Association between epidermal growth factor receptor gene mutation status and short-term efficacy of first-line platinum-containing chemotherapy in advanced non-small cell lung cancer

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Abstract. It remains undetermined whether there is an explicit association between the epidermal growth factor receptor (EGFR) gene mutation status and chemotherapy efficacy in non-small cell lung cancer (NSCLC) patients with advanced stages. Thus, the aim of the present retrospective study was to investigate the possible association between EGFR gene mutation status and the efficacy of first-line chemotherapy in patients with advanced NSCLC. In total, 52 patients who were diagnosed with NSCLC at Changzhou Tumor Hospital (Changzhou, China) from January 2015 to December 2018 were enrolled. All 52 patients received pemetrexed combined with platinum chemotherapy, for 21 days per cycle. After two cycles of treatment, the short-term clinical efficacy was assessed according to the Response Evaluation Criteria in Solid Tumours 1.1 guidelines. The objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) rate were calculated at the end of the study (December 31, 2019). These patients also underwent second-generation gene sequencing before the potential association between mutations in the EGFR gene and chemotherapy efficacy was analyzed. In this group of patients, 25 cases (48.1%) were found to be harboring EGFR gene mutation, whilst 27 cases (51.9%) expressed wild-type EGFR. After receiving the first-line chemotherapy regimen, the ORR was determined to be 36.5%, the DCR was 71.2%, whereas the PFS period was 207 days. Following first-line chemotherapy, the DCR of patients with EGFR mutations (52%) was higher compared with those in patients harboring the wild-type EGFR (22%). By contrast, the PFS (260 days) of patients with EGFR mutations was longer compared with those in patients harboring wild-type EGFR (100 days). These differences were statistically significant ($P<0.05$). Multivariate analysis revealed that EGFR gene mutation was an independent predictor of PFS in patients with advanced NSCLC ($P<0.05$). To conclude, data from the present study suggest that EGFR gene mutation has independent predictive value for the efficacy of first-line chemotherapy in patients with advanced NSCLC.

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Abbreviations: NSCLC, non-small lung cancer; EGFR, epidermal growth factor; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; CR, complete response; PR, partial response; SD, sTable disease; PD, progressive disease; DNA, deoxyribonucleic acid; NGS, next-generation sequencing; ECOG, Eastern Cooperative Oncology Group

Key words: non-small cell lung cancer, epidermal growth factor gene mutation, chemotherapy, progression-free survival

Introduction

Lung cancer currently ranks first in terms of mortality and morbidity compared with other types of malignancies worldwide. Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer subtypes (1), where lung adenocarcinoma is one of the most common types of NSCLC. Since typical criteria of early symptoms for NSCLC remain unavailable, ~50% patients are diagnosed with advanced NSCLC on presentation (2,3). Therefore, treatment of advanced lung cancer forms an important branch of the lung cancer treatment development research field, which is also incidentally the one that has experienced an acceleration in research progress over the past decade. Platinum-containing dual-drug chemotherapy is the standard first-line chemotherapy regimen for NSCLC (4). In addition, it is also an important method for the treatment of advanced NSCLC (4). However, the rate of efficacy from this treatment remains at only ~30%, with a median survival time of 8-10 months and a one-year survival rate of ≤40%. Exploring

novel biomarkers that can be used to predict the sensitivity of patients with NSCLC to chemotherapy is therefore currently a topic of intense research.

Epidermal growth factor receptor (EGFR) is an important driver of lung adenocarcinoma. Mutations in the EGFR gene is one of the main predictors of the efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs). For advanced or unresecTable lung adenocarcinoma, EGFR gene status detection has become an important parameter for the selection of clinical treatment options (5-9). Previous studies have found that the EGFR gene status can also influence the efficacy of chemotherapy in patients with lung adenocarcinoma. However, the accuracy of its predictive power remains controversial. A number of studies have previously reported that patients harboring EGFR gene mutations can benefit more from chemotherapy compared with those harboring wild-type EGFR in advanced stages. In addition, the Individualized Plan for Academic Success System (IPASS) subgroup analysis revealed that patients with NSCLC harboring EGFR mutations are more likely to benefit from paclitaxel combined with carboplatin chemotherapy compared with patients with wild-type EGFR in the Asian and non-smoking lung adenocarcinoma subgroups (10). Yang *et al* (11) and Hotta *et al* (12) also previously revealed the survival benefits of EGFR gene mutations for patients with NSCLC. However, several previous clinical studies have reached different conclusions. Okamoto *et al* (13) and Qin *et al* (14) observed that there was no significant difference in the efficacy of chemotherapy between patients with advanced lung adenocarcinoma harboring EGFR gene mutations and those with wild-type EGFR. Similarly, Zhang *et al* (15) reported that EGFR mutations did not confer survival benefits to patients with NSCLC following a meta-analysis (15). By contrast, Zhu *et al* (16) and as well as other studies (17,18) determined that the survival time of patients with NSCLC containing wild-type EGFR may be longer compared with that in patients with EGFR mutations. Therefore, it remains unknown whether there is an association between the EGFR gene mutation status and chemotherapy efficacy, or whether EGFR mutations can confer chemotherapy efficiency and thereby prolong patient survival time. At present, since ambiguities in the currently available findings remain, additional evidence-based analysis is required.

