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ORIGINAL RESEARCH

Correlation between *EGFR* mutation status and response to first-line platinum-based chemotherapy in patients with advanced non-small cell lung cancer

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Background: The purpose of this research was to investigate the relationship between epidermal growth factor receptor (*EGFR*) mutations and the response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC).

Methods: A total of 266 patients with stage IIIB or IV NSCLC who received platinum-based doublet therapies as first-line chemotherapy were investigated retrospectively, and their clinical data were assessed according to *EGFR* mutation.

Results: *EGFR* mutations were identified in 45.5% of patients. There was no significant difference in response rate between *EGFR* mutation carriers and *EGFR* wild-type carriers (P=0.484). Among the patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) wild-type, however, those with *EGFR* mutations responded better to treatment than *EGFR* wild-type patients (46.2% versus 20.8%, P=0.043). The disease control rate associated with pemetrexed-based treatments was higher than for vinorelbine-based therapies in *EGFR* mutation patients (P=0.001). *EGFR* mutation was found in patients with longer progression-free survival and median survival time, and improved 1-year and 2-year overall survival when compared with *EGFR* wild-type patients (6.1 versus 5.0 months, P=0.004; 18.9 versus 13.8 months, P=0.001; 81.0% versus 63.4%, P=0.002; and 33.9% versus 22.8% P=0.044, respectively). Patients with the *EGFR* exon 19 mutation had longer progression-free survival than those with *EGFR* exon 21 mutation (P=0.007). Multivariate analysis showed that the response to first-line chemotherapy and the presence of *EGFR* mutations were independent prognostic factors in patients with advanced NSCLC.

Conclusion: Our data showed that the presence of *EGFR* mutations meant longer survival times for patients with advanced NSCLC who received platinum-based doublet first-line chemotherapy, especially in those with the exon 19 deletion mutation. Among *KRAS* wild-type patients, those with *EGFR* mutation responded better to first-line chemotherapy than *EGFR* wild-type patients.

Keywords: non-small cell lung cancer, chemotherapeutic agents, epidermal growth factor receptor mutation, targeted therapy, prognosis

Introduction

Lung cancer continues to be the main cause of carcinoma-related death throughout the world,[1] and 75%–80% of these cancers are non-small cell lung cancer (NSCLC).[2] Although surgery is the most effective treatment for NSCLC, about 70% of patients with NSCLC miss the opportunity for surgical resection because of their advanced disease at presentation.[3] Chemotherapy is the preferred treatment for these patients.

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There has been research showing that NSCLC patients with the epidermal growth factor receptor (*EGFR*) mutation respond better to *EGFR* tyrosine kinase inhibitors (TKIs) in terms of long-term survival.[4] Several Phase III clinical trials also indicated that NSCLC patients with mutated *EGFR* had better clinical outcomes from treatment with erlotinib or gefitinib than from normal chemotherapy.[5–7] At present, *EGFR* is the primary predictor of a curative effect of EGFR TKIs, and the relevant research[8–10] has shown that the mutation status of *EGFR* is probably the main determinant of response to first-line chemotherapy and the prognosis in patients with advanced NSCLC.

The standard first-line regimen for advanced NSCLC is platinum-based doublet chemotherapy.[11,12] Common chemotherapeutic agents are gemcitabine, docetaxel, vinorelbine, and pemetrexed, but there continues to be a lack of predictive biomarkers to select drugs for first-line chemotherapy. On this background, we reviewed the clinical outcomes in patients with advanced NSCLC who received platinum-based doublet therapies as first-line chemotherapy, and analyzed the predictive value of *EGFR* mutation status with regard to short-term effects and long-term survival in order to optimize the treatment of individual patients with advanced NSCLC.

