PATIENTS WITH EGFR-MUTATED LUNG ADENOCARCINOMA AFTER PROGRESSION

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ABSTRACT

Objective: *To investigate the clinical efficacy and safety of dose-escalation of icotinib hydrochloride in targeted therapy of epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma patients after progression.*

Methods: *A total of 80 patients with EGFR-mutated lung adenocarcinoma who were diagnosed and treated in our hospital from January 2018 to January 2021 were selected and divided into the control group and the observation group according to the random number table method, with 40 cases in each group. The control group was given docetaxel combined with a conventional dose of icotinib hydrochloride targeted therapy, and the observation group was given an additional dose of icotinib hydrochloride after treatment resistance on the basis of the control group. The clinical efficacy, health status, cancer-related fatigue status, serological indicators, and toxic and side effects were compared between the two groups.*

Results: *The disease control rate (DCR) in the observation group was significantly higher than that in the control group ($P<0.05$). After treatment, the levels of CD4+, CD4+/CD8+ in the two groups were significantly lower than those before treatment, and the levels of $CD4^+/CD8^+$ and $CD4^+$ were significantly higher than those before treatment ($P<0.05$). The difference was not statistically significant ($P>0.05$). After treatment, the Piper fatigue scale (RPFS) score in the observation group was significantly lower than that before treatment and the control group, and the KPS score was significantly higher than that before treatment and the control group ($P<0.05$). The survival of the observation group was better than that of the control group ($\chi^2=4.240$, Lon RankP=0.039). There was no significant difference in the total incidence of toxic and side effects between the two groups ($P>0.05$). After treatment, the levels of cytokeratin 19 fragment (CYFRA21-1), carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125) in observation group were significantly lower than those before treatment and control group ($P<0.05$).*

Conclusions: *EGFR-mutated lung adenocarcinoma patients who are resistant to icotinib hydrochloride targeted therapy and then given icotinib hydrochloride plus dose therapy have good clinical efficacy. It is not only beneficial to inhibit the proliferation of tumor cells, reduce the tumor volume, improve the prognosis of patients, but also has no obvious malignant effect on the immune function of the body, the treatment effect is relatively safe and effective.*

Keywords: *Icotinib hydrochloride, targeted therapy, epidermal growth factor receptor mutation, lung adenocarcinoma, clinical efficacy.*

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Introduction

With the rapid development of the global economy and the acceleration of industrialization, the incidence of lung cancer has been increasing year by year[(1)]. Non-small cell lung cancer (NSCLC) is the main pathological type in clinical diagnosis of lung cancer, which accounts for about 80% of all lung cancer patients, with high mortality and morbidity[(2)]. Clinical studies have found that epidermal growth factor receptor (EGFR) exon 19 mutation is the most common mutation in NSCLC, which can trigger the enhancement of EGFR tyrosine kinase activity, promote the occurrence of tumor cell planting, metastasis, invasion and other biological behaviors, and then lead to tumor progression[(3)]. As NSCLC patients do not have obvious clinical symptoms in the early stage of the disease, most of the patients have advanced pathological lung cancer and distant metastasis when diagnosed, and the best

opportunity for surgical treatment has been lost[4]. Docetaxel is a second-line chemotherapy drug used in the clinical treatment of patients with advanced lung cancer. According to clinical studies, docetaxel alone is easy to cause obvious toxic and side effects on patients, especially the immune system toxicity, and patients are prone to drug resistance, and the long-term efficacy is often difficult to achieve the desired effect[5]. In recent years, with the continuous improvement of medical technology, molecular targeted therapy drugs have played an important role in the drug treatment of NSCLC patients with EGFR mutation, among which small molecule tyrosine kinase inhibitors can multi-target anti-angiogenesis and have significant clinical effects in pre-clinical studies[6]. As one of the tyrosine kinase inhibitors, erlotinib hydrochloride can effectively inhibit tumor growth by effectively inhibiting fibroblast growth factor receptor and epidermal growth factor receptor[7].

