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Original Article

Effect of EGFR-TKI targeted therapy in patients with advanced non-small cell lung cancer

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Abstract: Objective: To investigate the effect of EGFR-TKI targeted therapy in patients with advanced non-small cell lung cancer (NSCLC). Methods: Eighty-four cases of NSCLC were retrospectively assigned into an observation group (OG, n=42) and a control group (CG, n=42) according to the treatment methods. The CG received conventional chemotherapy, and the OG received icotinib hydrochloride EGFR-TKI targeted therapy. The clinical efficacy, cellular immunity, humoral immunity, quality of life, adverse reactions and survival time were compared between the two groups. Cox regression analysis was used to analyze the factors influencing the prognosis of advanced NSCLC. Results: The total response rate was substantially higher, and the incidence of adverse reactions was considerably lower in the OG than those in the CG (all P<0.05). The post-treatment SF-36 score was increased in both groups with significantly higher score in the OG than the CG (all P<0.001). The post-treatment $CD4^+$ counts in both groups were notably lower than those of pre-treatment, and the count was lower in the CG than that in the OG (all P<0.001). The post-treatment $CD8^+$ counts in both groups were notably higher after treatment than those of pre-treatment and was higher in the CG than that in the OG (all P<0.001). The post-treatment levels of IgM and IgA in both groups were declined compared with those of pre-treatment (P<0.001) with significantly lower levels in the OG than the CG (P<0.01). The 18-month mortality of the OG was significantly lower than that of the CG (P<0.05). Cox regression analysis showed that lesion diameter and differentiation degree of tumor cells were independent factors influencing the prognosis (P<0.05). Conclusion: EGFR-TKI targeted therapy can relieve clinical symptoms, and improve immune function and quality of life of patients with advanced NSCLC, which is worthy of clinical application.

Keywords: EGFR-TKI targeted therapy, non-small cell lung cancer (NSCLC), immune function, quality of life, efficacy

Introduction

Lung cancer, as one of the most common clinical malignant tumors, has a current incidence of 12.7% globally among tumor cases [1]. In recent years, with the change of the natural environment and living habits, the incidence of lung cancer has increased. The early diagnosis of lung cancer is relatively difficult because of the insignificant clinical symptoms. When symptoms like chest and back pain or sputum with blood appear, patients are usually in a middle or advanced stage [2]. Currently, chemotherapy is often given to patients with advanced lung cancer, but the patients usually have low immune function and poor physical fitness, which result in poor prognosis [3]. Study found that about 28.2% of the patients had epidermal growth factor receptor (EGFR) gene mutations, so the combination of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) with tyrosine kinase domain as a treatment for advanced non-small cell lung cancer (NSCLC) can block the EGFR pathway to a great extent, thereby eliminating cancer cells and promoting recovery [4]. Icotinib hydrochloride is a selective EGFR-TKI independently developed in China. It can inhibit EGFR tyrosine kinase to a great extent to prevent the continued invasion and proliferation of lung cancer cells, accelerate the apoptosis of the cells and slow progression of the lung cancer [5]. However, there are few cli-

nical reports on the effects of icotinib hydrochloride EGFR-TKI targeted therapy on the immune system and quality of life of patients with advanced NSCLC. The purpose of this study was to investigate the efficacy of icotinib hydrochloride EGFR-TKI targeted therapy in patients with advanced NSCLC and its effect on their immune function, quality of life and adverse reactions.

Materials and methods

General data

Retrospectively, 84 cases of advanced NSCLC treated in the 910th Hospital of Chinese People's Liberation Army from January 2017 to December 2019 were included in the study. The patients were assigned into an observation group (OG, n=42) and a control group (CG, n=42) according to the treatment methods. The study was approved by the Medical Ethics Committee of the 910th Hospital of Chinese People's Liberation Army.

Inclusion criteria: (1) Patients' who met the diagnostic criteria for advanced NSCLC in *Guidelines for the Diagnosis and Treatment of Lung Cancer* and were confirmed as NSCLC by pathological biopsy [6, 7]; (2) Patients who had genetic testing and showed no contraindications to the treatments used in this study; (3) Patients with an age of 20-75 years.

