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Effects of gefitinib on quality of life and expression of inflammatory cytokines, T cell subsets and serum tumor markers in senile patients with NSCLC.

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Abstract

The aim of the study is to observe the effect of gefitinib on the quality of life, the level of inflammatory factors, T cell subsets and serum tumor markers in elderly patients with Non-Small Cell Lung Cancer (NSCLC), and to explore its clinical value. 140 elderly patients with NSCLC admitted from Feb 2014-2016 were selected for prospective controlled analysis. According to the random number table method, the patients were divided into observation group, control group with 70 cases in each. All the patients were treated with routine supportive care. Patients in observation group were treated with gefitinib. Patients in control group received the GP regimen (gemcitabine+cisplatin). The changes of quality of life, inflammatory factors, T cell subsets, changes of serum tumor markers, the occurrence of adverse events and survival were compared between the two groups before and after treatment. The application value of gefitinib in the treatment of senile NSCLC was analyzed. The total effective rate was 47.14% in the observation group, which was higher than that in the control group (30.00%), the difference was statistically significant (P<0.05). The incidence of thrombocytopenia, anemia, granulocytopenia, nausea and vomiting in the observation group was lower than that in the control group. The incidence of diarrhoea and rash was higher than that of the control group (P<0.05). The quality of life of the two groups was improved compared with that before treatment, and the improvement of the observation group was more obvious (P<0.05). The levels of IL-2, IL-12 and IFN-γ in the two groups were significantly higher than those before treatment (P<0.05). The levels of CD4+, CD4+/CD8+ in the observation group significantly increased. CD3+ and VEGF decreased (P<0.05) after 2 courses. While no significant change was observed in the control group (P>0.05). In conclusion, gefitinib is safe and effective in the treatment of elderly patients with NSCLC, and can significantly improve their quality of life, inhibit the inflammatory response, improve immune function, down-regulate VEGF expression. It is expected to extend the survival of patients or win opportunities for radical surgery, which is worthy of further attention.

Keywords: Gefitinib, Senile, Non-small cell lung cancer, Quality of survival, Inflammatory factor, T-cell subsets, Tumor markers.

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Introduction

Non-Small Cell Lung Cancer (NSCLC), the most common type of lung cancer, accounts for more than 80% of lung cancer. Studies have shown that more than half of NSCLC patients are more than 65 y old when diagnosed. That is, NSCLC patients are most elderly population and the majority of patients with 5 y survival rate of only 15% [1].

Platinum-based chemotherapy regimen is the preferred treatment for patients without surgical indications for NSCLC. For elderly patients, the combined efficacy of the third-generation chemotherapeutic drug regimen is 25%-35%, resulting in a median survival extended to 8-10 months [2].

As a novel Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor, gefitinib has been widely concerned in the treatment of NSCLC in recent years. In addition, foreign literature research shows that the Asian population can acquire significant benefit in gefitinib treatment [3].

Since the approval of the market in early 2005, more and more domestic scholars tend to understand the role of gefitinib in the treatment of NSCLC. In this study, we studied 140 cases of elderly patients with NSCLC, to observe the mechanism, efficacy, and safety of gefitinib. It is reported below.

Materials and Methods

General data

A total of 140 elderly patients with NSCLC admitted from Feb 2014-2016 were selected for prospective controlled analysis. According to the random number table method, the patients were divided into observation group and control group, with 70 cases in each. There were no significant differences in age, sex, pathological type and clinical stage between the two groups (P>0.05, Table 1). The clinical study has been approved by the Medical Ethics Committee of our hospital. Patients and their families are informed consent and signed informed consent.

Table 1. Comparison of general clinical data between the two groups (n/%).

Indexes		Observation group (n=70)	Control group (n=70)	P
Age (y)		70.16 ± 6.23	70.52 ± 6.61	>0.05
Sex	Male	40 (57.14)	38 (54.29)	>0.05
	Female	30 (42.86)	32 (45.71)	
Pathological type	Adenocarcinoma	19 (27.14)	23 (32.86)	>0.05
	Squamous cell carcinoma	22 (31.43)	21 (30.00)	>0.05
	Others	29 (41.43)	26 (37.14)	>0.05
Clinical stage	Stage III	45 (64.29)	43 (61.43)	>0.05
	Stage IV	25 (35.71)	27 (38.57)	

Inclusion and exclusion criteria

Inclusion criteria: (1) Confirmed by the clinical pathology of NSCLC, age ≥ 65 years [4]; (2) Clinical stage III~IV, with no surgical indications; (3) Expected survival ≥ 6 months; (4) Volunteered to participate in the study.

