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Therapeutic effect of gefitinib on patients with advanced EGFR-mutation NSCLC

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Abstract: This study aims to study the role of gefitinib on patients with advanced EGFR-mutation NSCLC (Non-Small Cell Lung Cancer). Totally 115 patients with advanced EGFR-mutation NSCLC treated in our hospital were enrolled as research objects. They were randomly divided into control group (n=57) applied with cisplatin + pemetrexed and experimental group (n=58) subject to gefitinib+ cisplatin + pemetrexed, both groups were applied with treatment for 4 cycles. Clinical efficacy: The disease control rate (DCR) was 72.41% in the experimental group, which was higher than that of the control group (54.39%, $p<0.05$); Serum CEA, CYFRA21-1, MMP-9 levels: after 2 and 4 cycles of treatment, serum CEA, CYFRA21-1, and MMP-9 levels were lower in the experimental group ($p<0.05$); Immune function: after 2 and 4 cycles of treatment, Th1 cells and Th1/Th2 cell levels were higher in the experimental group, while Th2 cell level was higher in the control group ($p<0.05$); Angiogenesis related indicators: the levels of VEGF, HIF-1α and sCD105 were lower in the experimental group after 2 and 4 cycles of treatment ($p<0.05$); (5) Adverse reactions: After 2 and 4 cycles of treatment, the levels of VEGF, HIF-1α, and sCD105 were lower in the experimental group ($p<0.05$). The application of gefitinib in patients with advanced EGFR-mutation NSCLC can help down-regulate CEA, CYFRA21-1, and MMP-9 levels, inhibit angiopoiesis, enhance immune function, and increase disease control rate.

Keywords: NSCLC, EGFR, gefitinib, MMP-9, CYFRA21-1, immune function.

INTRODUCTION

NSCLC is the most common type of primary lung cancer. 35%-40% patients with such disease are already in advanced stages at first diagnosis, missing the best opportunity for surgery. The treatment for NSCLC is mainly platinum-containing two-agent combination chemotherapy (Rafei *et al*., 2017; Zeng *et al*., 2018). However, clinical practice has found that the total effective rate of platinum-containing two-agent combination therapy is only 30%, and the prognosis is generally poor, so its clinical application is limited (Chen *et al*., 2018). With the in-depth clinical research on tumor molecular biology, it is found that occurrence and development of most NSCLC depends on activation of EGFR gene, while both mutation and amplification of EGFR can stimulate its downstream signal transduction pathways, thereby promoting the occurrence and development of tumors, so EGFR expression regulation is clinically expected to control tumor malignancy (Peng *et al*., 2018; Leonetti *et al*., 2019). Gefitinib is an oral epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor, which is small molecule compound. Inhibition of EGFR-TK can inhibit tumor growth, metastasis and angiogenesis, and increase the apoptosis of tumor cells. Gefitinib is suitable for the treatment of locally advanced or metastatic NSCLC because of its advantages in inhibiting tumor formation, metastasis and angiogenesis. Existing studies have confirmed that gefitinib combined with chemotherapy has definite efficacy on advanced NSCLC (Zhao *et al*., 2018), but reports on the combination of the two in treatment of advanced EGFR-mutation NSCLC are very few. Hence, this study analyzes the therapeutic effect of gefitinib from tumor markers, immune function, angiogenesis, etc.

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MATERIALS AND METHODS

Clinical data

This study was approved by ethics committee of Anqiu Municipal Hospital (Reference No. 20170615A). A total of 115 patients with advanced EGFR-mutation NSCLC in our hospital from October 2017 to October 2019 were selected as the research objects. They were randomly divided into experimental group (n=58) and control group (n=57). There was no significant difference in data such as gender, age, body mass index (BMI), mutation type, TNM staging, tissue type, tumor location, tumor diameter between the two groups ($p>0.05$) (table 1).

Selection criteria

Inclusion criteria: Meeting the NSCLC diagnostic criteria of "Internal Medicine" (Wang *et al*., 2013), diagnosed by pathological and cytological examination; WHO physical status score (ECOG) 0-2 points; TNM staging IIIB ~ IV; Estimated survival time >3 months; Meeting the indications for non-surgical treatment such as chemotherapy; The amplification refractory mutation system (ARMS) shows mutation status; Patients and their families know and sign the consent form.

