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Effects of EGFR Mutations on NSCLC Patients Treated by Ramucirumab plus Docetaxel

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ABSTRACT The present paper attempted to define the effects of epidermal growth factor receptor (EGFR) mutations on patients with non-small cell lung cancer (NSCLC) treated by ramucirumab plus docetaxel. Of the 82 enrolled patients, 48 underwent EGFR mutations, showing relevance to sex and smoking history ($P<0.05$). The analysis yielded that EGFR-mutant (EGFR-Mut) group had a higher objective response rate versus EGFR-wild-type (EGFR-Wt) group ($P<0.05$). Subsequent to treatment, serum VEGF, bFGF, HDGF, CEA, CA153, CYFRA21-1 and CA199 levels dropped more significantly in EGFR-Mut group ($P<0.05$). Beyond that, EGFR-Mut exhibited a lower ZPS score and a higher KPS score versus EGFR-Wt group ($P<0.05$). Further, EGFR-Mut patients displayed strikingly longer median survival time versus EGFR-Wt patients ($P<0.05$). Ramucirumab plus docetaxel can safely inhibit tumour angiogenesis and regulate the levels of serum tumour markers. EGFR-Mut NSCLC patients with brain metastasis have better treatment outcomes and longer survival.

INTRODUCTION

Lung cancer (LC) is mainly classified into small cell lung cancer (SCLC) and non-SCLC (NSCLC), and NSCLC has three subtypes, namely, squamous cell carcinoma (SqCC), adenocarcinoma (Ad), and large cell carcinoma (LCC) (Lim et al. 2018). LC is caused by the reduction of bronchial glands and epithelial cells, with the highest incidence and death rates among all malignant tumours (Bai and Huang, 2020). NSCLC takes up eighty percent of all LC cases regarding the incidence rate, with brain metastasis at the late stage (Waqar et al. 2018). The metastatic brain tumour has strong invasive ability and a high mortality rate, with a median survival time (MST) of about 2 months, and such patients display a higher tendency of epidermal growth factor receptor (EGFR) mutations (Patil et al. 2018; Shi et al. 2021). The EGFR is a giant transmembrane glycoprotein with tyrosine kinase activity, the mutation of which can initiate genes in the nucleus and trigger cell division and proliferation. Ramucirumab is a polypeptide molecule composed of two heavy chains and two light chains with an extracellular domain that exhibits specific mutual action with vascular endothelial growth factor receptor (VEGFR)-2 and inhibit the binding of VEGFR-2 to the ligand, and the clearance rate is proportional to drug dosage (Chau et al. 2017; Chau et al. 2018). On the other hand, docetaxel is an M-phase-specific drug with broad-spectrum antitumor effects, which can promote tubulin assembly into stable microtubules while inhibiting their depolymerisation and destroy the microtubule network structure (Li et al. 2018; Zhu et al. 2020). Currently, there are few studies about the therapeutic effects of ramucirumab combined with docetaxel on EGFR-mutant (EGFR-Mut) NSCLC patients with brain metastasis. Herein, the present paper attempted to define the effects of EGFR mutations on NSCLC patients undergoing combined therapy with ramucirumab plus docetaxel.

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MATERIAL AND METHODS

General Data

Totalling 82 patients with metastatic NSCLC admitted to the researchers' hospital between January 2019 and January 2021 were selected. There

were 35 males and 45 females aged 28-72 years old, with (48.36±10.69) years old on average. In terms of pathological types, there were 67 SCC cases, 9 cases of alveolar carcinoma, 5 LCC cases and 1 case of adenosquamous carcinoma. Regarding the tumour-node-metastasis (TNM) stage, there were 15 cases in stage I, 40 cases in stage II and 27 cases in stage III. As for the single-organ metastatic site, there were 18 cases of brain metastasis, 10 cases of lung metastasis, 14 cases of bone metastasis, 5 cases of liver metastasis, and 35 cases of metastasis to other organs. This study gained the approval of the Ethics Committee of the hospital.