Exclusion criteria: (1) Combined with other malignant tumors; (2) Combined with severe injury of heart, liver, kidney or other organs; (3) Tumor has been serious and uncontrollable with brain metastases; (4) Had treatment history of molecule target drug or monoclonal antibody within 1 month before enrolment; (5) The presence of contraindications or the history of allergies.

Research methods

Treatment programs: The patients in the control group received GP regimen (gemcitabine+cisplatin) treatment: 1250 mg/m^2 gemcitabine (trade name: Gemini, Eli Lilly Co. Ltd., USA, registration number: H20110535, specifications: 200 mg) adding into 100 mL of saline by intravenous infusion for 30 min before the infusion is completed at the 1st and 8th d. 75 mg/m^2 cisplatin (trade name: Nuoxin, Jiangsu Haosen Pharmaceutical Co., Ltd. Chinese medicine Zhunzi H20040813, specifications: 30 mg) adding into 500 mL of saline by intravenous infusion from 1st d to 3rd d. During chemotherapy, patients were given conventional hydration, diuresis [5]. Patients in the observation group received gefitinib treatment: 0.25 g gefitinib (trade name: Iressa, AstraZeneca, USA, registration number: H20140471, specifications: 0.25 g) orally taken 1 h after the meal, once a day. Every course of treatment was 21 d for both groups of patients. The results were observed after 2 courses of treatment. Two groups of patients received antiemetic, analgesic, nutritional support and other comprehensive treatment [6,7].

Observe indicators: Clinical efficacy: the clinical efficacy referred to the new evaluation criteria of solid tumor (RECIST v1.1), to evaluate clinical efficacy on patients after treatment of 2 courses [8]. Complete Remission (CR): lesion completely disappeared. Partial Remission (PR): tumor volume was reduced by more than 30% than before treatment. Stable Disease (SD): tumor volume decreased by <30% or increased <20% than before treatment. Progressive Disease (PD): tumor volume increased by ≥ 20% than before treatment. Total efficiency=(CR+PR)/total number of cases × 100%.

Toxicity: toxicity was evaluated with reference to the World Health Organization (WHO) Evaluation Criteria for Adverse Drug Reactions to record the occurrence of toxic and side effects during treatment [9,10].

The quality of life: The quality of life before and after treatment was evaluated with reference to the Overall Quality of Life Scale (GHS) developed by the European Cancer Research Organization. GHS scale includes 5 dimensions: body function, role function, social function, emotional function and cognitive function. The higher the score, the better the overall quality of life.

Serum indicators: Morning fasting venous blood of 10 mL was extracted from two groups of patients before and after treatment, and then divided into three tubes. 5 mL of blood was taken for the detection of inflammatory factors, 2 mL for T cell subsets detection, and 3 mL of blood for tumor marker detection.

Wherein the inflammatory factors included interleukin-2 (IL-2), IL-12 and interferon-γ (IFN-γ). T cell subsets included CD3+, CD4+ and CD8+. Tumor markers included Carcinoembryonic Antigen (CEA), glycoprotein 125 (CA125), Cytokeratin 19 Fragment 21-1 (CYFRA21-1) and Vascular Endothelial Growth Factor (VEGF). Detection methods referred to the relevant literature [11,12].

Statistical analysis

All data on this clinical study were analyzed using SPSS 18.0, the count data was expressed in (n/%), and the chi-square test was used. The measurement data is expressed as ($\bar{x} \pm s$).

To meet the variance homogeneity, the independent sample t-test is used. If the variance is missing, then the correction t-test was used. P<0.05 for the difference was statistically significant.

Results

End of study

After 2 courses of treatment, all of the patients in the two groups were alive, with no removal or loss of patients. They were included in the results of analysis.

Clinical efficacy

The total effective rate of the observation group was 47.14%, which was higher than that of the control group (30.00%), the difference was statistically significant (P<0.05). There were no patients with CR in either of the group, after 2 courses of treatment (Table 2).