However, the standard treatment regimen of small molecule tyrosine kinase inhibitors combined with chemotherapy drugs in the treatment of lung adenocarcinoma has not been determined, and the clinical treatment regimen with definite efficacy and high safety still needs to be continued. Based on this, this study investigated the clinical efficacy and safety of icotinib hydrochloride targeted therapy after progression in lung adenocarcinoma patients with EGFR mutation, so as to provide reference for clinical treatment.

Data and methods

General information

A total of 80 lung adenocarcinoma patients with EGFR mutation treated in our hospital from January 2018 to January 2021 were selected and divided into control group and observation group according to the random number table method, with 40 cases in each group. There was no significant difference in general data between the two groups (P>0.05), which is comparable, as shown in Table 1.

Inclusion criteria:

• 18 years old ≤80 years old;

• Lung adenocarcinoma patients diagnosed with EGFR mutation[8];

• Predicted survival time ≥6 months;

• Patients with complete clinical records.

Exclusion criteria:

• Abnormal coagulation function or bleeding tendency;

• History of massive hemoptysis in the past 3 months;

• Patients with severe cardiac, hepatic and renal insufficiency;

• Patients with other malignant tumors.

Group	n	Diameter of tumor (cm)	Gender (n)		Age (year)	Pathological stage (n)	
			Man	Woman		III b	IV
Observation group	40	3.72±0.79	25	15	60.18±5.89	28	12
Control group	40	3.88±0.85	27	13	61.33±6.23	27	13
χ^2/t		-0.870	0.220		-0.848	0.058	
P		0.386	0.639		0.399	0.809	

Table 1: Comparison of general data between the two groups.

Methods

The control group received docetaxel combined with conventional dose of icotinib hydrochloride targeted therapy. Docetaxel injection (manufacturer: Chen Xin pharmaceutical co., LTD., approval number: sinophosphir H20093647, specifications: 0.5ml:20mg) was prepared with normal saline at a dose of 75mg/m^2, intravenically infused for 1 hour, once every three weeks, once for a course of treatment.

Conventional dose icotinib hydrochloride targeted therapy: Oral icotinib hydrochloride tablets (Approval number: Sinopharm H20110061, manufacturer: Beda Pharmaceutical Co., LTD., Specifications: 125 mg*21s), 1 tablet each time, 3 times a day, after 14 days of continuous medication, the drug was stopped for 7 days, 21 days was a course of treatment, and the continuous treatment was 4-6 cycles.

On the basis of the control group, after the treatment of drug resistance, the observation group was given single agent icotinib hydrochloride increased dose, 150-450 mg each time, 3 times a day, for 4-6 consecutive cycles.

Observation indicators

Serological indexes

Before and after treatment, 3ml venous blood of the two groups were collected, and the levels of carbohydrate antigen 125 (CA125) were detected by microparticle chemiluminescence method, and the levels of carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (cyfra21-1) were detected by chemiluminescence quantitative method.

DxFLEX flow cytometry (Beckman, USA) was used to detect the serum levels of $CD4^+$ and $CD8^+$ cells in the two groups, and the $CD4^+/CD8^+$ value was calculated.

Health status and cancer-related fatigue

The double-blind KPS scoring system was used to evaluate the health status of the two groups of patients, which consisted of 20 items, with scores ranging from 0 to 100, and the higher the score, the better the health status of the patients[9].

A double-blind Piper Fatigue Scale (RPFS) was used to evaluate the degree of cancer-related fatigue in patients of the two groups, which consisted of four dimensions: cognition, emotion, perception and behavior, with scores ranging from 0 to 10, and the higher the score, the more serious the cancer-related fatigue[10].

Toxic and side reactions

The occurrence of toxic and side effects, including neurotoxicity, thrombocytopenia, hypertension, nausea and vomiting, were observed and recorded during treatment in the two groups, and the total incidence of toxic and side effects was calculated.

Statistical methods

SPSS 20.0 was used for statistical analysis, χ^2 test was used for comparison of count data, measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), t-test was used for comparison, Kaplan-Meier method was used for survival analysis, $P<0.05$ was considered statistically significant.

Results

Comparison of clinical efficacy between the two groups

The DCR of the observation group was significantly higher than that of the control group ($P<0.05$), see Table 2.