Exclusion criteria: Those with drug intolerance in this study; Those with other lung diseases; Those with other malignant tumors; Those who refused to be followed up after treatment; Those with severe cardiovascular or cerebrovascular disease; Those with immeasurable lesion; Those with incomplete clinical data.

Method

Treatment method: The control group was given cisplatin + Pemetrexed. On the 1st d, intravenous drip of 500 mg/m2 pemetrexed + 100 ml normal saline (concentration 9%) was given for 30 min, followed by intravenous drip of 75mg/m2 cisplatin + 500ml glucose solution (concentration 5%) for 2h (Three weeks constitute a cycle and the treatment lasts for 4 consecutive cycles). Patients should take routine oral administration of folic acid, dexamethasone before and after pemetrexed use. On this basis, the experimental group was subject to oral administration of gefitinib, 0.25g/time, 1 time/d (Three weeks constitute a cycle and the treatment lasts for 4 consecutive cycles).

Detection method At 8:30~9:30 in the morning, collect 3~4 ml peripheral venous blood, let it stand for 20 min, centrifuge for 15 min (2500 r/min), collect the supernatant and store it at low temperature for later use. CEA and CYFRA21-1 were detected by Chemiluminescence. Mmp-9, VEGF, HIF-1α, sCD105 were detected by enzyme linked immunosorbent assay. Beckman CytoFLEX flow cytometer was used to measure Th1 and Th2 cells, and calculate the ratio of Th1/Th2 cells. The kit was provided by Shanghai Future Industrial Co., Ltd., and the operation was performed according to the kit instructions.

Efficacy evaluation

According to the efficacy evaluation standard RECIST 1.1 for solid tumor (Fang *et al*., 2019), it includes 4 levels of complete remission (CR), partial remission (PR), stable disease (SD), and disease progression (PD).

Observation indicators

(1) The clinical efficacy of the two groups. (2) Serum CEA, CYFRA21-1 and MMP-9 levels in the two groups before treatment, after 2 and 4 cycles of treatment. (3) The levels of Th1/Th2 cells in the two groups before treatment, after 2 and 4 cycles of treatment. (4) VEGF, HIF-1α and sCD105 in the two groups before treatment, after 2 and 4 cycles of treatment. (5) Adverse reactions in the two groups. Referring to the NCI-CTC 3.0 standard evaluation (Liu *et al*., 2018), adverse reactions are divided into 0, 1, 2, 3 and 4 grades according to severity. (6) The survival status of the two groups was followed up 6 months after treatment.

STATISTICAL ANALYSIS

The measurement data was expressed in a mean number ± average number (x±s) and group comparison was carried out by t test. The count data was expressed using natural numbers (n) and percentages (%) and $\chi 2$ was used for comparison between groups. $p<0.05$ indicates statistical value.

RESULTS

Clinical efficacy

The experimental group had higher disease control rate ($p<0.05$) and there was no significant difference in the total effective rate ($p>0.05$) (table 2).

Serum CEA, CYFRA21-1 and MMP-9 levels

Before treatment, the two groups had no significant difference in serum CEA, CYFRA21-1, and MMP-9 levels ($p>0.05$). After 2 and 4 cycles of treatment, the experimental group had lower serum CEA, CYFRA21-1, and MMP-9 levels ($p<0.05$) (table 3).

Immune function

The two groups had no significant difference in immune function indicators before treatment ($p>0.05$). After 2 and 4 cycles of treatment, the experimental group had higher levels of Th1 cells and Th1/Th2 cells, lower level of Th2 cells ($p<0.05$) (table 4).

Angiogenesis related indicators

Before treatment, the two groups had no significant difference in angiogenesis related indicators s ($p>0.05$). After 2 and 4 cycles of treatment, the levels of VEGF, HIF-1α, and sCD105 were lower in the experimental group ($p<0.05$) (table 5).

Adverse reactions

The two groups had no significant difference in the incidence of adverse reactions ($p>0.05$) (table 6).

Survival status

The survival rate of experiment group was 70.17% (40/57) and that of control group was 69.10% (38/55) ($\chi^2=0.016$, $p=0.901$); the progression-free survival period was 4.02 months, 3.98 months, respectively ($\chi^2=0.208$, $p=0.649$) (fig. 1).