Therefore, the present study statistically analyzed the clinical efficacy of first-line chemotherapy and its association with the EGFR gene mutation status in patients with advanced lung adenocarcinoma. The aim was to provide a theoretical basis for optimizing the therapeutic regimen for patients with advanced lung adenocarcinoma.

Patients and methods

Patients. Patients with pathologically diagnosed advanced lung adenocarcinoma at Changzhou Tumor Hospital (Changzhou, China) from January 2015 to December 2018, were selected as subjects in the present retrospective study. The Ethics Committee of Changzhou Tumor Hospital deemed the present study exempt from ethical approval due to it being retrospective in nature. The inclusion criteria were as follows: i) Lung adenocarcinoma was confirmed by cytology or histopathology analysis, where the foci could be measured definitively by computed tomography (CT) or magnetic resonance imaging (MRI); ii) stage III/IV confirmed by cytology or histopathology according to the lung cancer staging standard (8th edition) of the American Joint Committee on Cancer (AJCC) (19); iii) aged 18-75 years, with no sex discrimination; iv) the physical condition score according to the Eastern Cooperative Oncology Group guidelines (ECOG Performance Status) was 0-2 points (20); v) the blood samples for the examination of EGFR gene status were tested before treatment; vi) the routine blood test, liver and kidney function and electrocardiogram of patients were almost normal, such that no disease or dysfunction in the important organs could be detected; vii) after the diagnosis was confirmed, patients received standard first-line chemotherapy consisting of pemetrexed combined with cisplatin for ≥2 cycles, where their survival time was estimated to be >3 months; and viii) the patients or families of the patients consented to the content of this study and signed the informed consent form voluntarily. The exclusion criteria were as follows: i) Patients suffered from other malignant tumors and received other systemic antitumor treatment; ii) patients had a history of hypertension, hypertensive encephalopathy or uncontrolled hypertension at present; and iii) cases with incomplete clinical data.

Chemotherapy. In total, all 52 patients were treated with intramuscular injections of 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin on day 1. Subsequently, 1 week before chemotherapy, the patients started to take 400 μg folic acid once a day until the end of chemotherapy, and received an intramuscular injection of 1 mg Vitamin B12 once every 9 weeks. In addition, 4.0 mg dexamethasone was administered 30 min before pemetrexed twice a day for 3 consecutive days. Those who had attained disease control were treated for ≥7 cycles, following which the curative effect was evaluated after ≥2 cycles were completed. Finally, the 52 patients were treated for 215 cycles, with an average of 4.13 cycles per patient.

EGFR mutation test. EGFR gene mutations were assayed by high-throughput sequencing technology, using Illumina next-generation sequencing (NGS) protocols, including Illumina TruSeq library preparation, Illumina sample indexing, and Illumina synthesis by sequencing (SBS) protocols as recommended by Illumina, Inc. Plasma samples were isolated from 10 ml fresh peripheral blood, from which circulating tumor DNA (ctDNA) (to note, the patients were all diagnosed with advanced lung adenocarcinoma and thus there was no surgical tissue, and only puncture specimens were used to confirm the type of cancer; therefore, EGFR gene mutation detection was based on the ctDNA of the peripheral blood of patients) was extracted using QIAamp Circulating Nucleic Acid Kit (cat. no. 55114; Qiagen China Co., Ltd.). The DNA quantity was measured on Qubit 3.0 fluorometer with dsDNA HS Assay Kit (Life Technologies; Thermo Fisher Scientific, Inc.). A minimum of 6 ng of DNA was used as input for the amplicon-based enrichment step. Subsequently, libraries were prepared using the KAPA Hyper Prep Kit (cat. no. KK8500; KAPA Biosystems; Roche Diagnostics) according to manufacturer's protocols. Then, fragmented DNA was subjected to end-repairing, A-tailing, indexed-adapter ligation, size

Table I. Association between EGFR gene status and clinical features in 52 patients with NSCLC.