Exclusion criteria: (1) Patients with poor compliance with doctor's advice or the treatment; (2) Patients with cognitive impairment; (3) Patients with heart or kidney intolerance; (4) Patients with other malignant tumors; (5) Patients with immune system disorders; (6) Patients with other serious chronic underlying diseases; (7) Patients with abnormalities in the endocrine or coagulation system.

Methods

The CG was given conventional treatment. On the first day, 500 mg/m^2 pemetrexed and 0.9% sodium chloride solution were prepared and intravenously injected. From the second day, cisplatinum injection (75 mg/m^2) with 0.9% sodium chloride solution were prepared and intravenously infused in 3 times (3 days). One course of treatment was 21 days, and this treatment was given for 3 consecutive courses. The OG received EGFR-TKI targeted therapy with Icotinib hydrochloride tablets (Zhejiang Betta, China, batch number: A190404) orally, 125 mg/time, 3 times/d for 3 months [8].

Outcome measures and evaluation of clinical efficacy

The clinical responses of the two groups were accessed based on the criteria from RECIST version 1.1 [9]. The response can be divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). Response rate = (cases of CR + case of PR)/total number of cases × 100%.

Before and 3 months after treatment, 5 mL of fasting venous blood was collected from patients, separated and stored for testing. Flow cytometry (Beckman Coulter Co., Ltd., USA) was used to detect the cellular immune function of the two groups, including $CD4^+$ and $CD8^+$ (using lymphocyte subset detection kits, Art. No. E06271, Shanghai Walanbio, China), as well as humoral immune function, including IgM, IgG and IgA (using immunoglobulin detection kits, Art. No. SND-H1953, Shanghai Enzyme Linked Biology, China).

The short-form quality of life scale (SF-36) was employed to access the quality of life of the subjects before and 3 months after treatment [10]. The scale has a total of 36 items and 8 dimensions, with a total score of 100 points. Higher scores indicate better quality of life.

The incidence of adverse reactions, such as myelosuppression, gastrointestinal reactions, abnormal liver and renal functions, were counted.

Follow up was conducted by referring to patient records in the hospital's inpatient system or via telephone, and the follow-up deadline was June 2021. The 18-month survival was compared between the two groups.

Statistical processing

Statistical software SPSS 20.0 was applied for analyzing the data. All graphs were plotted using GraphPad Prism 6 software. Continuous variables with a normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The comparison within group was performed by paired t test, and comparison between two groups was done by independent sample t test. The count data were expressed as (n%) and

Table 1. Comparison of clinical data between the two groups ($\bar{x} \pm sd$)

Group	Gender (n)		Age (years)	BMI (kg/m^2)	Smoking history (n)	Course of disease (years)
	Male	Female				
Observation group (n=42)	22	20	50.4±3.1	22.09±2.33	19	2.5±1.1
Control group (n=42)	21	21	51.1±3.0	22.11±2.27	22	2.7±0.9
t/χ^2	0.048		1.052	0.040	0.429	0.912
P	0.927		0.296	0.968	0.512	0.364

Note: χ^2 is the statistical value of Chi-square test; t is the statistical value of t test. BMI: body mass index.

Table 2. Comparison of response rate between the two groups (n%)

Group	CR (n)	PR (n)	SD (n)	PD (n)	Response rate
Observation group (n=42)	3	16	13	10	19 (45.24)
Control group (n=42)	1	6	15	20	7 (16.67)
x^2	-	-	-	-	9.022
P	-	-	-	-	0.029