Patients and methods

Patients

A total of 665 cases of stage IIIB or IV NSCLC treated at Shandong Tumor Hospital from July 2008 to December 2011 were screened, and 266 who received platinum-based doublet chemotherapy as their first-line treatment were analyzed retrospectively. These patients satisfied the following selection criteria: having a pathological diagnosis of NSCLC, clear *EGFR* mutation status, platinum-based doublet first-line chemotherapy for at least two cycles, measurable lesions, no uncontrolled diabetes or other serious disease, and an Eastern Cooperative Oncology Group performance status of 0–1.[13]

EGFR mutation analysis

Sequence analysis of *EGFR* exons 18–21 was done by pyrosequencing, as described elsewhere.[14] Briefly, the presence of tumor cells was identified on sections stained with hematoxylin and eosin. Formalin-fixed paraffin-embedded tissue samples were microdissected to confirm that the samples contained not less than 80% tumor cells. Xylene and ethanol were used to remove paraffin from the tumor tissues, and the samples were placed in proteinase K. Genomic DNA was extracted using a QIAamp DNA formalin-fixed paraffin-embedded tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Subsequently, *EGFR* exons 18–21 were amplified by nested polymerase chain reaction and subjected to pyrosequencing. The polymerase chain reaction products were analyzed by electrophoresis in 3% agarose gel to confirm successful amplification. The pyrosequencing assay was performed using the PyroMark Q24 ID system (Qiagen) following the manufacturer's protocols. Samples harboring mutations were resequenced using the same test conditions.

Evaluation methods

Based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines,[15] the response to treatment was classified as a complete response, partial response, stable disease, or progression of disease. Complete response and partial response were defined as the response rate, and complete response, partial response, and stable disease were defined as the disease control rate.

Follow-up

Follow-up was undertaken in all patients. The last follow-up was in January 2014, and the median duration of follow-up was 25.1 months. Overall survival was defined as the time from the date of receiving the first-line chemotherapy to death or last follow-up. Progression-free survival was defined as the time from the date of receiving the first-line chemotherapy to disease progression or death.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences version 17.0 software (SPSS Inc., Chicago, IL, USA). Rates were compared using the χ^2 test. Fisher's exact test was used to analyze categorical variables. Median progression-free survival was calculated using the Kaplan–Meier method. The Cox regression model was used to identify independent prognostic factors for advanced NSCLC. We used the Kaplan–Meier method to draw survival curves and tested these by log-rank. Two-sided *P*-values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The research cohort comprised 266 NSCLC patients of median age 57 (range 28–81) years, with 53.4% being male. One hundred and eighty patients had stage IV disease (67.7%), and 242 had adenocarcinoma (91.0%). The most common

Table 1 Relationship between clinical characteristics and *EGFR* mutation state

Characteristics	*EGFR* mutation	*EGFR* wild-type	*P*
No of patients	121	145	
Age (range)	57 (31–77)	57 (28–81)	
Sex			
Male	58 (47.9%)	84 (57.9%)	0.104
Female	63 (52.1%)	61 (42.1%)	
Smoking history			
Yes	32 (26.4%)	82 (56.6%)	<0.001
No	89 (73.6%)	63 (43.4%)	
ECOG			
0	21 (17.4%)	27 (18.6%)	0.789
1	100 (82.6%)	118 (81.4%)	
Histologic type			
Adenocarcinoma	117 (96.7%)	125 (86.2%)	0.003
Squamous cell carcinoma	4 (3.3%)	20 (13.8%)	
Weight loss			
≥5%	14 (11.6%)	20 (13.8%)	0.589
<5%	107 (88.4%)	125 (86.2%)	
Clinical stage			
IIIB	42 (34.7%)	44 (30.3%)	0.448
IV	79 (65.3%)	101 (69.7%)	
Chemotherapeutic regimen			
Gemcitabine	26	30	
Docetaxel	21	41	
Vinorelbine	31	19	
Pemetrexed	43	55	
Response			
CR + PR	39 (32.2%)	41 (28.3%)	0.484
SD + PD	82 (67.8%)	104 (71.7%)	
After first-line			
Received TKIs	58 (47.9%)	24 (16.6%)	<0.001
Unreceived TKIs	63 (52.1%)	121 (83.4%)	

Abbreviations: *EGFR*, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; TKIs, tyrosine kinase inhibitors.