Group	n	CR	PR	SD	PD	DCR
Observation group	40	8 (20.00)	16 (40.00)	11 (27.50)	5 (12.50)	35 (87.50)
Control group	40	4 (10.00)	10 (25.00)	13 (32.50)	13 (32.50)	27 (70.00)
χ^2						4.588
P						0.032

Table 2: Comparison of efficacy between the two groups [case (%)].

Comparison of tumor marker levels between the two groups

Before treatment, there were no significant differences in CYFRA21-1, CA125 and VGEF levels between the two groups ($P>0.05$); After treatment, the levels of CYFRA21-1, CA125 and VGEF in the observation group were significantly lower than those before treatment and in the control group ($P<0.05$), see Table 3.

Group	n	CYFRA21-1 (μg/L)		CEA (μg/L)		CA125 (U/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	40	39.87± 7.51	17.58± 4.08*	51.79± 8.26	17.58± 4.94*	88.25± 11.13	41.89± 8.78*
Control group	40	40.33± 7.23	24.42± 5.23*	52.25± 10.39	31.31± 8.61*	87.75± 10.71	52.21± 9.21*
t		-0.279	-6.522	-0.219	-8.748	0.205	-5.129
P		0.781	0.000	0.827	0.001	0.838	0.000

Table 3: Comparison of tumor marker levels between the two groups ($\bar{x}\pm s$).
*Note: Comparison with pre-treatment: *P<0.05.*

Comparison of immune indexes between the two groups

Before treatment, there was no significant difference in T lymphocyte level between the two groups ($P>0.05$); After treatment, the levels of $CD4^+/CD8^+$ and $CD4^+$ were significantly lower than those before treatment, and the levels of $CD8^+$ in both groups were significantly higher than those before treatment ($P<0.05$); After treatment, there was no significant difference in T lymphocyte level between the two groups ($P>0.05$), see Table 4.

Group	n	$CD4^+$		$CD8^+$		$CD4^+/CD8^+$	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	40	28.13± 5.85	23.37± 7.42*	29.24± 5.47	35.22± 4.47*	0.95± 0.18	0.72± 0.14*
Control group	40	28.40± 5.12	22.72± 4.33*	29.75± 5.64	33.74± 6.61*	0.94± 0.16	0.67± 0.12*
t		-0.220	0.479	-0.411	1.173	0.263	1.715
P		0.827	0.634	0.683	0.244	0.794	0.090

Table 4: Comparison of immune index levels between the two groups [% ($\bar{x}\pm s$)].
*Note: Compared with patients before treatment, *P<0.05.*

Comparison of KPS and RPFS scores between the two groups

Before treatment, there was no significant difference in KPS and RPFS scores between the two groups ($P>0.05$); After treatment, the KPS score of the observation group was significantly

higher than that before treatment and the control group, and the RPFS score was significantly lower than that before treatment and the control group (P<0.05), see Table 5.

Group	n	KPS		PDF	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	40	64.21±8.73	85.87±12.62*	5.77±1.02	4.11±0.72*
Control group	40	65.75±10.42	76.21±11.35*	5.74±0.97	4.87±0.85*
t		-0.717	3.600	0.135	-4.315
P		0.476	0.001	0.893	0.000

Table 5: Comparison of KPS and RPFS scores between the two groups [% ($\bar{x}$±s)].
*Note: Compared with patients before treatment, *P<0.05.*

Comparison of survival between the two groups

The median survival time of the control group was 10.08 months (95%CI: 8.438-11.712), and the median survival time of the observation group was 12.53 months (95%CI: 10.829-14.221). The survival of patients in the observation group was better than that in the control group, and the difference was statistically significant (χ^2=4.240, Lon RankP=0.039), as shown in Figure 1.