Inclusion criteria involved: patients who met the diagnostic criteria in *Guidelines for Diagnosis and Treatment of Non-Small Cell Lung Cancer* (Kim et al. 2020), those with metastatic tumours diagnosed by brain MRI, chest computed tomography (CT), bone CT and adrenal CT, those without immune deficiency or cardiovascular diseases, those without lesions in important viscera and organs, those who were not allergic to drugs in this study, those who had no mental disorders, and those who or whose families signed the informed consent.

Exclusion criteria were set below: patients with metastasis to important lymphatic drainage areas, those with immunodeficiency, those suffering from serious damage by cardiovascular system diseases, those who were allergic to drugs, or those who refused to sign the informed consent.

Detection of EGFR Mutations

The human EGFR mutation detection kit (polymerase chain reaction method, Qiagen, Germany) containing 8 strip tubes was utilised. Tubes 1-7 contained EGFR mutation detection and internal control reagents, and Tube 8 contained external control regent. Corresponding operations were conducted according to the kit's instructions. The mutation detection using Tubes 1-8 was guided by FAM, and internal control reagents were used according to the instruction of HEX signals. Then fluorescence signals were collected at 60°C, and EGFR FAM signals and internal control CT values were marked as EGFR mutation and external control CT values, respectively. With the negative critical value as the standard, tumours were determined EGFR-Mut if CT value was less than negative critical value, otherwise they were EGFR wild-type (EGFR-Wt).

Treatment Methods

All the 82 patients with metastatic NSCLC were given 100 mg of ramucirumab (Eli Lilly and Company, USA) for one cycle (21 days). On the first day, they received intravenous infusion of 10 mg/kg ramucirumab combined with intravenous drip of docetaxel (Zhejiang Haisun Pharmaceutical Co., Ltd., NMPN H20093092, 0.5 mL: 20 mg/s) at 65 $mg \cdot m^{-2}/h$ once a week for 6 consecutive months.

Observation Indices

The following observation indices were maintained:

1. According to the response evaluation criteria for tumours (Yee et al. 2017), the treatment outcomes can be classified into complete response (CR, complete disappearance of all lesions was observed for over 4 weeks), partial response (PR, the maximum tumour lesion area was maintained at above fifty percent for over 4 weeks), stable disease (SD, no new lesions appeared, and the area of tumour lesions decreased or increased by less than twenty-five percent) and progressive disease (PD, new lesions appeared and the tumour area remained unchanged or increased). The disease control rate (%) was the total proportion of CR + PR + SD cases.
2. Serum specimen collection: Before treatment and at 6 months after treatment, 3 mL of fasting venous blood was collected from each patient, and then centrifuged for 5 minutes by Hettich MIKRO 220/220R centrifuge (Germany). Afterwards, the supernatant was collected and placed in an -80°C refrigerator prior to use.
3. VEGFs: Enzyme-linked immunosorbent assay was implemented for examining the levels of VEGFs, basic fibroblast growth factors (bFGFs) and hepatoma-derived growth factors (HDGFs) using corresponding kits provided by Shenzhen NeoBioscience Technology Co., Ltd. (China).
4. Serum tumour markers: The levels of carcinoembryonic antigen (CEA), cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), carbohydrate antigen 153 (CA153) and CA199 were measured by electrochemilumines-

cence immunoassay using corresponding kits provided by Beijing Biolot Diagnostics Co., Ltd. (China).