sites of metastasis were the lung (33.3%, 60/180), pleura (26.7%, 48/180), bone (24.4%, 44/180), brain (21.1%, 38/180), and liver (15.6%, 28/180). All patients were treated with platinum-based doublet chemotherapy as first-line treatment, with gemcitabine, docetaxel, vinorelbine, and pemetrexed regimens administered in 56 (21.1%), 62 (23.3%), 50 (18.8%), and 98 patients (36.8%), respectively. After first-line chemotherapy, 82 patients received an EGFR TKI as second-line or third-line therapy, while 106 cases received continuous chemotherapy. *EGFR* mutations were identified in 121 patients (45.5%). Sixty-four patients (52.9%) harbored in-frame deletions in exon 19, which were caused by loss of codons 746–750 (delE746–A750). Fifty patients (41.3%) had tumors harboring amino acid replacements in exon 21, ie, leucine to arginine at codon 858 (L858R). Exon 18 (G719S) and exon 20 (T790M) mutations were found in five (4.1%) and two (1.7%) patients, respectively. There were more women (50.8%, 63/124) than men (40.8%, 58/142), more nonsmokers (58.6%, 89/152) than smokers (28.1%, 32/114), more patients with an Eastern Cooperative Oncology Group performance status of 1 (45.9%, 100/218) than 0 (43.8%, 21/48), and more with a weight loss of <5% (46.1%, 107/232) than a weight loss ≥5% (41.2%, 14/34).

Association of *EGFR* mutations with response to first-line chemotherapy

All 266 patients were treated with platinum-based regimens. In these patients, a partial response was documented in 30.1% (80/266), stable disease in 51.1% (136/266), and progression of disease in 18.8% (50/266). The overall response and disease control rates were 30.1% and 81.2%, respectively. In 145 patients with wild-type *EGFR*, the response rate and disease control rate were 28.3% and 83.4%, respectively. No differences in response rate or disease control rate were found when gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based treatments were compared (30.0% versus 29.3%, 26.3% , 27.3%, and 76.7%, 85.4%, 84.2%, and 85.5%, respectively). We found that carriers of the *EGFR* mutation had a response rate of 32.2% to chemotherapy, which was similar to the 28.3% for wild-type *EGFR* carriers (P=0.484). The disease control rate was 78.5%. No differences in response rate were found between gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based therapy in 121 patients with *EGFR* mutations (34.6% versus 28.6%, 29.0%, and 34.9%). However, the disease control rate was higher in pemetrexed-treated patients than in vinorelbine-treated patients (90.7% versus 58.1%, respectively, P=0.001). Further, although not significantly different, the response rates for the exon 19 mutation and the exon 21 mutation were 37.5% (24/64) and 24.0% (12/50, P=0.124). Differences in characteristics and response to chemotherapy between patients who received gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based therapies are shown according to *EGFR* status in Table 2.

Relationship between *EGFR* mutation and survival

The median progression-free survival for the 266 patients was 5.7 months (95% confidence interval [CI] 5.4–6.0), the median survival time was 16.8 months, and the 1-year and 2-year overall survival was 72.2% and 28.6%, respectively. There was a significant difference in progression-free

Table 2 Characteristics of patients receiving different regimens and the response to chemotherapy according to *EGFR* status

Characteristics	*EGFR* mutations				Wild-type *EGFR*			
	Gemcitabine	Docetaxel	Vinorelbine	Pemetrexed	Gemcitabine	Docetaxel	Vinorelbine	Pemetrexed
No of patients	26	21	31	43	30	41	19	55
Age (median years)	58	59	58	55	54	58	59	56
Sex								
Male	9	12	14	23	27	20	8	29
Female	17	9	17	20	3	21	11	26
Smoking history								
Yes	4	2	14	12	22	22	16	22
No	22	19	17	31	8	19	3	33
Histologic type								
Adenocarcinoma	25	19	30	43	21	33	16	55
Squamous cell carcinoma	1	2	1	0	9	8	3	0
Clinical stage								
IIIB	10	8	12	12	16	10	8	10
IV	16	13	19	31	14	31	11	45
Response								
CR	0	0	0	0	0	0	0	0
PR	9	6	9	15	9	12	5	15
SD	12	11	9	24	14	23	11	32
PD	5	4	13	4	7	6	3	8