Table 2. *Comparison of clinical efficacy between the two groups (n/%).*

Clinical efficacy	Observation group (n=70)	Control group (n=70)	P
CR	0	0	
PR	33 (47.14)	21 (30.00)	
SD	32 (45.71)	37 (52.86)	
PD	5 (7.14)	12 (17.14)	
Total effective (rate)	33 (47.14)	21 (30.00)	<0.05

Toxic and side effects

The incidence of thrombocytopenia, anemia, granulocytopenia, nausea and vomiting in the observation group was lower than that in the control group, and the incidence of diarrhoea and rash was higher than that of the control group (P<0.05). Patients with adverse reactions received symptomatic treatment and all improved in both groups, without affecting the treatment process (Table 3).

Quality of life

The quality of life of the two groups after treatment was improved compared with that before treatment, the improvement of the observation group was more obvious, the difference was statistically significant (P<0.05, Table 4).

Serum indicators

The levels of IL-2, IL-12 and IFN-γ in the two groups were significantly higher than those before treatment (P<0.05). The levels of CD4+, CD4+/CD8+ in the observation group significantly increased. CD3+ and VEGF decreased (P<0.05) after 2 courses. While no significant change was observed in the control group (P>0.05, Table 5).

Table 3. *Comparison of toxic and side effects between the two groups.*

Toxic and side effects	Observation group (n=70)		Control group (n=70)	
	Stage I~II	Stage III~IV	Stage I~II	Stage III~IV
Thrombocytopenia	4 (5.71)	0	32 (45.71)*	22 (31.43)*
Anemia	2 (2.86)	0	18 (25.71)*	24 (34.29)*
Granulocytopenia	2 (2.86)	0	20 (28.57)*	28 (40.00)*
Elevated transaminase	6 (8.57)	16 (22.86)	14 (20.00)	12 (17.14)
Oral ulcers	8 (11.43)	0	10 (14.29)	2 (2.86)
Nausea and vomiting	12 (17.14)	10 (14.29)	14 (20.00)*	32 (45.71)*
Diarrhea	16 (22.86)	32 (45.71)	2 (2.86)*	2 (2.86)*
Rash	14 (20.00)	36 (51.73)	4 (5.71)*	1 (1.43)*

Note: Compared with observation group, *P<0.05

Table 4. *Comparison of changes in quality of life between the two groups (points, $\bar{x} \pm s$).*

Dimension	Observation group (n=70)		Control group (n=70)	
	Before treatment	After 2 courses of treatment	Before treatment	After 2 courses of treatment
Body function	59.26 ± 11.47	75.26 ± 18.84*	59.71 ± 11.38	67.31 ± 17.25*#
Role function	45.43 ± 17.26	66.26 ±14.57*	45.26 ± 17.13	56.53 ± 18.40*#
Social function	49.36 ± 17.08	69.87 ± 16.52*	49.42 ± 16.85	58.26 ± 16.47*#

Emotional function	62.63 ± 16.15	80.43 ± 15.54*	61.95 ± 16.33	70.36 ± 18.85*#
Cognitive function	63.22 ± 16.30	72.69 ± 16.18*	63.26 ± 16.71	68.94 ± 13.75*#

Note: Compared with before treatment, *P<0.05; Compared with the observation group, #P<0.05.

Table 5. Comparison of changes between the two groups.

Classification	Indexes	Observation group (n=70)		Control group (n=70)	
		Before treatment	After 2 courses of treatment	Before treatment	After 2 courses of treatment
Inflammatory factor	IL-2 (ng/L)	61.36 ± 7.71	71.63 ± 7.25*	61.30 ± 7.73	67.52 ± 7.36*#
	IL-12 (ng/L)	51.26 ± 6.34	68.65 ± 7.10*	50.89 ± 6.63	58.62 ± 6.39*#
	IFN-γ (ng/L)	52.36 ± 6.65	74.32 ± 8.26*	53.19 ± 6.58	59.47 ± 5.25*#
T cell subsets	CD3+(%)	63.26 ± 5.44	64.20 ± 4.47	63.30 ± 4.88	64.21 ± 4.43#
	CD4+(%)	33.21 ± 4.68	37.91 ± 5.08*	33.26 ± 4.05	33.21 ± 4.16#
	CD8+(%)	30.57 ± 3.35	27.04 ± 3.27*	30.31 ± 3.58	29.25 ± 3.05#
	CD4+/CD8+	1.16 ± 0.23	1.36 ± 0.25*	1.16 ± 0.25	1.17 ± 0.24#
Tumor markers	CEA (μg/L)	19.28 ± 7.71	21.29 ± 5.33	19.83 ± 7.26	20.49 ±8.81
	CA125 (U/mL)	35.36 ± 13.24	33.28 ± 4.48	30.37 ± 9.26	33.26 ± 11.43
	CYFRA21- 1(μg/L)	4.14 ± 1.08	3.87 ± 0.85	3.97 ± 0.99	3.87 ± 2.26
	VEGF (ng/L)	142.59 ± 38.16	102.25 ± 26.40*	144.26 ± 35.57	132.35 ± 40.68#

Note: Compared with before treatment, *P<0.05; Compared with the observation group, #P<0.05.