5. Quality of life (QoL): The 36-item Short Form Health Survey (SF-36) questionnaire was utilised for QoL evaluation before treatment and at 6 months after treatment, and the score was directly proportional to the QoL, ranging from 0 to 100 points. Later, Karnofsky Performance Status Scale (KPS) and Zubrod Performance Status Scale (ZPS) were utilised for assessment of the QoL of patients. Higher scores obtained from KPS using a percentile system meant better QoL, whereas higher scores obtained from ZPS with a 5-point system represented poorer QoL.
6. Incidence of adverse reactions: As of the follow-up deadline, the incidence of diarrhoea, oral ulcer, granulocytopenia, nausea and vomiting, and liver and kidney dysfunction was observed.
7. Progression-free survival (PFS) and overall survival (OS): PFS referred to the period from the date of operation for brain metastases to the date when the progression of primary LC lesions occurred, lung tumours began to metastasize, other complications appeared, or the patients died. OS referred to the period from the date of operation for brain metastases to the date when the patients died due to complications or to the deadline of follow-up (1 January 2021).

Statistical Processing

Statistical processing was implemented with the aid of SPSS 23.0 software. The Shapiro-Wilk test was employed to detect normality. Normally distributed measurement data were presented by ($X \pm s$). Intragroup comparison was conducted using the paired samples *t*-test, while intergroup comparison was implemented by use of the independent samples *t*-test. Enumeration data were presented by percentage and detected *via* the χ^2 test. If the expected value of the minimum of a table cell was lower than 5, the Fisher's exact test was performed. The survival was assessed by use of Kaplan-Meier curve and log-rank test. $P<0.05$ meant a statistically significant difference.

RESULTS

Correlations of Clinicopathological Features of Patients with EGFR Mutations

Among all the 82 patients, 48 had EGFR mutations, including 23 cases of exon 19 mutation, 6 cases of exon 20 mutation and 19 cases of exon 21 mutation. EGFR mutations were related to sex and smoking history ($P<0.05$), but not to age, tumour pathological type, metastatic site or TNM stage ($P>0.05$) (Table 1).

Table 1: Correlations of clinicopathological features of patients with EGFR mutations

Characteristic	*EGFR-mutant (n=48)*	*EGFR wild-type (n=34)*	χ^2	*P*
Gender				
Male	25	10	4.181	0.041
Female	23	24		
Age				
<60 years old	23	16	0.006	0.939
>60 years old	25	18		
History of Smoking				
Yes	28	27	4.004	0.045
No	20	7		
Pathological Type				
Squamous cell carcinoma	40	27	1.487	0.685
Alveolar carcinoma	5	4		
Large cell carcinoma	2	3		
Adenosquamous carcinoma	1	0		
TNM Stage				
Stage I	9	6	0.769	0.681
Stage II	25	15		
Stage III	14	13		
Single-Organ Metastatic Site				
Brain	8	10	4.124	0.390
Lung	5	5		
Bone	11	3		
Liver	3	2		
Other organs	21	14		

EGFR mutations showed relevance to sex and smoking history ($P<0.05$), but not to age, tumour pathological type, metastatic site or TNM stage ($P>0.05$). EGFR: Epidermal growth factor receptor; TNM: tumor-node-metastasis.

Short-term Treatment Outcomes

Among the 82 patients, there were 55 cases of CR, 12 cases of PR, 8 cases of SD and 7 cases of PD, with the objective response rate (ORR) of 91.46 percent (75/82). EGFR-Mut group had a higher ORR (97.92%) than that of the EGFR-Wt group (82.35%)

(P<0.05) (Table 2). As suggested by the maximum tumour change from the baseline, the EGFR-Mut patients were superior to EGFR-Wt patients (Figs. 1 and 2).

VEGF Levels

Prior to treatment, EGFR-Mut group displayed higher levels of serum VEGFs, bFGFs and HDGFs versus EGFR-Wt group (P<0.05). After treatment, the levels of both groups declined remarkably, exhibiting no significant intergroup differences (P>0.05), and the decline was sharper in EGFR-Mut group (P<0.05) (Table 3).