Abbreviations: *EGFR*, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

survival between patients with *EGFR* mutation and those with *EGFR* wild-type (6.1 versus 5.0 months, respectively, *P*=0.004, Figure 1). *EGFR* mutation was found in patients with a longer median survival time (18.9 months, 95% CI 18–19.8) and 1-year and 2-year overall survival (81.0% and 33.9%, respectively) when compared with wild-type *EGFR* patients (13.8 months, 95% CI 12.7–15.1, and 63.4% and 22.8%, respectively, *P*=0.001, Figure 2). Patients with the *EGFR* exon 19 mutation had longer progression-free survival than those with the *EGFR* exon 21 mutation (*P*=0.007). Patients with the *EGFR* exon 19 mutation had a longer median survival time and 1-year and 2-year overall survival

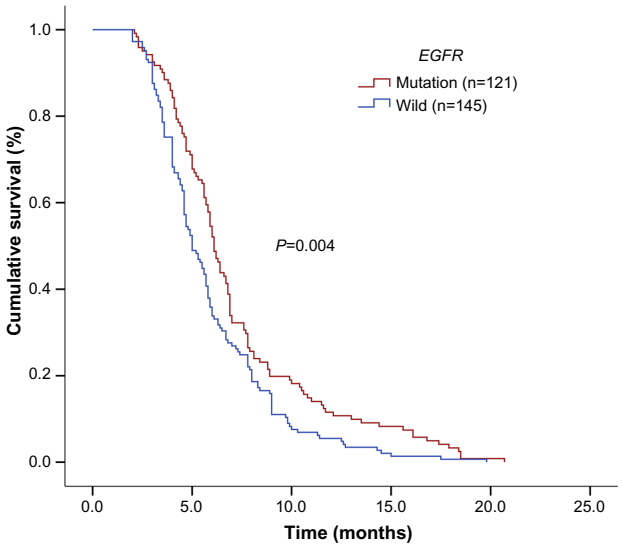

Figure 1 Kaplan–Meier estimates of progression-free survival according to *EGFR* status (*EGFR* mutation and *EGFR* wild-type).
Note: Kaplan–Meier analysis showed that NSCLC patients with *EGFR* mutations had longer progression-free survival than *EGFR* wild-type patients (6.1 versus 5.0 months, *P*=0.004).
Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

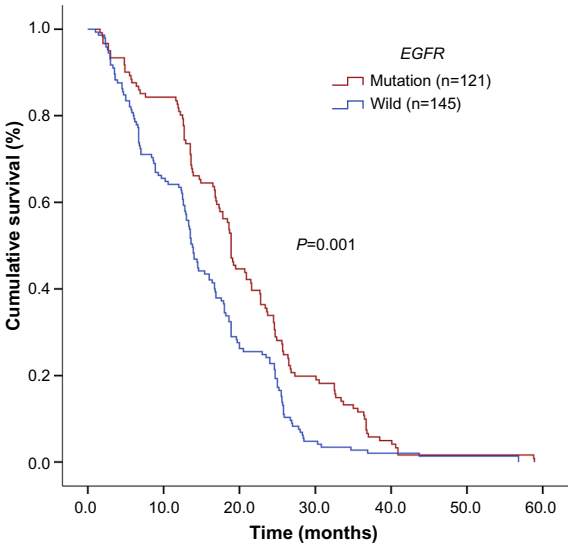

Figure 2 Kaplan–Meier estimates of overall survival according to *EGFR* status (*EGFR* mutation and *EGFR* wild-type).
Note: Kaplan–Meier analysis showed that NSCLC patients with *EGFR* mutation had longer overall survival than *EGFR* wild-type patients (18.9 versus 13.8 months, *P*=0.001).
Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

than those with the *EGFR* exon 21 mutation (19.2 months, 90.6%, and 37.5% versus 17.8 months, 70.0%, and 30.0%, respectively), but the difference was not statistically significant (P=0.908). Moreover, in 180 patients with stage IV disease, those with *EGFR* mutation had a longer median survival time, and better 1-year and 2-year survival rates, than those with wild-type *EGFR* (P=0.028). The relationship between clinical characteristics, *EGFR* mutation state, and survival is shown in Table 3.

