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Original Article

The efficacy and safety of gefitinib combined with conventional chemotherapy in the treatment of advanced non-small-cell lung cancer

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Abstract: Objective: To explore the effectiveness and safety of gefitinib combined with conventional chemotherapy in treating advanced non-small-cell lung cancer (NSCLC). Methods: From August 2014 to September 2016, 114 patients with advanced NSCLC treated in our hospital were included in this study. Among them, 46 patients underwent conventional chemotherapy and were included in group A (GA), and the other 68 patients were administered gefitinib combined with conventional chemotherapy and were included in group B (GB). The two groups' clinical curative effects were compared. The changes in the tumor markers and immune function indexes were compared in both groups before and after the therapy. The incidences of toxic side effects were compared between the two groups during the treatment. The two groups' PFS and OS were compared for 3 years. The quality of life was compared in both groups. Results: After the therapy, the ORR and DCR in GB were significantly higher than they were in GA, and the expression levels of the tumor markers in GB were significantly lower than they were in GA. There was no significant difference in the patients' immune function indexes in GB compared with their levels before the therapy, but they were significantly lower in GA. The incidence of toxic side effects in GB was significantly lower than it was in GA. The PFS and OS in GB were significantly longer than they were in GA. The quality of life in GB was significantly higher than it was in GA. Conclusion: Compared with chemotherapy alone, gefitinib combined with conventional chemotherapy is more effective and safer in treating advanced NSCLC, and it can improve patient survival, so it is worthy of clinical promotion.

Keywords: Gefitinib, conventional chemotherapy, advanced non-small-cell lung cancer, efficacy, safety

Introduction

Lung carcinoma is the primary cause of cancer deaths in the world, among which NSCLC is the most common pathological type, accounting for about 80% of all lung carcinoma cases [1-3]. In terms of morbidity and mortality, lung carcinoma is also the most common carcinoma type in China [4]. According to American research data, national, early lung screening can reduce the mortality rate of high-risk populations by 20% [5]. Lung carcinoma symptoms usually develop in the advanced stages of the disease. Moreover, advanced patients cannot be cured using the current clinical treatment methods, so the treatment of patients in the advanced stages of the disease still faces great challenges [6].

At present, platinum-based chemotherapy is the typical first-line method for treating advanced NSCLC [7]. The treatment of NSCLC has progressed in recent years, but its overall cure and survival rates are still very low, especially in patients with metastasis [8]. Therefore, it is necessary to develop new drugs and combination therapies to ameliorate the prognoses of NSCLC patients [9]. Studies by Arbour et al. [10] have revealed that tyrosine kinase inhibitors ameliorate the progression-free survival of patients susceptible to EGFR mutations. Gefitinib is a tyrosine kinase inhibitor that can inhibit the expression of the vascular endothelial growth factor receptor (VEGF), thus suppressing tumor cells' growth, invasion, metastasis, and angiogenesis [11]. Studies have shown that treating NSCLC with gefitinib alone increases the risk of

drug resistance and accelerated disease development, and it promotes the epithelial-mesenchymal transition (EMT) [12]. Therefore, gefitinib combined with chemotherapy may be a better treatment option. Hosomi et al. [13] revealed that, compared with gefitinib alone, gefitinib combined with carboplatin and pemetrexed can improve the progression free survival (PFS) of advanced NSCLC patients with EGFR mutations, and its toxicity is acceptable, but the overall survival (OS) still needs to be further explored.

Therefore, this study was designed to apply gefitinib combined with conventional chemotherapy in patients with advanced NSCLC to investigate the therapeutic effect and safety of this therapy.

Data and methods

Collection of the patients' clinical data

From December 2014 to December 2016, 114 patients with advanced NSCLC treated in Quzhou People's Hospital were recruited as the study cohort. Among them, 46 cases underwent conventional chemotherapy and were included in GA, and the other 68 cases were administered gefitinib combined with conventional chemotherapy and included in GB.

Inclusion criteria: All the patients were diagnosed with NSCLC through pathological examinations, and the diagnostic criteria referred to the relevant diagnostic guidelines in 2013 [14]. The patients' TNM stagings were III and IV. The patients' estimated survival times were > 6 months. The patients and their families agreed and signed the informed consent forms. The patients cooperated with the follow-up.