Levels of Serum Tumour Markers

Before treatment, EGFR-Mut group had higher levels of serum CEA, CA153, CYFRA21-1 and CA199 versus EGFR-Wt group (P<0.05). After

Table 2: Short-term treatment outcomes in EGFR-Mut group and EGFR-Wt group [n (percent)]

Group	*CR*	*PR*	*SD*	*PD*	*ORR*
EGFR wild-type (n=34)	3 (11.08)	11 (32.35)	14 (41.18)	6 (17.65)	28 (82.35)
EGFR-mutant (n=48)	10 (20.83)	15 (31.25)	22 (45.83)	1 (2.08)	47 (97.92)
x^2	-	-	-		6.175
P	-	-	-		0.013

EGFR-Mut group had a higher ORR relative to EGFR-Wt group (P<0.05). CR: complete response; EGFR: epidermal growth factor receptor; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

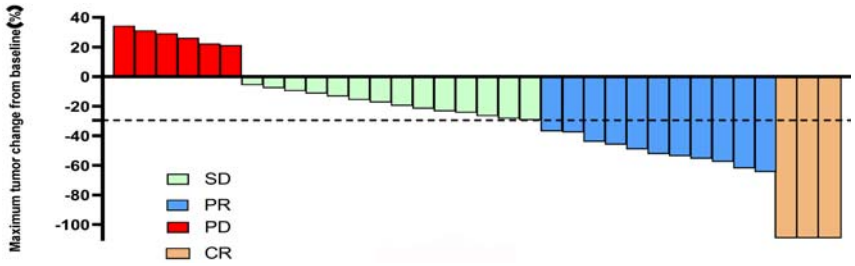

Fig. 1. Maximum tumour changes from baseline in EGFR-Wt group
CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.

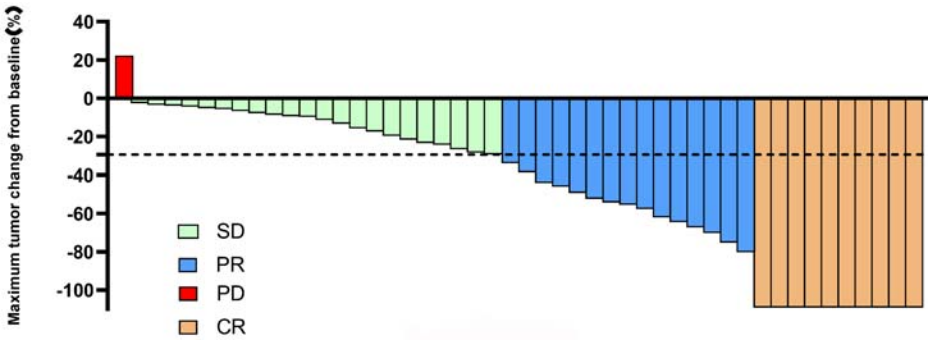

Fig. 2. Maximum tumour changes from baseline in EGFR-Mut group
As suggested by the maximum tumour changes from the baseline, the EGFR-Mut group was superior to EGFR-Wt group. CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.

Table 3: VEGF level in EGFR-Mut group and EGFR-Wt group (X± s)

Group	*VEGF (ig/L)*		*BFGF (ng/L)*		*HDGF (ng/mL)*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
EGFR wild-type (n=34)	82.35±10.24	71.36±8.02[a]	24.62±3.37	20.13±3.19[a]	17.02±2.35	14.16±3.38[a]
EGFR-mutant (n=48)	102.34±12.13	72.16±9.35[a]	28.03±4.61	19.75±2.98[a]	20.98±4.58	13.76±2.94[a]
t	-7.831	-0.404	-3.671	0.552	-4.623	0.570
P	<0.001	0.687	<0.001	0.582	<0.001	0.570

Prior to treatment, the levels of serum VEGFs, bFGFs and HDGFs in EGFR-Mut group were higher than those in EGFR-Wt group (P<0.05). After treatment, the levels of both groups declined remarkably, exhibiting no significant intergroup differences (P>0.05), and the reduction was sharper in EGFR-Mut group (P<0.05). [a]P<0.05 *vs.* before treatment in the same group. BFGF: Basic fibroblast growth factor; EGFR: epidermal growth factor receptor; HDGF: hepatoma-derived growth factor; VEGF: vascular endothelial growth factor.

treatment, the levels of both groups dramatically dropped, without significant intergroup differences (P>0.05), and the decrease was more obvious in the EGFR-Mut group (P<0.05) (Table 4).