Note: CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

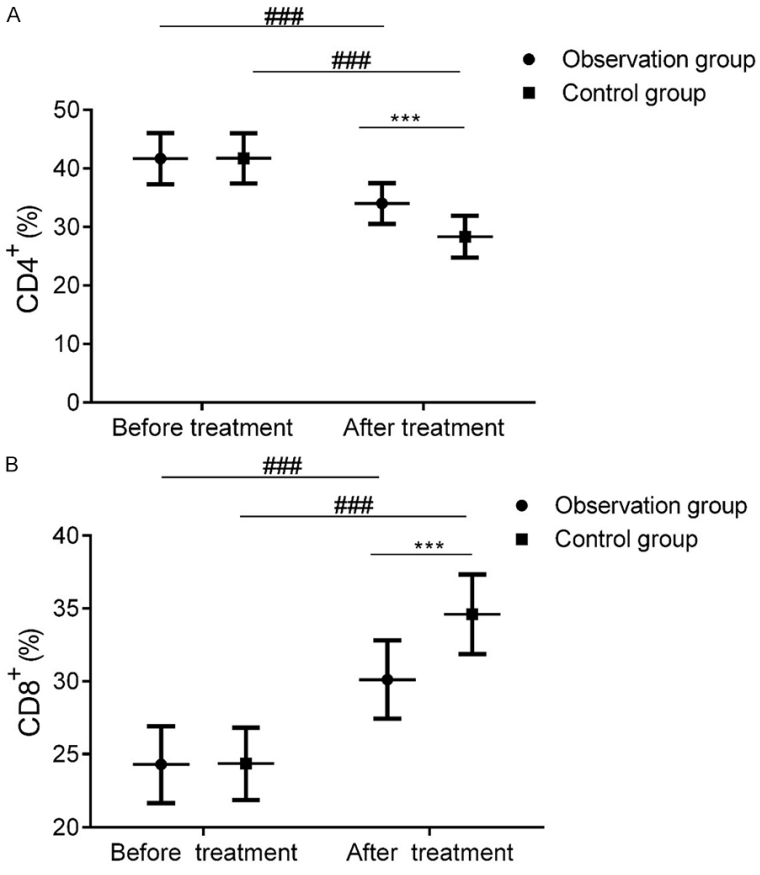

Figure 1. Comparison of cellular immune function between the two groups. A: Comparison of $CD4^+$ before and after treatment; B: Comparison of $CD8^+$ before and after treatment. Paired t test was used to compare data between before and after treatment within the group, ###P<0.001. Independent sample t test was used to compare data between the two groups, ***P<0.001.

subjected to Pearson's chi-square test. Cox regression analysis was used to analyze the factors influencing the prognosis of advanced NSCLC. P<0.05 was considered with statistical difference.

Results

Comparison of baseline data

No statistical difference was revealed in clinical baseline data between the two groups, such as age, gender, BMI, smoking history and course of disease, showing the comparability between the two groups (all P>0.05). See **Table 1**.

Comparison of response rate

The response rate in the OG was appreciably higher as compared with that in the CG (P<0.05). See **Table 2**.

Comparison of cellular immune function

The post-treatment $CD4^+$ cell counts in both groups were appreciably decreased as compared with those of pretreatment, and the CG showed lower count than the OG (all P<0.001). The post-treatment $CD8^+$ cell counts in both groups were elevated comparing with those of pre-treatment, and the CG showed higher count than the OG (all P<0.001). See **Figure 1**.

Table 3. Comparison of humoral immune function between the two groups (g/L, $\bar{x} \pm sd$)

Group	Time	IgM	IgA	IgG
Observation group (n=42)	Before treatment	0.92±0.33	3.88±0.40	10.75±1.29
	After treatment	0.50±0.22$^{**,\#\#\#}$	1.69±0.31$^{**,\#\#\#}$	10.72±1.24
Control group (n=42)	Before treatment	0.95±0.31	3.82±0.41	10.70±1.31
	After treatment	0.73±0.17$^{\#\#\#}$	2.10±0.28$^{\#\#\#}$	10.71±1.27

Note: Paired t test was used to compare data between before and after treatment within the group, $^{\#\#\#}$P<0.001. Independent sample t test was used to compare data between the two groups, **P<0.01.

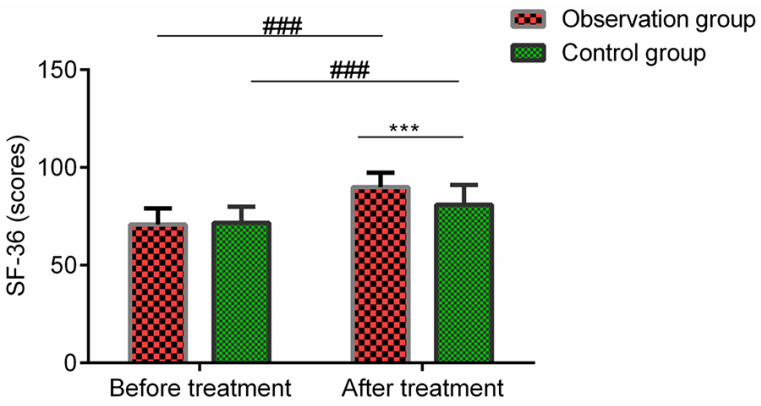

Figure 2. Comparison of quality of life before and after treatment in the two groups. Paired t test was used to compare data between before and after treatment within the group, $^{\#\#\#}$P<0.001. Independent sample t test was used to compare data between the two groups, ***P<0.001.