Characteristics	No. of patients		Total	χ^2	P-value
	EGFR mutation	EGFR wild-type			
Total	25	27	52		
Sex				6.385	0.0115
Male	7	17	24		
Female	18	10	28		
Age, years				0.2614	0.6092
<65	11	10	21		
≥65	14	17	31		
Clinical stage				0.0342	0.8532
III	8	8	16		
IV	17	19	36		
ECOG PS				-	0.1339
0-1	23	27	50		
2	2	0	2		
Smoking status				-	0.1696
Nonsmoker	16	22	38		
Smoker	3	11	14		

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

selection and PCR amplification. In brief, tumor DNA was amplified using either TruSeq kit or custom primers, and amplification products were confirmed with gel electrophoresis using a 2% agarose E-gel (Thermo Fisher Scientific, Inc.). Samples were indexed and pooled. The library fragments were then copied with the primer probe for 416 predefined cancer-associated genes, including all exons of EGFR. For targeted enrichment, indexed DNA libraries were pooled together for hybridization with customized xGen lockdown probes (Integrated DNA Technologies, Inc.) for 416 predefined cancer-relevant genes (21). Enriched libraries were amplified and subjected to NGS on Illumina Hiseq4000 platforms (Illumina, Inc.) to a targeted mean coverage depth of 3000X for ctDNA samples.

Observation and follow-up. Using the inpatient system of Changzhou Tumor Hospital, the clinical data of all cases were obtained and recorded, where the patients were followed up by outpatient, telephone or other means. Data that were collected at follow-up included the efficacy of chemotherapy, time to disease progression and time to mortality. The date of final follow-up was December 31, 2019.

Efficacy evaluation. According to the response evaluation criteria in solid tumors (RECIST) version 1.1 published in 2009 (22), all patients were evaluated at baseline before treatment, and after every 2 cycles of treatment. The efficacy evaluation was divided into complete response (CR), partial response (PR), sTable disease (SD) and progressive disease (PD). The objective response rate (ORR) was calculated as CR + PR, whereas the disease control rate (DCR) was calculated as CR + PR + SD. Progression-free survival (PFS) was defined as the time from the beginning of treatment to disease progression or death. Patients who did not progress or succumb to the disease at the end of the follow-up period were treated according to the follow-up deadline (December 31, 2019).

Statistical analysis. The statistical software SPSS 18.0 (SPSS, Inc.) was used for statistical analysis. Pearson's F test or Fisher's exact test were used to analyze the relationship among the EGFR gene status, clinical characteristics and chemotherapy efficacy. Kaplan-Meier survival curve and log-rank testing were used to analyze PFS, whereas Cox regression was used for multivariate analysis. Bilateral probability test was used in all statistical analyses, were $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients characteristics. As shown in Table I, amongst the 52 patients, 24 were male (46.2%) and 28 were female (53.8%). The age of the patients ranged from 36 to 75 years (median, 65±0.5), 21 were aged <65 years (40.4%), while 31 were aged ≥65 years (59.6%). In total, 16 patients were diagnosed with stage III (30.8%) and 36 patients were diagnosed with stage IV (69.2%). In total, PS scores of 50 patients were <2 (96.2%) whereas 2 patients scored 2 (3.8%). Furthermore, 14 patients were smokers (26.9%), while 38 cases were non-smokers (73.1%). A total of 25 patients were found with EGFR gene mutations (48.1%), whilst 27 patients were harboring wild-type EGFR (51.9%). The age, clinical staging, PS scores and

Table II. Efficacy evaluation of patients with different EGFR gene status.

EGFR gene status	CR (%) (n=0)	PR (%) (n=19)	SD (%) (n=18)	PD (%) (n=15)
EGFR gene mutation (n=25)	0	52.0 (13/25)	40.0 (10/25)	8.0 (2/25)
EGFR wild-type (n=27)	0	22.2 (6/27)	29.6 (8/27)	48.1 (13/27)

EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, sTable disease; PD, progressive disease.

Table III. Association between ORR, DCR and clinical features of 52 patients with NSCLC who were treated with chemotherapy.