Exclusion criteria: Patients comorbid with other malignant tumors, patients who withdrew from the study, patients who had received anti-tumor treatment before prior to the study, patients with immune and blood system diseases, patients who were pregnant or lactating. This study was approved by the medical ethics committee of our hospital.

Treatment plan

The manufacturers of gemcitabine, cisplatin and gefitinib were Qilu Pharmaceutical Co., Ltd. In GA, the patients were treated with a GP chemotherapy regimen: gemcitabine (SFDA approval No. H20113286, 1.0 g/branch) 1 $g{\cdot}m^{-2}$, ivd, d1, d8+cisplatin (SFDA Approval No. H370-21358, 10 mg/branch) 25 $mg{\cdot}m^{-2}$, ivd, d1~3. In GB, the patients were administered gefitinib tablets (SFDA approval No. H20163465, 0.25 g/tablet) 0.25 g, po (after breakfast), qd, d1~24 in addition to the treatment the GP underwent. Four weeks was a treatment cycle. Chest CT examinations were performed during each treatment cycle and the disease progression was closely monitored.

Measurement methods

Fasting peripheral venous blood (5 mL) was drawn from patients in both groups before and after the treatment in 3 cycles. The blood was placed at room temperature for 30 min and centrifuged at 3000 g and 4°C for 10 min, and the supernatant was obtained and stored in a freezer at -80°C for testing.

Flow cytometry: The serum CD3+, CD4+, and CD8+ immune cell levels in the serum were measured using flow cytometry (Flow Cytometer, American ACEA Biosciences Company, CytoFLEX).

ELISA test: The sample hole to be tested, the standard hole, and the blank hole were set up. There was no reagent in the blank hole, and the samples or standards to be tested were added to the other holes. After mixing it evenly, the enzyme-labeling plate was covered with a membrane and incubated for 2 h. After discarding the liquid in each hole, the working solution A was incubated for 1 hour. Next, the liquid in each hole was discarded, and the washing liquid was added to wash the plate 3 times. Then, working solution B was added to each hole and incubated for 1 hour. The liquid in each hole was discarded, and the washing liquid was added to wash the plate 3 times. The substrate solution was added into each hole to develop the color at 37°C in a dark place for 10-15 min. After that, the terminal liquid was added into each hole to terminate the reaction. The OD value of each hole was measured at the wavelength of 450 nm, and the concentrations of neuron-specific enolase (NSE) and the tumor markers CA72-4 and CA19-9 were calculated.

Patient follow-up

The patients underwent a survival follow up using the internet, the telephone, and outpatient re-examinations. The patients were followed up every 3 months in the first year, and then every 6 months every year after the first year.

Outcome measures

Main outcome measures: The clinical efficacy was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) in accordance with the criterion of solid tumor efficacy evaluation (RECIST) [15]. The disease control rate (DCR) (%) = (Cr+PR)/total number of cases × 100%. Objective remission rate (ORR) (%) = (CR+PR+SD)/total number of cases × 100%. The patients' clinical efficacy was observed in both groups. The incidences of toxic and side effects were compared in the two groups during the treatment, and the two groups' OS and PFS were compared.

Secondary outcome measures: The tumor marker levels, including NSE, CA72-4, and CA19-9, were compared between the two groups. The immune function indexes were compared in the two groups, including CD3+, CD4+, and CD8+. The WHOQOL-100 scale [16] was applied to assess the quality of life in both groups, with a total score of 100. The higher the score, the better the quality of life.

Statistical analysis

In this research, SPSS 20.0 (Shanghai Cabit Information Technology Co., Ltd., China) was used for the statistical analysis of the collected data. Prism 7 (Shenzhen Qiruitian Software Technology Co., Ltd., China) was used to draw the figures. The enumeration data were represented as a percentage (%). Chi-square tests were applied for the comparisons and represented by χ^2. The measurement data were expressed as the (means ± SD). Independent sample t tests were applied to compare the normally distributed data in the two groups. Paired t tests were used to compare the two groups before and after the therapy, and represented by t. There was a significant difference between the two groups when $P < 0.05$.

Results

Baseline patient data

The baseline data were analyzed in both groups. The results revealed that there were no significant differences in terms of age, gender, body mass index (BMI), or other clinical characteristics in both groups (P>0.05), which were comparable (**Table 1**).

Comparison of the clinical curative effects between the two groups

After the therapy, the clinical curative effects in the two groups were analyzed using RECIST. We found that the ORR and DCR in GB were significantly higher than they were in GA after the treatment (P<0.001) (**Table 2**).