QoL

Differences in the scores of SF-36, ZPS and KPS were not significant between EGFR-Mut and EGFR-Wt groups prior to treatment (P>0.05). In both groups after treatment, the SF-36 and KPS scores markedly rose, while the ZPS score evidently declined, and the variations were more significant in EGFR-Mut group (P<0.05). Moreover, the EGFR-Mut group exhibited a higher KPS score and a lower ZPS score versus EGFR-Wt group (P<0.05) (Table 5).

Adverse Reactions

Difference in the incidence rate of adverse reactions between EGFR-Mut group and EGFR-Wt group (12.50% *vs.* 8.82%) showed no significance (P>0.05) (Table 6).

Influences of Different Metastatic Sites on Prognosis of EGFR-Mut and EGFR-Wt Patients

EGFR-Mut patients displayed longer MST relative to EGFR-Wt patients (log rank=4.953, P=0.034). Additionally, the MST of patients with brain, lung, bone and liver metastases was (15.2 *vs.* 10.2), (14.5 *vs.* 6.5), (11.2 *vs.* 7.2) and (10.1 *vs.* 7.3) months in EGFR-Mut and EGFR-Wt groups, respectively (Table 7).

Table 4: Levels of serum tumour markers in EGFR-Mut group and EGFR-Wt group (X ± s)

Group	*CEA (ng/mL)*		*CA153 (U/mL)*		*CYFRA21-1 (ig/L)*		*CA199 (U/mL)*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
EGFR wild-type (n=34)	13.02±3.11	9.06±2.31[a]	40.16±6.03	31.26±5.13[a]	3.16±0.25	1.35±0.29[a]	43.16±5.16	26.38±5.02[a]
EGFR-mutant (n=48)	15.83±3.94	9.03±2.11[a]	44.05±5.73	30.08±5.91[a]	3.86±0.37	1.46±0.19[a]	47.29±7.03	25.59±4.03[a]
t	-3.462	0.061	-2.964	0.940	-9.582	-1.937	-2.913	0.789
P	0.001	0.952	0.004	0.350	<0.001	0.058	0.005	0.432

Before treatment, EGFR-Mut group had higher levels of serum CEA, CA153, CYFRA21-1 and CA199 than EGFR-Wt group (P<0.05). After treatment, the levels of both groups dramatically dropped, without significant intergroup differences (P>0.05), and the decrease was more obvious in EGFR-Mut group (P<0.05). [a]P<0.05 *vs.* before treatment in the same group. CA153: carbohydrate antigen 153; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragment antigen 21-1; EGFR: epidermal growth factor receptor.

Table 5: SF-36, ZPS and KPS scores in EGFR-Mut group and EGFR-Wt group (X ± s, point)

Group	*SF-36*		*ZPS*		*KPS*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
EGFR wild-type (n=34)	50.11±4.38	69.53±5.32[a]	2.65±0.32	1.86±0.28[a]	58.46±5.18	67.73±4.68[a]
EGFR-mutant (n=48)	48.69±5.01	80.76±2.31[a]	2.59±0.41	1.06±0.31[a]	59.93±4.86	73.34±5.82[a]
t	1.331	-13.018	0.713	11.977	-1.313	-4.653
P	0.187	<0.001	0.478	<0.001	0.193	<0.001

Differences in the scores of SF-36, ZPS and KPS were not significant between EGFR-Mut and EGFR-Wt groups prior to treatment (P>0.05). In both groups after treatment, the SF-36 and KPS scores markedly rose, while the ZPS score evidently declined, and the variations were more notable in EGFR-Mut group (P<0.05). Moreover, EGFR-Mut group had a higher KPS score and a lower ZPS score relative to EGFR-Wt group (P<0.05). [a]P<0.05 *vs.* before treatment in the same group. EGFR: epidermal growth factor receptor; KPS: Karnofsky Performance Status Scale; SF-36: 36-Item Short Form Health Survey questionnaire; ZPS: Zubrod Performance Status Scale.