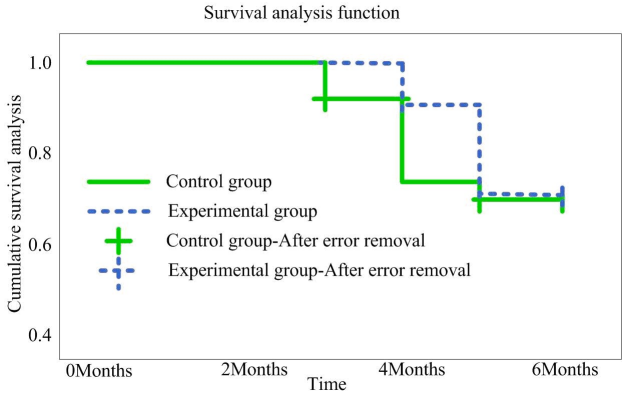

Fig. 1: Survival curve

Table 1: Clinical data

Clinical data	Experimental group (n=58)	Control group (n=57)	t/χ2	p
Gender (Male/Female)	30/28	27/30	0.218	0.640
Age (years)	40～78(59.93±8.74)	41～80(60.51±7.87)	0.374	0.710
BMI (kg/m2)	18～26(20.53±1.26)	19～25(20.48±1.31)	0.208	0.835
Tumor diameter (cm)				
＜5	40(68.97)	37(64.91)	0.214	0.644
≥5	18(31.03)	20(35.09)		
Mutation type				
Del19 mutation	20(34.48)	21(36.84)	0.123	0.941
L858R mutation	32(55.17)	31(54.39)		
G719X mutation	6(10.35)	5(8.77)		
TNM staging				
IIIB	26(44.83)	27(47.37)	0.075	0.785
IV	32(55.17)	30(52.63)		
Tissue type				
Adenocarcinoma	30(51.72)	33(57.90)	0.442	0.506
Squamous cell carcinoma	28(48.28)	24(42.10)		
Tumor location				
Left	27(46.55)	29(50.88)	0.215	0.643
Right	31(53.45)	28(49.12)		

Table 2: Clinical efficacy n (%)

Group	n	CR	PR	SD	PD	Total effective rate	Disease control rate
Experimental group	58	6(10.35)	17(29.31)	19(32.75)	16(27.59)	23(39.66)[a]	42(72.41)[b]
Control group	57	4(7.02)	16(28.07)	11(19.30)	26(45.61)	20(35.09)	31(54.39)
χ^2	-	-	-	-	-	0.256	4.030
p	-	-	-	-	-	0.613	0.044

Note: Complete remission (CR), Partial remission (PR), Stable disease (SD), Disease progression (PD). Compared with Control group, [a]p>0.05, [b]p<0.05.

Table 3: Serum CEA, CYFRA21-1 and MMP-9 levels in the two groups ($\bar{x}$ ±s, ng/ml)

Item	Group	n	Before treatment	After 2 cycles of treatment	After 4 cycles of treatment
CEA	Experimental group	58	(5.71±1.41)[a]	(4.35±1.05)[b]	(3.98±0.87)[b]
	Control group	57	(6.12±1.23)	(5.64±1.16)	(4.55±0.99)
	t		1.661	6.254	3.281
	p		0.099	0.000	0.001
CYFRA21-1	Experimental group	58	(12.34±2.26)[a]	(9.51±1.58)[b]	(6.04±1.13)[b]
	Control group	57	(12.18±2.43)	(11.26±1.82)	(8.42±1.47)
	t		0.366	5.510	9.744
	p		0.715	0.000	0.000
MMP-9	Experimental group	58	(430.85±46.69)[a]	(357.77±36.32)[b]	(261.88±30.42)[b]
	Control group	57	(433.12±44.87)	(404.78±40.05)	(349.95±32.38)
	t		0.266	6.596	15.035
	p		0.791	0.000	0.000

Note: Compared with Control group, before treatment, [a]p>0.05; Compared with Control group, after 2 and 4 cycles of treatment, [b]p<0.05.