In *EGFR* wild-type patients, there were no statistically significant differences in progression-free survival between the gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based treatments (5.7 months versus 4.6, 5.6, and 4.9 months, respectively, P=0.946, Figure 3). Further, there was no statistically significant difference in progression-free survival between the four treatment groups in patients with *EGFR* mutation (6.0 months versus 6.3, 6.4, and 5.9 months, P=0.814, Figure 4).

Univariate analysis of various prognostic factors, and the data showed that the important ones were clinical stage (P=0.001), response to first-line chemotherapy (P=0.001), histological type (P=0.008), whether TKIs were received after first-line chemotherapy (P=0.023), and *EGFR* mutation status (P=0.001). Cox multivariate regression analysis was used to determine underlying factors influencing survival, eg, age, sex, smoking history, Eastern Cooperative Oncology Group status, histological diagnosis, weight loss, whether TKIs are received after first-line chemotherapy, tumor stage, *EGFR* mutation,

Table 3 Results of the univariate analysis of *EGFR* mutation with prognosis

	No	MST	1YOS	2YOS	*P*
Total	266	16.8	72.2%	28.6%	
EGFR					
Mutation	121	18.9	81.0%	33.9%	0.001
Wild	145	13.8	63.4%	22.8%	
EGFR mutation					
19 exon	64	19.2	90.6%	37.5%	0.908
21 exon	50	17.8	70.0%	30.0%	
After first-line					
Received TKIs	82	19.5	83.0%	36.6%	0.023
Unreceived TKIs	184	13.9	67.4%	25.0%	
Histologic type					
Adenocarcinoma	242	16.2	78.8%	30.8%	0.008
Squamous cell carcinoma	24	18.4	80.3%	35.3%	
Clinical stage					
IIIB	86	19.6	81.4%	45.3%	<0.001
IV	180	13.9	67.8%	20.6%	
Response to first-line					
CR + PR	80	20.5	90.0%	48.8%	<0.001
SD + PD	186	14.0	64.5%	21.0%	

Abbreviations: *EGFR*, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; MST, median survival time; YOS, year overall survival.

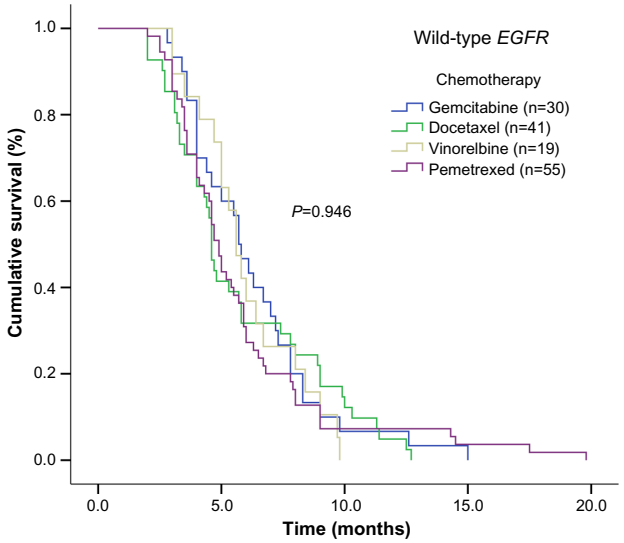

Figure 3 Kaplan–Meier estimates of progression-free survival for gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based treatments in wild-type *EGFR* patients.
Note: Kaplan–Meier analysis showed that there were no statistically significant differences in progression-free survival among gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based treatments in wild-type *EGFR* patients (5.7 versus 4.6 versus 5.6 versus 4.9, P=0.946).
Abbreviation: *EGFR*, epidermal growth factor receptor.