Table 6: Adverse reactions in EGFR-Mut group and EGFR-Wt group [n (percent)]

Group	*Diarrhea*	*Oral ulcer*	*Granulocytopenia*	*Nausea and vomiting*	*Total*
EGFR wild-type (n=34)	1 (2.94)	1 (2.94)	0	1 (2.94)	3 (8.82)
EGFR-mutant (n=48)	2 (4.17)	2 (4.17)	1 (2.08)	1 (2.08)	6 (12.50)
χ^2	-	-	-		0.275
P	-	-	-		0.729*

The difference in the incidence rate of adverse reactions between EGFR-Mut group and EGFR-Wt group was not significant (P>0.05). *Fisher's exact test results. EGFR: Epidermal growth factor receptor.

Table 7: MST of patients with metastases to different organs in EGFR-Mut and EGFR-Wt groups (reference: brain metastasis)

Metastatic site	*EGFR-mutant (n=48)*	*EGFR wild-type n=34)*	*HR (95%CI)*
Brain	15.2	10.2	Reference
Lung	14.5	6.5	
Bone	11.2	7.2	
Liver	10.1	7.3	
Other organs	12.9	9.2	

EGFR-Mut group displayed significantly longer MST relative to EGFR-Wt group (log rank=4.953, P=0.034). CI: Confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio.

Survival of EGFR-Mut and EGFR-Wt Patients

In EGFR-Mut and EGFR-Wt groups, the time to disease progression (TDP) was [(10.36±2.03) *vs.* (6.05±1.35)] months, MST was [(7.36±1.37) *vs.* (12.31±2.96)] months, and OS was [(21.53±7.86) *vs.* (28.59±5.92)] months, respectively (P<0.05) (Table 8, Table 9, Figs. 3 and 4).

DISCUSSION

LC is a frequently found malignant tumour worldwide, and the incidence rate of brain metastasis is twenty-five to forty percent (Li et al. 2019). In the case of EGFR mutations, the proliferation of NSCLC cells accelerates, jeopardising the QoL of patients (Yu et al. 2018). Currently, the EGFR-Mut NSCLC patients with brain metastasis are commonly treated by whole brain radiotherapy (WBRT), ramucirumab and docetaxel (Cobo et al. 2017; Onesti et al. 2019; Peng et al. 2020). Compared with WBRT, local radiotherapy can raise the local control rate (Brown et al. 2017).

In this study, ORR of 82 patients was 91.46 percent, and the score of QoL was markedly raised after treatment. Therefore, ramucirumab plus docetaxel effectively improved the QoL and prolonged the survival of patients, as a new treatment regimen for brain metastasis in EGFR-Mut NSCLC patients. Probably, the combination of these two drugs can further suppress tumour growth (Chau et al. 2017; Harris et al. 2018). Similar to this study, it has previously been reported that ramucirumab