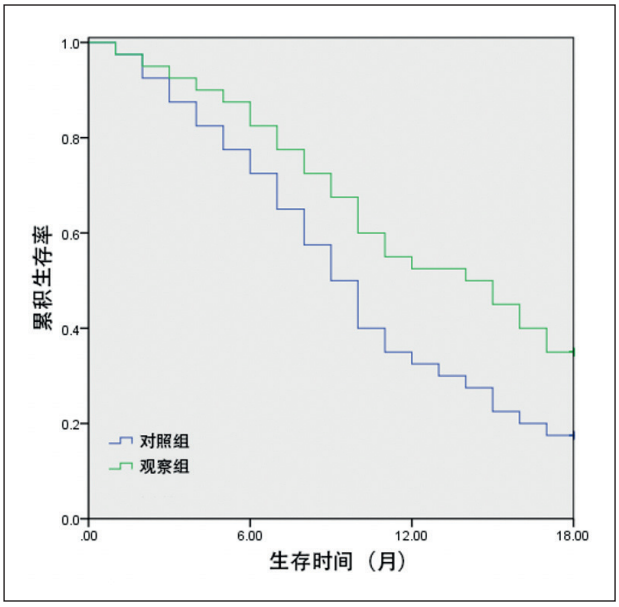

Figure 1: .....

Comparison of toxic reactions between the two groups

There was no significant difference in the total incidence of toxic and side effects between the two groups (P>0.05), see Table 6.

Group	n	Neurotoxicity	Cytopenia	Hypertension	Nausea and vomiting	The total incidence
Observation group	40	4 (10.00)	3 (7.50)	1 (2.50)	4 (10.00)	12 (30.00)
Control group	40	2 (5.00)	1 (2.50)	0 (0.00)	2 (5.00)	5 (12.50)
χ^2						3.660
P						0.056

Table 6: Comparison of toxicity and side effects between the two groups [n (%)].

Discussion

As the most common histopathological type of lung cancer, NSCLC has the characteristics of high metastasis rate, high degree of malignancy and strong invasiveness. Most patients are already advanced at the time of diagnosis. Surgery is one of the important treatment methods in the clinical treatment of NSCLC, and also the first choice and most effective treatment method for patients with early and middle stage NSCLC. However, EGFR mutant NSCLC, as the most common histopathological type of lung cancer, is characterized by strong invasiveness, high degree of malignancy and high rate of metastasis. Most patients are advanced at the time of diagnosis, and the best opportunity for surgical treatment is lost, and the mortality rate is high. Other effective treatment methods are urgently needed[11]. With the further research of tumor molecular genetics, tumor molecular targeted drugs are gradually widely used in the clinical treatment of cancer patients. Docetaxel is a commonly used second-line chemotherapy drug in clinical practice, but the effective rate of clinical treatment alone is limited[12]. In recent years, with the continuous improvement of medical technology, molecular targeted therapy drugs have played an important role in the drug treatment of NSCLC.

Erlotinib hydrochloride is a commonly used tumor molecular targeted drug in clinical practice, which can effectively inhibit tumor growth[13]. Studies have found that, although EGFR-mutant NSCLC patients treated with small molecule tyrosine kinase inhibitors are effective, disease progression usually occurs 9 to 14 months after conventional-dose treatment[14]. Current guidelines recommend that NSCLC patients with EGFR exon 19 mutation continue to receive the same small-molecule tyrosine kinase inhibitor after the conventional dose or change to a combination of small-molecule tyrosine kinase inhibitor and platinum, however, the standard regimen is still inconclusive[15]. In this study, patients

with lung adenocarcinoma with EGFR mutation were treated with icotinib hydrochloride after the progress of targeted therapy, and it was found that this treatment has good clinical efficacy and safety.

The results of this study showed that the DCR and ORR of the observation group were significantly lower than those of the control group. After treatment, RPFS score was significantly lower than before treatment and control group, and KPS score of observation group was significantly higher than before treatment and control group. The survival status of the patients in the observation group was better than that in the control group. It shows that compared with the application of docetaxel combined conventional dose ectinib hydrochloride targeted therapy, in patients with ectinib hydrochloride targeted therapy resistance, giving ectinib hydrochloride plus quantity treatment is more conducive to regulate EGFR mutation of lung adenocarcinoma patients with systemic health state, alleviate cancer fatigue, reduce tumor volume, improve lung function, improve the treatment effect. CA125 is a polyglycan protein, which will be released into the blood when the body tissue is destroyed by invasive tumors, leading to the increasing of serum CA125 content in patients, and its detection level can be used to reflect the short-term efficacy of tumor treatment[16]. CEA is an acidic glycoprotein secreted by the secretory cells of the adult gastrointestinal tract and has the specificity of human embryonic antigen, which plays an important role in the prognosis assessment of lung cancer[17].