Changes in both groups' tumor markers

The ELISA results revealed that there were no significant differences in the NSE, CA72-4, or CA19-9 levels in both groups before the therapy (P>0.05). But the NSE, CA72-4, and CA19-9 levels in both groups after the treatment were significantly lower than they were before the therapy (P<0.001), and the tumor marker levels in GB were significantly lower than the levels in GA (P<0.001) (**Figure 1**).

The immune function indicator levels in both groups

The flow cytometry results showed that there were no significant differences in the CD3+, CD4+, or CD8+ levels in both groups before the therapy (P>0.05). After the therapy, the CD3+ and CD8+ levels were significantly decreased in both groups (P<0.01), and the CD3+ and CD8+ levels in GB were significantly higher than the levels in GA (P<0.001). After the therapy, the CD4+ level was significantly decreased in the GA (P<0.001), but there was no significant difference in GB compared with the pre-treatment level (P>0.05), and there was a significant difference in the CD4+ levels in both groups (P<0.001) (**Figures 2**, **3**).

Incidences of toxic side effects

The incidences of toxic side effects were analyzed between the two groups during the treatment. The results showed that the incidence of rash in GA was significantly lower than it was in GB (P<0.001), but there was no significant dif-

Table 1. Baseline data of the patients in the two groups

Factors		GA (n=46)	GB (n=68)	t/χ^2	P
Age/years old		58.61±7.52	60.32±7.24	1.218	0.226
Gender	Male	27 (58.70)	33 (48.53)	1.137	0.286
	Female	19 (41.30)	35 (51.47)		
BMI (kg/m^2)		21.92±1.75	22.16±1.88	0.687	0.493
Pathological types	Adenocarcinoma	28 (60.87)	49 (72.06)	2.094	0.351
	Squamous cell carcinoma	15 (32.61)	14 (20.59)		
	Large cell carcinoma	3 (6.52)	5 (7.35)		
ECOG score	< 3 points	18 (39.13)	21 (30.88)	0.829	0.363
	≥ 3 points	28 (60.87)	47 (69.12)		
Degree of differentiation	Moderately differentiated	31 (67.39)	50 (73.53)	0.503	0.478
	Well differentiated	15 (32.61)	18 (26.47)		
TNM staging	Stage III	25 (54.35)	43 (63.24)	0.901	0.343
	Stage IV	21 (45.65)	25 (36.76)		
Smoking history	Yes	38 (82.61)	53 (77.94)	0.371	0.542
	No	8 (17.39)	15 (22.06)		
Alcoholism history	Yes	25 (54.35)	44 (64.71)	1.232	0.267
	No	21 (45.65)	24 (35.29)		
Place of residence	City	26 (56.52)	33 (48.53)	0.702	0.402
	Rural	20 (43.48)	35 (51.47)		
Exercise habit	Yes	19 (41.30)	21 (30.88)	1.309	0.253
	No	27 (58.70)	47 (69.12)		

Table 2. Comparison of the clinical efficacy between the two groups

Grouping	CR	PR	PD	SD	ORR	DCR
GA (n=46)	3 (6.52)	14 (30.43)	5 (10.87)	24 (52.18)	22 (47.82)	17 (36.95)
GB (n=68)	14 (20.59)	34 (50.00)	14 (20.59)	6 (8.82)	62 (91.18)	48 (70.59)
χ^2					26.59	12.66
P					<0.001	<0.001

ference in the incidence of toxic side effects in GB (P<0.001) (**Table 3**).

Comparison of the prognoses in the two groups

We counted the PFS and OS in both groups by following up the patients. The results showed that the PFS and OS in GB were significantly longer than they were in GA (P<0.001) (**Table 4**).

Comparison of the quality of life

The WHOQOL-100 scale was applied to assess the quality of life in the two groups before and after the treatment. The results showed that there was no significant difference in the WHOQOL-100 scores in both groups before the treatment, but the WHOQOL-100 scores of the patients in GB were significantly higher than the scores in GA after the therapy (**Table 5**).