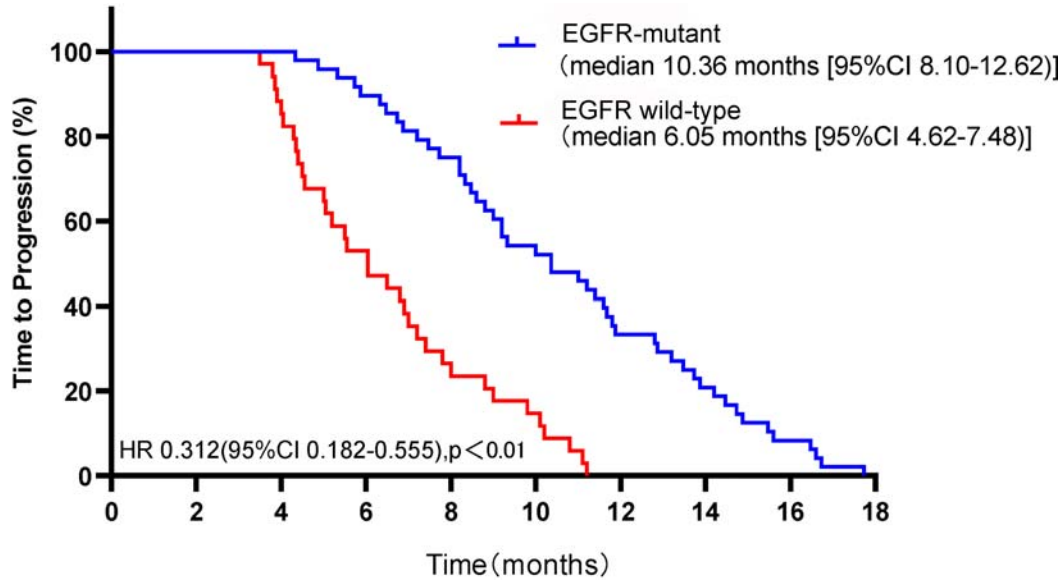

Fig. 3. TDP curves
EGFR-Mut patients had significantly longer TDP than EGFR-Wt patients (P<0.05). CI: confidence interval; EGFR: epidermal growth factor receptor.

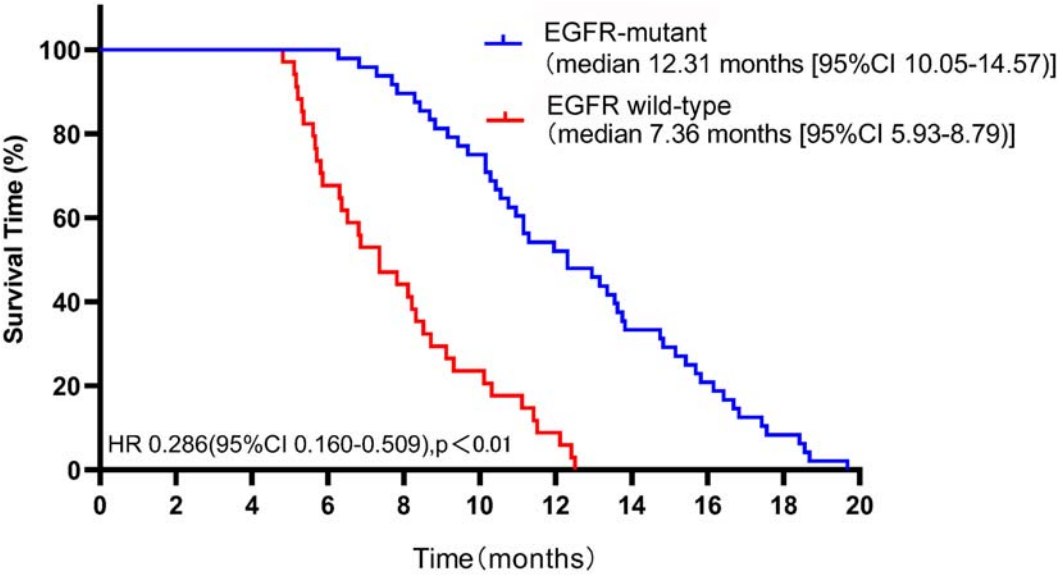

Fig. 4. Survival time curves
The survival time of EGFR-Mut patients was significantly longer than that of EGFR-Wt patients (P<0.05). CI: Confidence interval; EGFR: epidermal growth factor receptor.

combined with docetaxel can decrease the incidence rate of adverse reactions in treating brain metastasis in NSCLC patients, with high safety (Iwai et al. 2018; Zang and Sun 2020).