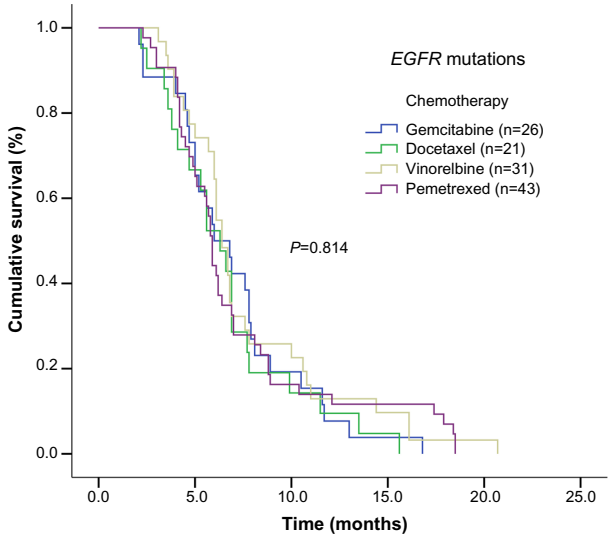

Figure 4 Kaplan–Meier estimates of progression-free survival for gemcitabine-, docetaxel-, vinorelbine- and pemetrexed-based treatments in patients with *EGFR* mutations.
Note: Kaplan–Meier analysis showed there were no statistical differences in progression-free survival among gemcitabine-based, docetaxel-based, vinorelbine-based, and pemetrexed-based treatments in patients with *EGFR* mutation (6.0 months versus 6.3, 6.4, and 5.9 months, P=0.814).
Abbreviation: *EGFR*, epidermal growth factor receptor.

and the efficacy of first-line chemotherapy. The results showed that response to front-line chemotherapy and *EGFR* mutation status were independent prognostic factors (Table 4).

Relationship between *EGFR* mutation and response to first-line chemotherapy and survival in *KRAS* wild-type patients

Among the 266 cases, a subgroup of 83 patients was evaluated for Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status. Twenty patients (24.1%) had *KRAS* mutation and 63 (75.9%) were *KRAS* wild-type. *KRAS* wild-type patients with *EGFR* mutation responded better to first-line chemotherapy (46.2% versus 20.8%, *P*=0.043) and longer progression-free survival (7.0 months versus 4.6 months, *P*=0.042, Figure 5).

Relationship between *EGFR* mutation and response to second-line treatment

After failure of first-line chemotherapy, 82 patients accepted EGFR TKIs (as second-line chemotherapy in 62 cases and as third-line chemotherapy in 20 cases). The remaining 106 patients continued their systemic chemotherapy, while 78 decided not to continue treatment. Compared with those who did not receive TKI therapy, patients who accepted EGFR TKIs had a statistically significant increase in long-term survival (*P*=0.023). Comparing patients treated with EGFR TKIs (n=62) and those given conventional chemotherapy (n=106) as their second-line therapeutic regimen, we did not find a statistically significant difference in median survival time (21.6 months versus 18.0 months, respectively, *P*=0.573).

Discussion

These data show that active *EGFR* mutations portend a longer survival time in patients with advanced NSCLC, especially those with the exon 19 mutation. *KRAS* wild-type patients with the *EGFR* mutation responded better to first-line chemotherapy, and *EGFR* mutation and curative first-line chemotherapy were independent prognostic factors for advanced NSCLC.

Platinum-based doublet chemotherapy is presently the most common first-line treatment for advanced NSCLC.[11,12] Therefore, it is important to explore the relationship between *EGFR* mutation, effect of chemotherapy, and clinical outcome. The relationship between *EGFR* mutation status and response to chemotherapy is not well understood. Kalikaki et al[16] reported that chemotherapy was more effective in patients with *EGFR* mutation than in *EGFR* wild-type patients (*P*=0.023). The Iressa Pan-Asia Study[17] indicated that the response rate was higher in the patients with *EGFR* mutations compared with wild-type *EGFR* cases who received paclitaxel/carboplatin as the first-line chemotherapy (47.3% versus 23.5%). A study reported by Lee et al[9] found no obvious relationship between presence of *EGFR* mutation and the effectiveness of first-line chemotherapy. However, a recent Japanese study indicated that patients with the *EGFR* mutation were less sensitive to docetaxel than those with wild-type *EGFR*.[10] Our study showed that the response rate and disease control rate of the first-line chemotherapy platinum containing regimens were both higher in patients with the *EGFR* mutation than in patients with *EGFR* wild-type in advanced NSCLC. No statistically significant differences were found between these two groups, which is probably due to the small sample size. However, we did find that patients with the

Table 4 Cox proportional hazards model for progression-free survival and overall survival

