

Following EGFR-TKI treatment, the median OS in the patients with NSCLC who had deletions in exon 19 was 30.2 months, while it was 25.6 months in patients with a mutation in exon 21 (Fig. 2). The difference between the two groups' OS was statistically significant (χ^2=4.700; P=0.030). Cox multivariate analysis demonstrated that the median OS in females (P=0.018), patients with adenocarcinoma (P=0.009) and non-smoking patients (P=0.003) were significantly higher compared with the median OS of males, patients with squamous cell carcinoma and smoking patients, respectively (Table IV). No statistically significant differences in OS were observed in relation to the patients' age, tumor stage, PS score, whether the patient had received gefitinib or erlotinib and whether the patient had mutations in exon 19 or 21 of EGFR.

Patients with deletions in exon 19 are similarly affected by adverse reactions as patients with a mutation in exon 21. The most common adverse reactions, which included rashes (48.6%), diarrhea (26.4%), coughs (2.8%), stomatitis (4.17%), anorexia (26.4%), nausea (11.1%) and vomiting (4.17%), occurred in a similar frequency in patients with deletions in exon 19 compared with those with a mutation in exon 21 (Table V). The majority of these reactions were mild and moderate, while a small number were classified as third degree adverse reactions according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Discussion

The present study demonstrated that, following EGFR-TKI treatment for patients with NSCLC, the curative effect in patients with deletions in exon 19 was significantly higher compared with patients with a mutation in exon 21 (ORR, 75.7 vs. 51.4%; DCR, 89.2 vs. 68.6%). Furthermore, significantly higher modified median PFS (13.2 months) and median OS (30.2 months) times were observed in patients with deletions in exon 19 compared with patients with a mutation in
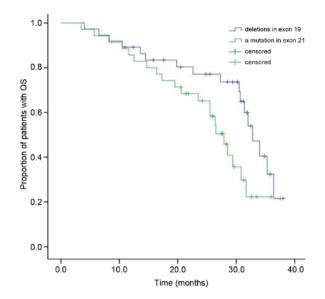
exon 21 (median PFS, 10.8 months; median OS, 25.6 months). Additionally, Cox multivariate analysis revealed that the PFS and OS were higher in female patients, patients with adeno-carcinoma cell carcinoma and non-smoking patients, and PFS was higher in patients with deletions in exon 19. No significant differences in PFS and OS were observed in relation to patients' age, tumor stage, PS score and whether the patient had received gefitinib or erlotinib, and no significant difference in OS was identified in patients with exon mutations.

Eight randomized phase III trials (IPASS, Fist-SIGNAL, W3405, NEJ002, OPTIMAL, EURTAC, LUX-Lung 3, LUX-Lung 6) demonstrated the excellent efficacy of EGFR-TKI against NSCLC. Compared with platinum-based chemotherapy, which had a 30% remission rate and median PFS of 5-6 months, EGFR-TKI was determined to be a better first-line treatment for NSCLC patients with EGFR mutations, with a 70% remission rate and median PFS of 10-11 months. Consequently, the consistency of EGFR-TKI demonstrated significant benefit in PFS and ORR as the first-line treatment in patients with EGFR mutations, thus it was established as a first-line treatment in these patients. According to some previous studies, patients with advanced NSCLC, an unknown EGFR mutation status or without any mutations, the first-line chemotherapy was revealed to be superior to first-line EGFR-TKI treatment (15-20). The LUX-Lung 3 clinical trail demonstrated that the median survival time for the patients with EGFR exon 19 deletions in the afatinib treatment group (33.3 months) was significantly longer compared with that of the chemotherapy treatment group (pemetrexed plus cisplatin; 21.1 months). For the patients with EGFR exon 21 mutations in the aforementioned trial, the survival time in the afatinib treatment group (27.6 months) was shorter compared with the chemotherapy treatent group (40.3 months). Furthermore, the LUX-Lung 6 clinical trail demonstrated that the median survival time for the patients with EGFR exon 19 deletions in the afatinib treatment group (31.4 months) was significantly longer compared with that of the chemotherapy treatment

Table III. Cox multivariate analysis of PFS and clinical characteristics among 72 patients with advanced non-small cell lung cancer carrying EGFR mutation.

Clinical characteristics	Exp (B)	95%CI	P-value
Sex			0.009
Male vs. female	4.600	1.455-14.546	
Age (years)			0.468
<70 vs. ≥70	1.378	0.579-3.280	
Histological type			<0.001
Adenocacinoma vs. squamous	0.011	0.001-0.119	
Clinical stage			0.340
IIIB vs. IV	0.653	0.272-1.567	
PS score			0.748
0 or 1 vs. 2	0.849	0.314-2.297	
Smoking history			0.004
Smoker vs. non-smoker	9.742	2.026-46.672	
EGFR-TKI			0.789
Gefitinib vs. erlotinib	0.887	0.368-2.136	
Group			0.046
Exon 19 deletions vs. an exon 21 mutation	2.256	1.013-5.025	

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PS, performance status; PFS, progression-free survival; CI, confidence interval; Exp (B), exponentiation of the B coefficient, an odds ratio.

Table IV. Cox multivariate analysis of OS and clinical characteristics among 72 patients with advanced non-small cell lung cancer carrying EGFR mutation.