Table 4: Immune function ($\bar{x}$±s)

Item	Group	n	Before treatment	After 2 cycles of treatment	After 4 cycles of treatment
Th1 (%)	Experimental group	58	(9.83±1.54)[a]	(11.99±2.03)[b]	(12.34±2.16)[b]
	Control group	57	(10.18±1.26)	(9.45±1.47)	(8.95±1.52)
	t		1.333	7.674	9.718
	p		0.185	0.000	0.000
Th2 (%)	Experimental group	58	(12.28±2.26)[a]	(10.51±1.87)[b]	(9.78±1.36)[b]
	Control group	57	(12.13±2.51)	(12.87±2.69)	(13.02±2.88)
	t		0.337	5.471	7.735
	p		0.737	0.000	0.000
Th1/Th2	Experimental group	58	(0.80±0.43)[a]	(1.14±0.57)[b]	(1.26±0.61)[b]
	Control group	57	(0.84±0.40)	(0.73±0.35)	(0.69±0.34)
	t		0.516	4.639	6.175
	p		0.607	0.000	0.000

Table 5: Angiogenesis related indicators ($\bar{x}$±s)

Item	Group	n	Before treatment	After 2 cycles of treatment	After 4 cycles of treatment
VEGF(pg/ml)	Experimental group	58	(133.58±15.51)[a]	(80.05±8.74)[b]	(68.11±6.69)[b]
	Control group	57	(135.12±13.39)	(99.97±10.03)	(79.96±7.22)
	t		0.570	11.361	9.132
	p		0.571	0.000	0.000
HIF-1α(ng/L)	Experimental group	58	(65.13±7.34)[a]	(43.31±6.28)[b]	(30.44±5.06)[b]
	Control group	57	(64.56±7.89)	(50.59±6.63)	(42.28±5.49)
	t		0.401	6.046	12.029
	p		0.689	0.000	0.000
sCD105(ng/ml)	Experimental group	58	(6.74±1.02)[a]	(5.16±0.89)[b]	(3.53±0.56)[b]
	Control group	57	(6.53±1.28)	(6.01±0.95)	(4.81±0.79)
	t		0.974	4.953	10.038
	p		0.332	0.000	0.000

Note: Compared with Control group, before treatment, [a]p>0.05; Compared with Control group, after 2 and 4 cycles of treatment, [b]p<0.05.

Table 6: Adverse reactions n (%)

Group	n	Nausea and vomiting		Decreased white blood cell count		Thrombocytopenia		Abnormal liver function	
		1~2	3~4	1~2	3~4	1~2	3~4	1~2	3~4
Experimental group	58	9(15.52)[a]	4(6.90)[a]	7(12.07)[a]	3(5.17)[a]	6(10.35)[a]	2(3.45)[a]	8(13.79)[a]	4(6.90)[a]
Control group	57	13(22.81)	7(12.28)	12(21.05)	6(10.53)	11(19.30)	5(8.77)	12(21.05)	7(12.28)
χ^2		0.987	0.963	1.682	0.521	1.830	0.646	1.055	0.963
p		0.320	0.326	0.195	0.471	0.176	0.422	0.305	0.326

Note: Compared with Control group, [a]p>0.05.

DISCUSSION

NSCLC is a common clinical malignant tumor with EGFR mutation rate of about 30%-40% (Bie and Feng, 2018; Wu and Shih, 2018). Traditionally, platinum-based chemotherapy regimens are mostly used in treatment of advanced EGFR-mutation NSCLC to relieve clinical symptoms to a certain extent and prolong survival. However, related studies have pointed out that the effective rate of this chemotherapy regimen is merely 25%～35% (Wang and Pi, 2018).

With the in-depth research on tumor cell signal transduction pathways, the molecular mechanism of tumor occurrence and development has become more and more clear. It is particularly important to select targeted molecular targeted drugs to reverse malignant lesions in normal cells from a molecular perspective, and then

inhibit tumor tissue generation, recurrence, and metastasis (Castellanos *et al*., 2017). At present, the most extensive research is carried out on EGFR in terms of molecular targeted drugs, which can bind to receptors through ligands, cause EGFR dimerization and C-terminal tyrosine phosphorylation, stimulate tyrosine kinase subregions and downstream signal transduction pathways, thereby promoting tumor cell proliferation, differentiation and apoptosis. Relevant data has shown that EGFR is mainly over expressed in NSCLC solid tumors, which can frequently stimulate downstream signaling pathways, leading to invasive growth of normal cells (Feng *et al*., 2018). Clinically, EGFR inhibitors can be selected to hinder cell cycle progression, accelerate cell apoptosis, and inhibit angiogenesis by inhibiting activation of tyrosine kinase and EGFR receptor, thereby achieving enhanced chemotherapy effect. Gefitinib is the earliest EGFR-targeted drug marketed in our country. Several studies have confirmed that it has good efficacy on patients with advanced EGFR-mutation NSCLC, which is consistent with the conclusions of this study (Tian *et al*., 2018; Wang *et al*., 2018). At the same time, this study showed that levels of CEA, CYFRA21-1 and MMP-9 were lower in the experimental group after 2 and 4 cycles ($p<0.05$). CEA is a broad-spectrum tumor marker, which has extremely low content in healthy adults or patients with benign diseases, but with high content in patients with lung, ovarian, colorectal, and liver cancer.