Factors	Progression-free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.998	0.986–1.009	0.694	0.995	0.984–1.006	0.391
Sex (male vs female)	1.176	0.906–1.526	0.223	1.196	0.914–1.565	0.192
Smoking history (yes vs no)	1.144	0.858–1.526	0.359	1.012	0.758–1.351	0.935
ECOG (1 vs 0)	1.188	0.817–1.726	0.367	1.357	0.931–1.978	0.112
Histologic type (adenocarcinoma vs squamous cell carcinoma)	1.301	0.832–2.035	0.249	1.498	0.914–2.455	0.109
Weight loss (≥5% vs <5%)	1.088	0.678–1.746	0.728	1.142	0.698–1.869	0.596
EGFR mutation (yes vs no)	0.661	0.487–0.898	0.008	0.649	0.481–0.875	0.005
Response to the front-line chemotherapy (CR + PR vs SD + PD)	0.552	0.412–0.741	<0.001	0.523	0.390–0.700	<0.001
Whether receiving TKIs after first-line chemotherapy (yes vs no)	0.852	0.638–1.138	0.278	0.893	0.673–1.185	0.434
Clinical stage (IIIB vs IV)	0.826	0.622–1.097	0.186	0.854	0.633–1.153	0.304

Abbreviations: vs, versus; *EGFR*, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; TKIs, tyrosine kinase inhibitors; HR, hazard ratio; CI, confidence interval.

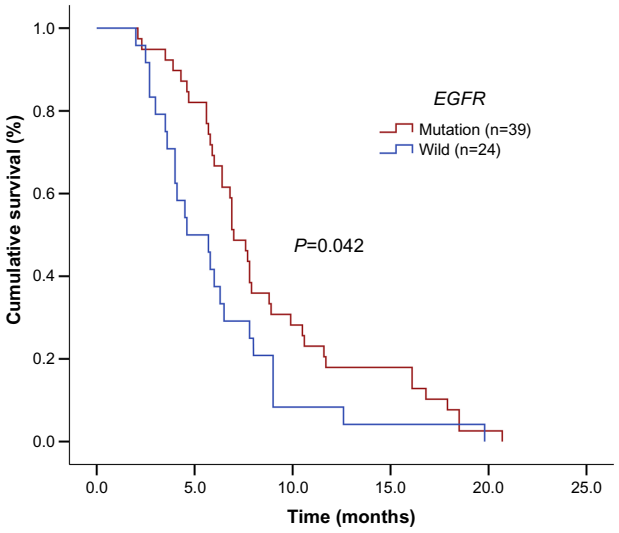

Figure 5 Kaplan–Meier estimates of progression-free survival according to *EGFR* mutation status (*EGFR* mutation and *EGFR* wild-type) in wild-type *KRAS* patients.
Note: Kaplan–Meier analysis showed NSCLC patients with *EGFR* mutations had a longer progression-free survival than *EGFR* wild-type patients in wild-type *KRAS* patients (7.0 versus 4.6 months, *P*=0.042).
Abbreviations: *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer.

EGFR mutation responded better to first-line chemotherapy (46.2% versus 20.8%, *P*=0.043) and a longer progression-free survival (7.0 months versus 4.6 months, *P*=0.042) than those without *EGFR* mutation in *KRAS* wild-type patients. Earlier research[18] showed that patients with the *KRAS* mutation had shorter survival than their *KRAS* wild-type counterparts, suggesting that *KRAS* mutation and *EGFR* mutation might have opposing effects. Both the *EGFR* and *KRAS* genes predict the prognosis of NSCLC.[19,20]

Exon 19 deletion mutation and a mutation in exon 21 (L858R) are the two main types of *EGFR* mutation. Riely et al[21] found that patients with the *EGFR* exon 19 mutation had a longer median survival time than those with the *EGFR* exon 21 mutation after receiving gefitinib or erlotinib (34 versus 8 months, respectively; *P*=0.01, log-rank). Park et al[22] investigated 217 patients with NSCLC and found that those with *EGFR* mutations who received paclitaxel had a better disease control rate and longer progression-free survival, which was more pronounced in patients with the exon 19 deletion mutation. Cappuzzo et al[8] found no clear relationship between *EGFR* mutation status and the effectiveness of first-line chemotherapy, but patients with the exon 19 mutation showed a higher objective response rate after receiving chemotherapy (46.6% versus 0%, *P*=0.02). Our research also indicates that patients with the exon 19 deletion mutation had a longer survival time after first-line platinum-based chemotherapy than those with the exon 21 mutation (*P*=0.007). Further, the effectiveness of first-line chemotherapy was greater in patients with the exon 19 mutation than in those with the exon 21 mutation (37.5% versus 24.0%, *P*=0.124), but the difference was not statistically significant.