Discussion

With the development of medical technology, the treatment of malignant tumors has made great progress, but advanced NSCLC is still an incurable disease. The current first-line chemotherapy drug efficacy has reached the platform. Elderly patients with physical and psychological difficulty are often difficult to bear the high intensity of second-line, third-line chemotherapy. In addition, the elderly population has a high incidence of NSCLC, causing short survival time of NSCLC patients, with bad quality of life [13,14]. In recent years, the research and development of gefitinib have opened up a new way of thinking for the NSCLC treatment in senile patients. But the introduction time of gefitinib in China is short, the research on the drug treatment of elderly patients with NSCLC is still relatively lacking.

As a small molecule Tyrosine Kinase Inhibitor (EGFR-TKI) for EGFR, gefitinib competes with ATP to bind extracellular ligand-binding domains, specifically inhibiting EGFR tyrosine kinase activity for cell proliferation and angiogenesis, and ultimately plays a role in promoting apoptosis [15]. Previous studies have shown that 250 mg/d of gefitinib is comparable to that of 500 mg/d, but the high-dose regimen can lead to a significant increase in toxic side effects [16]. Therefore, in this study, oral administration of 250 mg of gefitinib was observed. The results showed that although there were no CR patients in both groups, the total effective rate of the observation group was 47.14%, which was significantly higher than that of the control group (30.00%), which confirmed the good curative effect of the drug. At the same time, although gefitinib can effectively avoid the risk of high blood system toxicity, immune system toxicity in GP system, the incidence of rash and diarrhoea is higher. In the future clinical application, symptomatic treatment measures should be emphasized and stressed actively to improve drug safety and to ensure patient's tolerance.

The treatment of the current clinical malignancy has not only limited to the extension of survival but more emphasis on the improvement of the quality of life. Due to physical weakness, decreased immune function and multiple disease-ridden, the quality of life of elderly patients with NSCLC is greatly reduced. However, conventional first-line chemotherapy regimen can improve the quality of life of patients to a certain extent, but the obvious adverse reactions and the limitations of the efficacy significantly limited the recovery of the quality of life in patients [17]. In this study, quality of life improved in the control group after 2 courses of treatment, but the extent was less than the observation group, which confirmed the above conclusions. Gefitinib with its more convenient mode of treatment, lower incidence of toxic side effects and more accurate clinical efficacy, the overall quality of life has been significantly improved, which was in line with the needs of malignant tumor treatment.

In the development of NSCLC, IL-2, IL-12, IFN-γ decreased and the balance disorder of T cell subsets showed that patients were in immune dysfunction. When the GP program in the killing of tumor cells, it is often difficult to avoid damaging normal cells. And even further exacerbate the decline in immune function, resulting in decreasing of the anti-tumor capacity of the body, causing disease progression [18]. This may be the main reason for the patient's PD rate as high as 17.14%. While gefitinib can target EGFR, down-regulate VEGF expression, playing a specific anti-tumor effect, with little effect on the immune function of patients [19]. At the same time, with the reduction of tumor load, the immune function of the patients can be gradually improved. The immune function has positive significance in tumor cell recognition, the recovery of the killing ability, the improvement of patient's quality of life [20]. In this study, the levels of inflammatory factors and T cell subsets in the observation group were more significantly improved than those in the control group, confirming the above findings.

In conclusion, gefitinib has a better effect in the treatment of elderly NSCLC patients compared to the GP regimen. It not only reduced the incidence of toxic side effects, its inflammatory factors, T cell subsets and VEGF regulation to a certain extent but also significantly improved the patient's quality of life. Therefore, in future clinical studies, it is advisable to further focus on the long-term effects of gefitinib in the treatment of elderly NSCLC patients, to lay a firmer theoretical basis for the promotion of the drug.

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