Clinical characteristics	Exp (B)	95%CI	P-value
Sex			0.018
Male vs. female	3.152	1.220-8.141	
Age (year)			0.411
<70 vs. ≥70	1.455	0.595-3.559	
Histological type			0.009
Adenocacinoma vs. squamous	0.059	0.007-0.494	
Clinical stage			0.764
IIIB vs. IV	0.875	0.366-2.094	
PS score			0.368
0 or 1 vs. 2	0.646	0.250-1.671	
Smoking history			0.003
Smoker vs. non-smoker	8.322	2.061-33.614	
EGFR-TKI			0.787
Gefitinib vs. erlotinib	1.072	0.649-1.771	
Group			0.426
Exon 19 deletions vs. an exon 21 mutation	1.388	0.618-3.117	

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PS, performance status; OS, overall survival; CI, confidence interval; Exp (B), exponentiation of the B coefficient, an odds ratio.

group (18.4 months). As for the patients with EGFR exon 21 mutations, the survival time in the afatinib treatment group (19.6 months) was shorter compared with that of the chemotherapy treatment group (24.3 months). The two clinical trials

Table V. Adverse reactions among 72 patients with advanced non-small cell lung cancer and epidermal growth factor receptor mutations.

Adverse reaction	Exon 19 deletions (n=37)	An exon 21 mutation (n=35)	χ^2	P-value
Rash	18 (48.6)	17 (48.6)	<0.001	0.995
Degree III	1	1		
Degree IV	0	0		
Diarrhea	10 (27.0)	9 (25.7)	0.016	0.899
Degree III	0	1		
Degree IV	0	0		
Nausea	4 (10.8)	4 (11.4)	0.007	0.934
Degree III	0	0		
Degree IV	0	0		
Vomiting	2 (5.4)	1 (2.9)	0.292	0.589
Degree III	0	0		
Degree IV	0	0		
Fatigue	2 (5.4)	2 (5.7)	0.003	0.954
Degree III	0	0		
Degree IV	0	0		
Cough	1 (2.7)	2 (5.7)	0.049	0.523
Stomatitis	2 (5.4)	1 (2.9)	0.292	0.589
Anorexia	9 (24.3)	10 (28.6)	0.167	0.683
Interstitial pneumonia	0	0		

Data are presented as n or n (%).

demonstrated that afatinib could significantly prolong the survival time for patients with NSCLC and EGFR deletions of exon 19, but it could not prolong the survival time for the patients with exon 21 mutations (21,22).

Banno *et al* (23) confirmed that patients with NSCLC and EGFR exon 19 deletions had a distinct advantage following the treatment of afatinib compared with the patients with EGFR exon 21 mutations. The report from the NEJ002 study revealed that the patients with NSCLC and 21 exon mutations exhibited a relatively poor response to gefitinib, while the patients with NSCLC and exon 19 deletions had a greater response following gefitinib treatment (24). A meta-analysis revealed that, following EGFR-TKI as the first-line treatment for patients with NSCLC, the PFS for the patients with exon 19 deletions were markedly prolonged compared with patients with EGFR exon 21 mutations, however the study did not analyze OS (25). Additionally, a systematic review and meta-analysis revealed that in the patients with NSCLC and exon 19 deletions, OS was significantly improved following the EGFR-TKI treatment compared with those who had chemotherapy, while the patients with EGFR exon 21 mutations had no OS benefits with different treatments (5). Another study demonstrated that among the patients with advanced NSCLC that were treated with first-line TKI therapy, those with exon 19 deletions had longer PFS compared with those with exon 21 mutations (25). However, a retrospective clinical study conducted by Igawa *et al* (26) determined that no significant difference in ORR, PFS and OS was identified between patients with exon 19 deletions and patients with exon 21 mutations treated with gefitinib. In conclusion, the efficacy and survival rate of the afatinib treatment in patients with NSCLC and exon 19 deletions was better compared with those with exon 21 mutations. Only a small number of studies contradict the aforementioned studies regarding the comparison of the efficacy and survival rate between the two different mutations following EGFR-TKI treatment (10).

The studies described in the literature review had similar results to those obtained in the current study, indicating that following the administration of EGFR-TKI as the first-line treatment, patients with advanced NSCLC and deletions in exon 19 have greater ORRs, DCRs, PFS and OS compared with patients with mutations in exon 21. These rates and survival times were markedly improved in female patients, non-smoking and adenocarcinoma patients. Additionally, the two groups manifested predominantly mild side effects.

Therefore, the EGFR mutation status can be used as a predictive factor for the efficacy of EGFR-TKI as the first-line treatment among patients with advanced NSCLC. Furthermore, the patients with deletions in exon 19 of EGFR have significantly better outcomes in terms of response and survival rates compared with patients with a mutation in exon 21 of EGFR. However, due to the fact that the number of cases in the current study was quite small, further prospective and multicenter studies are required. The EGFR mutation status of patients with non-small cell lung cancer may predict the efficacy and prognosis of EGFR-TKI.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HJ performed the studies, participated in collecting data and drafted the manuscript. MZ and YF performed the statistical analysis and participated in its design. QL helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committees of Xuzhou Cancer Hospital (Xuzhou, China) and all patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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