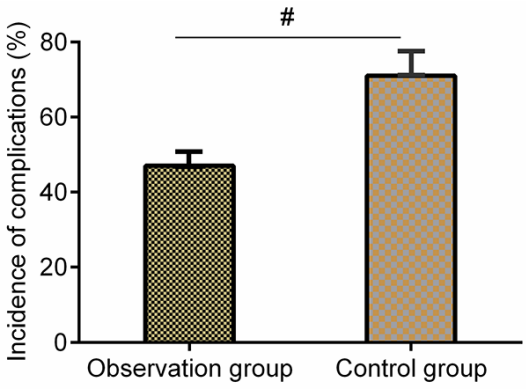

Figure 3. Comparison of incidence of complications. The comparison was conducted using Chi-square test. Compared with the control group, $^{\#}$P<0.05.

Comparison of humoral immune function

The post-treatment levels of IgM and IgA in both groups were significantly declined compared with those of pre-treatment (P<0.001), and their levels in the OG were lower than those in the CG (P<0.01). No significant difference was found in IgG levels between before and after treatment or between the groups. See **Table 3**.

Comparison of quality of life

A significant elevation in the post-treatment SF-36 scores was revealed in both groups, and the OG had considerably higher score than the CG (all P<0.001). See **Figure 2**.

Comparison of incidence of complications

In the OG, there were 3 cases of myelosuppression, 5 cases of abnormal liver and renal functions, 4 cases of gastrointestinal reactions and 8 cases of other complications. In the CG, there were 7 cases of myelosuppression, 8 cases of abnormal liver and renal functions, 8 cases of gastrointestinal reactions and 7 cases of other complications. The incidence of adverse reactions in the OG (47.62%) was appreciably lower than that in the CG (71.43%; P=0.026, χ^2=4.941). See **Figure 3**.

Comparison of survival rate

There were 6 deaths in the OG and 17 deaths in the CG, and the 18-month mortality in the OG was significantly lower than that of the CG (14.29% vs. 40.48%, P=0.007, χ^2=7.240). See **Figure 4**.

Influencing factors of 18-month prognosis

In the OG, there was no significant difference in gender and age distribution (P>0.05), but there were statistically significant differences in lesion diameter, number of dissected lymph nodes and differentiation degree of tumor cells (P<0.05) between patients who survived and

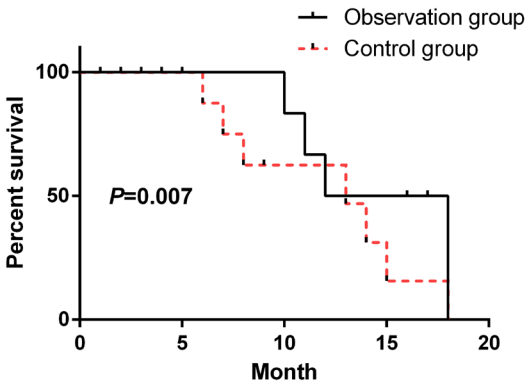

Figure 4. Comparison of 18-month mortality.

those who died 18-month after EGFR-TKI treatment. See **Table 4**.

Cox regression analysis of factors influencing prognosis

The above factors with P<0.05 were seen as the independent variable X (assignment: lesion diameter: <2 cm =0, ≥2 cm =1; number of dissected lymph nodes: ≥6=0, <5=1; degree of differentiation: moderate to high differentiation =0, low differentiation =1). The outcome was the dependent variable Y (0= survival, 1= death). Cox regression analysis showed that the diameter of the lesion and the differentiation degree of tumor cells were independent factors influencing the prognosis of patients (P<0.05). See **Table 5**.

Discussion

The occurrence and development of NSCLC is highly related to work and living environment, resting habits, chronic diseases, and smoking [11, 12]. Most patients were diagnosed in the middle or advanced stage, with a high rate of death and disability. At present, chemotherapy is usually used to treat lung cancer, mostly with conventional drugs such as pemetrexed and cisplatin. However, the effect is limited for some seriously ill and elderly patients due to severe side effects [13, 14]. In recent years, targeted therapy has provided a new treatment direction, and EGFR-TKI therapy has been widely used in cases of NSCLC [15]. Compared with traditional chemotherapy, EGFR-TKI has a special drug mechanism, which acts significantly in the treatment of NSCLC [16].