Discussion

First-line platinum chemotherapy is the treatment standard for most patients with advanced NSCLC, and this method can only maintain a median PFS of about 6 months and a 30% of remission rate [17]. Some patients will relapse again after several courses of chemotherapy or at the end of their chemotherapy [18]. VEGF is a vascular endothelial growth factor with the highest specificity and strongest effect known at present. It is an important cancer promoting factor, as it can promote the formation of tumor blood vessels [19]. Gefitinib can effectively inhibit the expression of VEGF, thereby inhibiting the generation, metastasis, and growth of

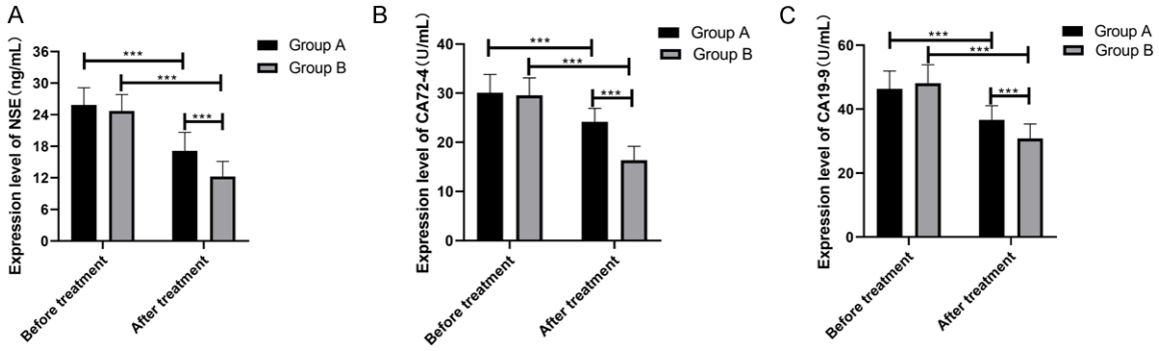

Figure 1. Changes in the tumor markers in the two groups. A/B/C. Before treatment, there was no significant difference in the NSE/CA72-4/CA19-9 levels between the two groups, but the NSE/CA72-4/CA19-9 levels in the two groups after the treatment were significantly lower than they were before the treatment, and the tumor marker levels in GB were significantly lower than they were in GA. *** means P<0.001.

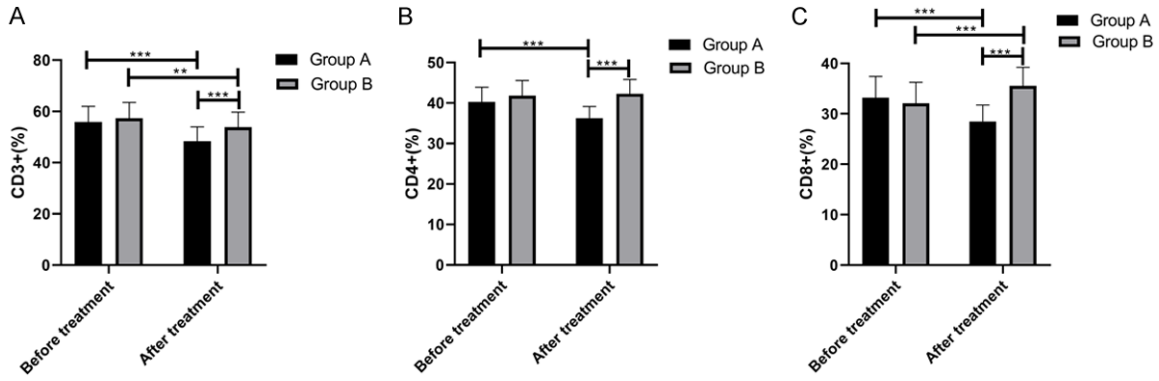

Figure 2. The immune function indicator levels in the two groups. A. Before the treatment, there was no significant difference in the CD3+ levels between the two groups. After the treatment, the CD3+ levels were significantly decreased in both groups, and the CD3+ level in GB was significantly higher than it was in GA. B. Before the treatment, there was no significant difference in the CD4+ levels between the two groups. After the treatment, the CD4+ level was significantly decreased in GA, but there was no significant difference in GB compared with before the treatment. C. Before the treatment, there was no significant difference in CD8+ level between the two groups. After the treatment, the CD8+ levels was significantly decreased in both groups, while the CD8+ level in GB was significantly higher than it was in GA. ** means P<0.01. *** means P<0.001.

tumor blood vessels, facilitating the apoptosis of tumor cells [20, 21]. Therefore, gefitinib combined with the GP regimen was used to treat advanced NSCLC to explore its therapeutic effect and safety in this study.