Cyfra21-1 is a soluble fragment of cytokeratin, which exists in the cytosol of epithelial cells and is released into the blood when tumor cells are lysed or necrotized. It is a serum tumor marker in NSCLC patients[18]. The results of this study showed that after treatment, the levels of CA125, CEA and CYFRA21-1 in the observation group were significantly lower than those before treatment and in the control group. It is suggested that compared with docetaxel combined with conventional dose of icotinib hydrochloride targeted therapy, increased dose of icotinib hydrochloride is more beneficial to inhibit tumor cell proliferation and control the condition of NSCLC patients after resistance to icotinib hydrochloride targeted therapy.

Icotinib hydrochloride is a commonly used molecular tumor-targeting drug in clinical practice, which can effectively inhibit tumor growth. Icotinib hydrochloride can inhibit the activity of tyrosine kinase by competing with adenosine triphosphate for the enzyme binding site of epidermal growth factor receptor (EGFR), prevent the activation of EGFR downstream signaling pathway, and then inhibit the proliferation, invasion and metastasis of tumor cells, and promote the apoptosis of tumor cells[19]. In addition, icotinib hydrochloride can exert a stronger anti-angiogenesis effect by inhibiting microvessel density and the proliferation of small blood vessels, thereby inhibiting tumor angiogenesis and effectively reducing tumor volume[20].

In addition, icotinib hydrochloride has a short half-life and a wide therapeutic window. The recommended therapeutic dose is 125 mg, 3 times/day, and the maximum tolerated dose is 500 mg/ time[21]. According to clinical studies, the bioavailability of icotinib hydrochloride is linearly correlated with drug concentration, that is, the higher the drug concentration of icotinib hydrochloride, the greater its bioavailability[22]. Other studies have found that advanced NSCLC patients with a large amount of pretreatment have good pharmacokinetic characteristics and antitumor activity, which provides the possibility of increasing the dose of icotinib hydrochloride after targeted therapy resistance in patients[23]. Therefore, in this study, after the drug resistance of targeted therapy, the dosage of icotinib hydrochloride was given to patients, which was beneficial to improve the treatment effect, alleviate cancer-related fatigue, improve the lung function of patients, and prolong the survival time of lung adenocarcinoma patients with EGFR mutation.

Related studies have shown that one of the important reasons for treatment failure of cancer patients is that cancer cells inhibit the function of peripheral blood immune cells, thereby escaping the immune response of the body[24]. T lymphocyte-mediated cellular immunity is the main anti-tumor mechanism in cancer patients. $CD4^+$ cells, as the helper cells of T cells, play a major role in cellular immune response. $CD8^+$ cells are inhibitory T cells, which can inhibit the function of $CD4^+$ cells. The ratio of $CD4^+/CD8^+$ is a sensitive indicator for clinical diagnosis of disorders of human immune function, and the decrease of its level indicates the disorder of cellular immune function of the body[25]. The results of this study showed that there was no significant difference in the total incidence of toxic side effects between the two groups after treatment. The results indicate that the increased dose of icotinib hydrochloride has no obvious malignant effect on immune function in patients with icotinib hydrochloride targeted therapy

resistance, and the therapeutic effect is relatively safe and effective. Ecketinib hydrochloride can inhibit the microvascular density and small vascular proliferation, inhibit tyrosine kinase activity, play a stronger anti-angiogenic effect, and effectively reduce the tumor volume, prevent the activation of EGFR downstream signaling pathway, improve the treatment effect, and the body immune function without obvious malignant effect, treatment effect is relatively safe and effective.

In conclusion, in EGFR mutations of lung adenocarcinoma patients receiving ectinib hydrochloride targeted therapy resistance, give ectinib hydrochloride plus quantity treatment has good clinical effect, is beneficial to inhibit tumor cell proliferation, reduce tumor volume, improve the prognosis of patients, and no obvious malignant effect on the body immune function, the treatment effect is relatively safe and effective.

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