Previous clinical report showed that Icotinib hydrochloride had a positive effect on improving the clinical symptoms and curative effect in elderly cases of NSCLC, without recurrence during 1-year follow-up [17]. In addition, some scholars reported that targeted therapy with Icotinib hydrochloride had a higher safety and better clinical efficacy than traditional chemotherapy in cases of advanced NSCLC [18, 19]. In this study, the included patients were treated in two ways. Our results showed that compared with the CG, the OG showed notably elevated response rate and reduced incidence of adverse reactions. It suggests that EGFR-TKI helps to eliminate cancer cells in the body, possibly because this treatment method can specifically inhibit the activation of EGFR on the signaling pathway, thereby preventing the proliferation and differentiation of cancer cells in the body and hindering the progression of lung cancer [19, 20]. Some other clinical results showed that with reduced immune function, the body is more likely to be invaded by cancer cells. Therefore, active recovery of the immune system plays a pivotal role in cancer treatment [21-23]. The cellular immune function of the body is usually expressed by the ratio of T lymphocytes. The changes in T lymphocyte $CD4^+$ and $CD8^+$ counts can directly reflect the cellular immune status of the body. A decline in the ratio of the two indicates that the cellular immune function of the body is suppressed. It has been reported that Icotinib hydrochloride tablets can facilitate the proliferation and differentiation of T cell subsets and play an important role in immune function recovery [24]. Both groups in this study showed considerably diminished $CD4^+$ count and upraised $CD8^+$ count after treatment. Additionally, the post-treatment levels of IgM and IgA in the two groups were appreciably declined as compared with that of pre-treatment, and the decline was more obvious in the OG than that of the CG. It is indicated that EGFR-TKI targeted therapy could improve the immune function of patients with NSCLC, potentially because Icotinib hydrochloride can directly affect the immune response of patients through downstream target molecules, thereby effectively inhibiting the immune process of $CD8^+$ cells, reducing the ratio of $CD4^+/CD8^+$ and improving immune function. Our results also revealed that the post-treatment SF-36 score was significantly higher in both groups than those of pre-treatment. It shows that EGFR-TKI targeted therapy for cases of advanced NSCLC can markedly inhibit the progression of the disease and benefit the quality of life. Possible reasons

Table 4. Univariate analysis of factors influencing the 18-month prognosis in the observation group

Factors	Survival (n=36)	Death (n=6)	χ^2	P
Sex (n)			0.573	0.449
Male	18	4		
Female	18	2		
Age (years)			2.053	0.152
<70	28	3		
≥70	8	3		
Lesion diameter (cm)			0.330	0.038
<2.0	25	5		
≥2.0	11	1		
Number of dissected lymph nodes			0.118	0.019
<5	20	4		
≥5	16	2		
Differentiation degree of tumor cells			0.029	0.028
Moderate to high	30	4		
Low	6	2		

Table 5. Cox regression analysis of factors influencing the prognosis

Factors	β	S.E.	Wald χ^2 value	P	95% CI
Lesion diameter (cm)	1.599	0.698	4.010	0.029	5.012
Number of dissected lymph nodes	-4.976	1.120	10.392	0.111	0.031
Differentiation degree of tumor cells	2.165	0.594	8.677	0.037	8.420

are that Icotinib hydrochloride tablets can effectively inhibit the proliferation and differentiation of lung cancer cells *in vivo*, and minimize the surface tumor-associated antigens that continue to proliferate to prevent disease progression so as to improve the quality of life [25]. Furthermore, Cox regression analysis showed that lesion diameter and differentiation degree of tumor cells were independent factors influencing the prognosis of patients. However, the number of cases included in this study is small, and the case collection period is short. Besides, we did not study the exact mechanism of Icotinib hydrochloride tablets on NSCLC cells in depth. Therefore, further large-scale multi-center research is still needed.

In conclusion, EGFR-TKI targeted therapy for advanced NSCLC can significantly relieve the clinical symptoms and is conducive to the improvement of immune function and quality of life, so it is worthy of clinical application.

Disclosure of conflict of interest

None.

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