We first evaluated the therapeutic effect of conventional chemotherapy and gefitinib combined with conventional chemotherapy in treating advanced NSCLC. The results showed that gefitinib combined with conventional chemotherapy can effectively improve ORR and DCR compared with conventional chemotherapy. Gefitinib is a first-line treatment for advanced NSCLC patients with positive EGFR mutations, but it may develop resistance, so it is necessary to conduct combination therapy [22]. Studies by Maemondo et al. [23] reported that gefitinib has better efficacy than conventional chemotherapy, and its toxicity is acceptable, so it is suitable for advanced NSCLC patients with EGFR mutations. Therefore, gefitinib combined with conventional chemotherapy was used to treat patients with advanced NSCLC in our study. The results showed that the combination therapy had a better clinical efficacy, and the patients' conditions were effectively controlled, which might be attributed to the reduction of drug resistance by the combined treatment. NSE, CA72-4, and CA19-9 are common tumor biomarkers for lung carcinoma, and they are up-regulated in patients' serum and tumor tissues and can be used for diagnostic and effi-

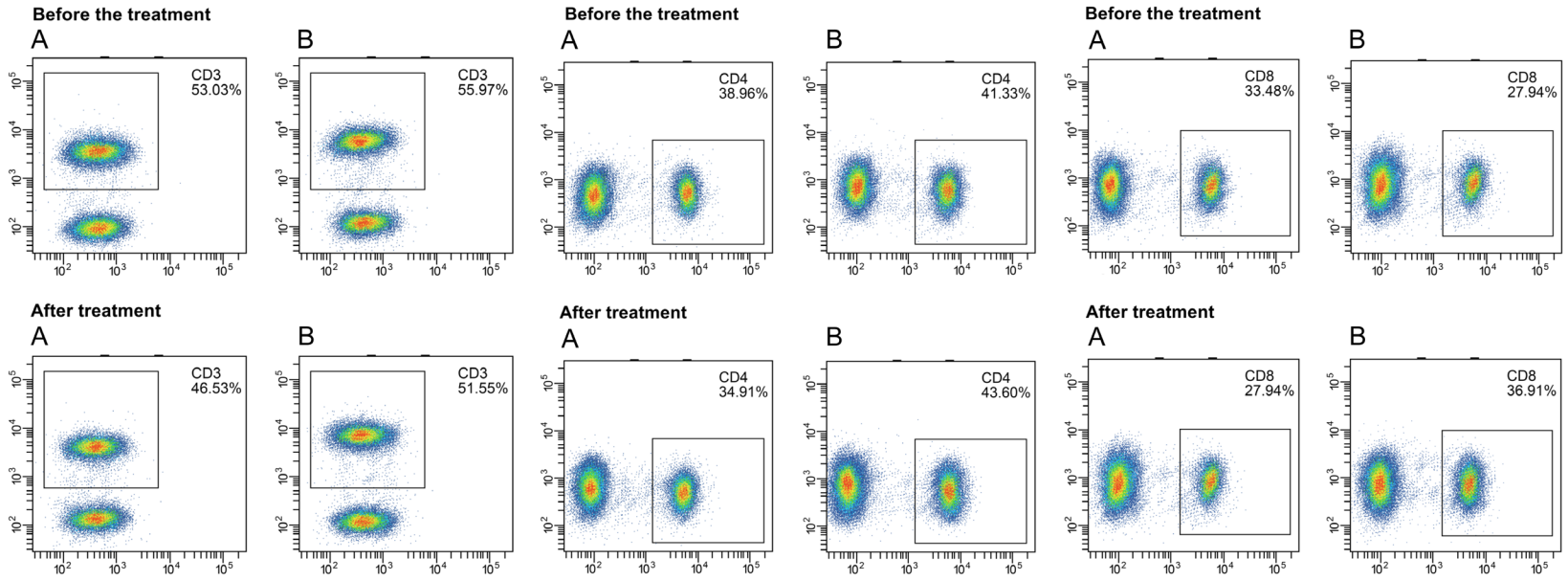

Figure 3. Flow cytometry.