Characteristics	Total	No. of patients	ORR (χ^2)	P-value	No. of patients	DCR (χ^2)	P-value
EGFR status			4.964	0.0259		-	0.0019
EGFR mutation	25	13			23		
EGFR wild-type	27	6			14		
Sex			-	0.0001		-	0.0024
Male	24	2			12		
Female	28	17			25		
Age, years			0.0368	0.8478		0.0013	0.9713
<65	21	8			15		
≥65	31	11			22		
Clinical stage			3.873	0.0491		-	0.7522
III	16	9			12		
IV	36	10			25		
ECOG PS			-	-		-	-
0-1	50	19			37		
2	2	0			0		
Smoking status			-	0.0019		7.474	0.0063
Nonsmoker	38	17			31		
Smoker	14	2			6		

ORR, objective response rate; DCR, disease control rate; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

smoking status of the patients were not found to be significantly different between the EGFR mutation and wild-type groups. However, the incidence of EGFR gene mutations in female patients was significantly higher compared with that in male patients (P=0.0115).

Effect of EGFR mutation on the response rate. Among the 52 patients, none achieved CR. By contrast, PR accounted for 36.5% (19/52), SD accounted for 34.6% (18/52) and PD accounted for 28.9% (15/52) (Table II). The ORR and DCR were calculated to be 36.5 and 71.2%, respectively. In 25 patients with EGFR gene mutation, the number of patients with PR, SD and PD were 13, 10 and 2, respectively. In 27 patients with EGFR wild-type, the number of patients with PR, SD and PD were 6, 8 and 13, respectively (Table II). The incidence of PR (52.0 vs. 22.2%), SD (40.0 vs. 29.6%) and PD (8.0 vs. 48.1%) were observed at higher frequencies in patients with EGFR gene mutations compared with those in patients with wild-type EGFR (Table II). In addition, it was found that both the ORR (52.0 vs. 22.2%; P=0.0259) and DCR (92.0 vs. 51.9%; P=0.0019) were higher in patients with the EGFR gene mutation compared with those in patients with the wild-type EGFR. Association analysis of the ORR and DCR with other clinicopathological features was also performed (Table III). ORR was found to be associated with sex (P<0.0001), clinical stage (P=0.0491), ECOG-PS (38.0 vs. 0%) and smoking history (P=0.0019). However, no differences in ORR could be found when age (38.1 vs. 35.5%) was compared. The DCR was only found to be associated with sex (P=0.0024), ECOG-PS (74.0 vs. 0%) and smoking history (P=0.0063), but not with age and clinical staging. Neither of the two patients with a PS score of 2 achieved CR, PR and SD, thus the chi-square test was not applicable.

Effect of EGFR mutation on survival. The clinical cases were followed up until December 31, 2019. As shown in Table IV, the median PFS was 207 days in the 52 cases. The patients with EGFR gene mutations had a significantly longer median PFS compared with that of patients with wild-type EGFR (260 days vs. 100 days, P=0.0005; Fig. 1 and Table IV). The median PFS of the female patients (300 days) was significantly longer (P=0.0001) compared with those in male patients

Table IV. Prognostic evaluation of PFS and clinical characteristics in all patients with NSCLC.

Characteristics	No. of patients	Median PFS (days)	P-value	Multivariate analysis	
				P-value	HR (95% CI)
EGFR status			0.0005	0.040	2.056 (1.035-4.087)
EGFR mutation	25	260			
EGFR wild-type	27	100			
Sex			0.0001	0.026	0.377 (0.160-0.889)
Male	24	99			
Female	28	300			
Age, years			0.1393	0.142	1.598 (0.855-2.990)
<65	21	256			
≥65	31	161			
Clinical stage			0.2402	0.953	0.980 (0.504-1.907)
III	16	186			
IV	36	258			
ECOG PS			0.0512	0.077	1.434 (0.046-1.171)
0-1	50	210			
2	2	90			
Smoking status			0.0001	0.467	0.233 (0.543-3.787)
Nonsmoker	38	255			
Smoker	14	90			

Independent variables with P<0.30 in the univariate analyses were included in the multivariate analysis of PFS in all patients after platinum-based chemotherapy. Cox's model was used for multivariate analyses with forward elimination. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

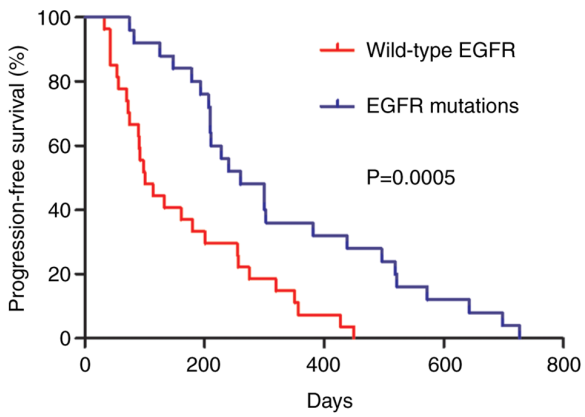

Figure 1. Analysis of PFS in EGFR gene mutant vs. wild-type patients with NSCLC. Kaplan-Meier analysis and log-rank testing revealed that NSCLC patients with EGFR gene mutation had longer PFS than EGFR wild-type patients (260 days vs. 100 days; χ^2=12.17; P=0.0005). PFS, progression-free survival; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