It can be used as an auxiliary indicator for differential diagnosis, disease monitoring, and efficacy evaluation of NSCLC (Dal Bello *et al*., 2019). MMP-9 can degrade and remodel the dynamic balance of extracellular matrix. Studies in recent years have found that MMP-9 is highly expressed in the serum of NSCLC patients, which may be related to mechanisms such as destroying vascular basement membrane type IV collagen and affecting tumor cell adhesion (He *et al*., 2018). CYFRA21-1 is mainly distributed in tumor cells and epithelial cells, whose increased level indicates tumor growth and metastasis, thus reflecting the tumor load and providing reference information for clinical evaluation of NSCLC. Cisplatin can bind to DNA, cause cross-linking and disrupt DNA function. Pemetrexed can disrupt the folate-dependent metabolic process in the cell, hinder cell replication, and inhibit tumor growth. After gefitinib enters the human body, it can compete with ATP for specific binding sites of EGFR, reduce tyrosine kinase activity, inhibit tumor angiogenesis and hinder tumor growth and progression. At the same time, gefitinib can enhance anticancer activity of chemotherapeutic drugs such as cisplatin and pemetrexed, inhibit tumor cell growth, regulate serum tumor marker levels and accelerate disease prognosis.

Under physiological conditions, Th1 and Th2 cells promote and inhibit each other, jointly maintaining the body's immune balance. Once the body is attacked by alien antigens, Th1/Th2 cells can drift. Related studies have shown imbalance of Th1/Th2 cells in NSCLC patients, which is manifested as relative advantage of Th2 cells and relative disadvantage of Th1 cells (Lin *et al*., 2019). Before treatment in this study, Th1, Th2, Th1/Th2 were in line with the above trends, indicating that immune imbalance exists in patients with advanced EGFR-mutation NSCLC. Timely correction of Th1/Th2 imbalance means great significance for preventing tumor occurrence and development. After treatment, control group had lower levels of Th1 cells and Th1/Th2 cells and higher level of Th2 cells. This is due to that chemotherapy kills cancer cells and affects normal metabolism of other cells in the body at the same time, thus aggravating immune function damage. Zhang Dan *et al*. (Zhang *et al*., 2015) found that gefitinib significantly improved patients' immune function and clinical efficacy. Guo Gang *et al*. (Guo *et al*., 2016) found that gefitinib regulated the level of peripheral blood T lymphocytes in NSCLC patients and improved immune function of the body. Unlike the above studies, this study takes Th1/Th2 cells as the observation indicator, and it is not known whether the same effect can be achieved. Therefore, this study investigated this aspect and found that the experimental group had higher levels of Th1 cells and Th1/Th2 cells but lower Th2 cell level ($p<0.05$).

Tumor infiltration, growth and metastasis are all dependent on tumor angiogenesis. It is currently known that both VEGF and HIF-1α can participate in tumor angiogenesis (Zhou *et al*., 2017; Zhang *et al*., 2018). VEGF is currently known as the most powerful pro-angiogenic factor, which can directly promote mitosis of vascular endothelial cells, form new blood vessels, thus providing conditions for NSCLC infiltration and metastasis. HIF-1α is an important transcription factor that regulates the internal environment of oxygen, which plays a key role in cellular adaptive responses such as angiogenesis, metabolism, and apoptosis. Foreign studies have shown that sCD105 is related to lung cancer [24]. The possible mechanism is that sCD105 participates in angiogenesis and remodeling by inhibiting cell response to transforming TGF-β, thereby promoting tumor growth. This study showed that VEGF, HIF-1α and sCD105 levels were lower in the experimental group after 2 and 4 cycles of treatment ($p<0.05$). The follow-up found that the two groups had less difference in survival rate and progression-free survival, which may be related to the short follow-up time. Therefore, more follow-up time is needed for further confirmation.

CONCLUSIONS

In summary, the application of gefitinib for in patients with advanced EGFR-mutation NSCLC can help down-regulate CEA, CYFRA21-1, and MMP-9 levels, inhibit angiopoiesis, enhance immune function, and increase disease control rate.

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