Table 3. The incidences of toxic side effects between the two groups during treatment

Grouping	Rash	Gastrointestinal reaction	Leukopenia	Thrombocytopenia	Total
GA (n=46)	3 (6.52)	6 (13.04)	5 (10.87)	5 (10.87)	19 (41.30)
GB (n=68)	25 (36.76)	3 (4.41)	2 (2.94)	4 (5.89)	34 (50.00)
χ^2	13.54	2.811	2.993	0.939	0.468
P	<0.001	0.094	0.084	0.333	0.494

Table 4. Comparison of the PFS and OS in the two groups

Grouping	PFS	OS
GA (n=46)	13.27±1.31	17.53±1.45
GB (n=68)	23.18±2.43	29.64±2.58
t	25.26	28.87
P	<0.001	<0.001

Table 5. Comparison of the WHOQOL-100 scores

Grouping	Before treatment	After treatment
GA (n=46)	40.52±6.24	61.25±4.61*
GB (n=68)	42.32±6.14	82.13±5.78*
t	1.526	20.48
P	0.130	<0.001

*: P<0.05

cacy monitoring [24-26]. In this study, the expressions of NSE, CA72-4, and CA19-9 were measured using ELISA in both groups before and after therapy. The findings showed that the tumor biomarkers in both groups were at a high level before the treatment, and the NSE, CA72-4, and CA19-9 expressions in the two groups were down-regulated after the treatment, and the NSE, CA72-4, and CA19-9 expressions in GB were significantly lower than those in GA, which indicated that gefitinib combined with conventional chemotherapy can effectively inhibit the tumor marker expressions and slow down the tumor progression.

The T cell subset levels in patients with malignant tumors are significantly abnormal, an indication that their immune function is low [27]. Patients with NSCLC have poor immune function and abnormal expressions of T lymphocytes [28]. We measured the immune cell levels before and after the treatment using flow cytometry. The results showed that there was no significant difference in the CD3+, CD4+, and CD8+ levels in both groups before the therapy. After the therapy, the CD3+ and CD8+ levels in GA were significantly lower than they were in GB, and the CD4+ level in GA was significantly decreased, but there was no significant difference in GB compared with the pre-treatment level. This indicated that conventional chemotherapy results in an abnormal expression of immune cells in patients, suggesting that the patients' immune function decreased, while gefitinib combined with conventional chemotherapy had no significant difference on the patients' immune function. Then, we counted the incidences of toxic side effects between the two groups. The results showed that the incidence of rashes in the patients receiving gefitinib combined with conventional chemotherapy was significantly higher than it was in the patients receiving chemotherapy alone, but there was no significant difference in the total incidences of toxic side effects in both groups. This showed that gefitinib combined with conventional chemotherapy did not increase the incidence of toxic side effects and had a higher safety. Rashes, dry skin, and diarrhea are the common adverse reactions during gefitinib treatment, reactions which are mostly mild and moderate and easy to treat [29]. In the studies of gefitinib combined with chemotherapy in the treatment of patients with advanced NSCLC, Jian et al. [30] reported that there were no emergency treatment adverse events that caused treatment interruption and the increase of interstitial lung diseases caused by gefitinib, so gefitinib combined with chemotherapy is safer and more effective. This is similar to our research results. In this research, the patients were followed up for survival. The results revealed that the ORR and PFS of the patients receiving gefitinib combined with chemotherapy were significantly longer than those of the patients receiving chemotherapy alone, which indicated that gefitinib combined with chemotherapy can effectively improve patients' survival. The studies of Sim et al. [31] reported that gefitinib combined with chemotherapy seems to be superior to gefitinib alone or to chemotherapy in improving PFS in patients with advanced NSCLC, and it has fewer side effects,

but the overall survival rate has not been improved. This is similar to our research results. At the end of the research, we evaluated the patients' quality of life in the two groups, and the result was no accident. The quality of life of patients receiving gefitinib combined with chemotherapy was significantly higher than it was in the patients receiving chemotherapy alone. This might be because the combined treatment showed a better therapeutic effect, which improved the treatment compliance, controlled the disease more effectively and improved the patients' quality of life.

This research revealed that gefitinib combined with conventional chemotherapy has better efficacy and safety, but there are still some shortcomings to our study. The optimal dosage of gefitinib was not investigated in this study, so it is not clear whether the dosage used in this study can achieve the best efficacy. Therefore, we hope to supplement different doses of gefitinib in future studies to improve the shortcomings of this study.

To sum up, gefitinib combined with conventional chemotherapy is more effective and safer in treating advanced NSCLC, and it can improve patient survival, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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