(99 days). The median PFS of nonsmokers (255 days) was also significantly longer (P=0.0001) compared with that of smokers (90 days). The PFS of age, clinical staging and ECOG PS were not found to be statistically significant. Cox multivariate regression analysis was subsequently used to determine the independent influencing factors of PFS by incorporating multiple factors, such as the EGFR gene mutation status, sex, age, clinical staging, smoking history and ECOG PS. The results demonstrated that the EGFR gene mutation status [hazard ratio (HR)=2.056; 95% confidence interval (CI)=1.035-4.087; P=0.04] and female sex (HR=0.377; 95% CI=0.160-0.889; P=0.026) were independent prognostic factors of PFS in patients with NSCLC after receiving platinum-containing chemotherapy.

Discussion

EGFR is one of the most studied molecular targets in lung cancer because its activity is closely associated with tumor growth, invasion and metastasis. EGFR is one of the most important drivers of NSCLC pathogenesis (23). EGFR gene mutations are major predictors of the efficacy of EGFR-TKIs in Asian patients with lung adenocarcinoma, where various studies have previously shown that patients with EGFR gene mutations tended to benefit more from concurrent treatment with EGFR-TKIs and standard first-line chemotherapy regimens (17,24-29). However, the relationship between the efficacy of chemotherapy and the EGFR gene status remains controversial.

Fang *et al* (29) previously reported that first-line chemotherapy was more effective in patients with KRAS-negative EGFR gene mutations compared with those with wild-type EGFR, amongst 266 patients with advanced NSCLC (29). In addition, Kalikaki *et al* (30) reported that patients with EGFR gene mutations were more sensitive to chemotherapy compared

with that in patients with wild-type EGFR, amongst patients with advanced NSCLC. Multi-factorial analysis revealed that EGFR gene mutation was an independent predictor of PFS in patients with advanced lung adenocarcinoma. Lou *et al* (17) previously suggested that paclitaxel in combination with carboplatin as first-line chemotherapy was more effective in patients with EGFR gene mutations compared with patients with wild-type EGFR. However, Lee *et al* (31) found no significant associations between the EGFR gene mutation status and the efficacy of first-line chemotherapy. Another study from Japan also found that patients with EGFR gene mutations and advanced NSCLC who were treated with doxorubicin chemotherapy exhibited worse outcome compared with patients with wild-type EGFR (32). The reasons for these ambiguous results may be due to the chemotherapeutic regimens and timing used not being completely uniform, such that the pathological types of lung cancer were not completely uniform and the sample sizes of a number of clinical studies were small. In addition, the EGFR gene mutation status may change during the course of the chemotherapeutic treatment period, which may also be associated with factors, such as region and ethnicity.

In the present study, 52 patients with advanced lung adenocarcinoma were tested for EGFR gene mutation status before the efficacy of first-line chemotherapy was analyzed retrospectively. The results revealed that for all patients with advanced lung adenocarcinoma treated with pemetrexed in combination with platinum-based regimens first line, the ORR, DCR and PFS of patients with EGFR gene mutations were superior compared with those of patients with wild-type EGFR, with the differences being statistically significant. Subsequently, Cox multivariate analysis showed that EGFR gene mutation was an independent predictor of PFS in patients with advanced lung adenocarcinoma, which is consistent with the results of previous studies (29,30).

In conclusion, following first-line chemotherapy for advanced lung adenocarcinoma, PFS was superior in patients with EGFR gene mutations compared with that in patients with wild-type EGFR. In addition, patients on pemetrexed-containing regimens had longer PFS regardless of EGFR gene mutations, which was more pronounced in those harboring EGFR mutations, suggesting that the EGFR gene mutation status can be an indicator for screening the pemetrexed-benefit population. However, the present study is a retrospective study that has a small sample size. Therefore, results found in the present study would need to be confirmed by prospective studies.

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Availability of data and materials

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

Authors' contributions

LC, QQ, MZ, YZ, YP and YL contributed to the conceptualization, analysis and methodology of the study. LC and YL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Ethics Committee of Changzhou Tumor Hospital deemed the present study exempt from ethical approval due to it being retrospective in nature. All enrolled subjects or family members of the patients consented to the content of this study and signed the informed consent form.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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