In the study of Zhao et al. (2014), 396 NSCLC patients with EGFR19/21 mutations were included, among whom 265 cases received conventional chemotherapy and 131 underwent TKIs treatment. The risk of brain metastasis in the conventional chemotherapy group was 3.32 times that of the TKIs group, suggesting that EGFR mutations had close associations with brain metastasis in NSCLC patients. Therefore, the researcher postulated that EGFR mutations can guide TKIs treatment, and contribute to the effective risk prediction of brain metastasis in NSCLC patients. Consistently, the researchers herein found that the MST of EGFR-Mut patients with different metastatic lesions was notably longer than that of EGFR-Wt patients, and that EGFR-Mut patients with brain metastasis survived longer.

Numerous factors are involved in the process of angiogenesis, among which VEGFs can speed up the proliferation and enhance the angiogenesis-promoting effect of vascular endothelial cells, and transfer EGFR-triggered stimuli into the cells, thus accelerating tumour progression (Le et al. 2021). The overexpression of HDGFs is associated with tumour differentiation, metastasis of blood vessels and lymph nodes and relapse (Bao et al. 2014). Moreover, bFGFs can facilitate the growth of cell fibres and exert a synergistic effect with VEGFs to enhance the angiogenesis ability of cells (Yamamoto et al. 2020). In the present study, the serum VEGF, bFGF and HDGF levels in EGFR-Mut group were higher than those in EGFR-Wt group before treatment, and the decline in the above indices in EGFR-Mut group was more remarkable after treatment. Accordingly, VEGFs were closely associated with the EGFR mutation state, probably because EGFRs mediated tumour angiogenesis in the process of signal transduction, and EGFR mutations can raise the VEGF level *in vivo*, further leading to apoptosis. Furthermore, it was found in this study that EGFR-Mut group had higher serum CEA, CA153, CYFRA21-1 and CA199 levels than EGFR-Wt group before treatment, possibly because EGFR mutations activated the downstream signalling pathway, and then accelerated the differentiation of tumour cells, thereby enhancing the synthesis of CEA, CA153 and other proteins. The serum levels of CEA, CA153, CYFRA21-1 and CA199 in the patients treated with ramucirumab plus docetaxel all declined, and this decline was sharper in EGFR-Mut group, suggesting that the use of ramucirumab plus docetaxel is worthy of promotion in treating EGFR-Mut patients with brain metastasis.

CONCLUSION

In conclusion, ramucirumab plus docetaxel exhibits high efficiency in treating NSCLC patients with metastatic tumours. With high safety, this therapy improves the QoL, inhibits tumour angiogenesis and regulates the levels of serum tumour markers. Moreover, this regimen can prolong the survival of EGFR-Mut patients with brain metastasis.

RECOMMENDATIONS

The use of ramucirumab plus docetaxel is worthy of promotion in the treatment of EGFR-Mut patients with brain metastasis.

ABBREVIATIONS

bFGF: basic fibroblast growth factor
CA153: carbohydrate antigen 153
CEA: carcinoembryonic antigen
CR: complete response
CT: computed tomography
CYFRA21-1: cytokeratin 19 fragment antigen 21-1
EGFR: epidermal growth factor receptor
HDGF: hepatoma-derived growth factor
KPS: Karnofsky Performance Status Scale
NSCLC: non-small cell lung cancer
ORR: objective response rate
OS: overall survival
PD: progressive disease
PFS: progression-free survival
PR: partial response
SD: stable disease
SF-36: 36-item Short Form Health Survey questionnaire
TNM: tumour-node-metastasis
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor
WBRT: whole brain radiotherapy
ZPS: Zubrod Performance Status Scale

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