Pemetrexed is a new-generation multitargeted antifolate agent that maintains tumor cell division in S phase by destroying the folate-dependent metabolic pathway within the cells, thereby limiting tumor growth.[23] Pemetrexed is now the preferred second-line treatment for NSCLC in the USA.[24] In recent years, clinical researchers had demonstrated the positive effects of this agent in advanced NSCLC, and pemetrexed has gradually become a first-line agent for treatment of the disease.[23] Meanwhile, there is some prospective and retrospective evidence[25,26] from Phase III research showing longer overall survival in patients with nonsquamous NSCLC treated with pemetrexed than in their counterparts treated with gemcitabine or docetaxel. These observations indicate that pemetrexed had higher activity in nonsquamous cell cancer. In the present study, we found that the disease control rate was higher for pemetrexed-based chemotherapy than for vinorelbine-based chemotherapy in patients with *EGFR* mutation. However, we cannot conclude that *EGFR* mutation improves the sensitivity to pemetrexed, because our results might have arisen from the fact that the majority of our patients with the *EGFR* mutation had adenocarcinoma of the lung (96.7%, 117/121) and pemetrexed has been shown to be more effective than other chemotherapeutic agents in this type of cancer.[25,26] Our retrospective analysis has some limitations, and there remains a need for prospective research in large samples to resolve whether *EGFR* mutation could improve the sensitivity to pemetrexed in advanced NSCLC patients.

Our analysis of survival in 266 patients with NSCLC indicates that those with *EGFR* mutations had longer progression-free survival than those with wild-type *EGFR*. This finding is similar to that of Hotta et al,[27] who analyzed survival data in 194 patients and found that patients with *EGFR* mutation had longer progression-free survival. However, other researchers have reported that *EGFR* mutation status has no impact on the effect of chemotherapy or long-term survival.[9] The current research analyzed the relationship between *EGFR* mutation status and progression-free survival, and indicated that *EGFR* mutation had a greater survival benefit when compared with wild-type status (*P*=0.004). Multifactorial analysis revealed that *EGFR* mutation and efficacy of first-line chemotherapy were independent prognostic factors in patients with advanced NSCLC, which is consistent with the results of other research.[28]

Currently, the international recommendations for second-line treatment are docetaxel, pemetrexed, and EGFR TKIs. One hundred and forty-six patients were included in the Phase III INTEREST (Gefitinib versus docetaxel in previously treated non-small-cell lung cancer) trial,[29] the main aim of which was to compare overall survival between gefitinib and docetaxel by testing for noninferiority. Overall survival was 7.6 months in the gefitinib group and 8.0 months in the docetaxel group, and the 1-year survival rate was 32% and 34%, respectively (hazards ratio 1.020, 96% CI 0.905–1.150), which met the preset requirement that the hazards ratio be <1.154. Gefitinib was significantly higher than that of docetaxel in the quality of life improvement, drug safety, and tolerability. The results of this study, albeit not reaching statistical significance, indicate that survival time in patients with advanced NSCLC is longer with second-line use of EGFR TKIs when compared with conventional chemotherapy.

Conclusion

Our research indicates that active *EGFR* mutations mean higher survival time for patients with advanced NSCLC who receive platinum-based doublet first-line chemotherapy, especially those with the exon 19 deletion mutation. Among *KRAS* wild-type patients, those with *EGFR* mutation responded better to first-line chemotherapy. In this study, *EGFR* mutation and a curative effect of first-line chemotherapy were independent prognostic factors in advanced NSCLC.

Disclosure

The authors report no conflicts of interest in this work.

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