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ORIGINAL ARTICLE

The influence of autologous cytokine-induced killer cell treatment on the objective efficacy and safety of gefitinib in advanced non-small cell lung cancer

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Abstract

Objective The aim of the study was to observe the influence of autologous cytokine-induced killer cell (CIK) treatment on the objective efficacy and safety of gefitinib in advanced non-small cell lung cancer (NSCLC).

Methods Sixty-six patients with NSCLC received gefitinib as second-line treatment. They were randomly divided into 2 groups, and informed consent forms were signed before grouping. Gefitinib was administrated to the control group, and autologous CIK treatment was added to the observation group. The objective treatment and adverse reactions were evaluated in both groups.

Results The objective response rate (ORR) and the disease control rate (DCR) of the observation group were slightly higher than those of the control group, although no statistical differences were found between the 2 groups ($P > 0.05$). The incidences of diarrhea, fatigue, anorexia, oral ulcers, and myelosuppression in the observation group were much lower than those in the control group ($P < 0.05$). However, there were no statistical differences between the incidences of skin rash, and liver and kidney toxicities ($P > 0.05$).

Conclusion Autologous CIK in combination with gefitinib is effective as second-line treatment for advanced NSCLC, and can significantly reduce adverse reactions and improve the objective efficacy.

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Key words: non-small cell lung cancer (NSCLC); gefitinib; cytokine-induced killer (CIK) cell

Gefitinib is the world's first epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which selectively blocks the proliferation and metastasis of advanced solid tumors with high expression of EGFR. Gefitinib has been recommended by the National Comprehensive Cancer Network (NCCN) guidelines as the drug of choice for the second or third-line treatment of non-small cell lung cancer (NSCLC). The use of gefitinib significantly improves the overall survival and quality of life in NSCLC patients [1–2]. However, the accompanying adverse effects of treatment are one of the most difficult problems in clinical practice, which affect patient compliance and can even lead to drug withdrawal. Cytokine-induced killer cells (CIK) can kill the tumor cells directly by *in vitro* amplification, adjust the host's immune function, and improve the quality of life. It has become one of the biological treatment modes for the solid tumors [3–4]. The purpose of this study was to explore the influence of autologous CIK treatment on the objective efficacy and safety of gefitinib in advanced NSCLC.

Patients and methods

Clinical data

Between March 2009 and March 2014, 66 patients with stage IV NSCLC at the General Hospital of Shenyang Military Region (China) were enrolled in the study. The patient's ages ranged from 35 to 77 years, with the median age of 55 years. Thirty patients were men, and 36 were women. All patients had a histopathological diagnosis and evaluable lesions. Fifty-three patients had adenocarcinoma, and 13 had squamous carcinomas. The patients received platinum-doublet chemotherapy, including docetaxel, gemcitabine, and pemetrexed. The pre-treat-

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Table 1 Clinical characteristics of patients before treatment (*n*)

Clinical characteristics	All	Observation group	Control group
Median age (years)	55	56	55
Sex			
Male	30	14	16
Female	36	19	17
Pathological type			
Adenocarcinoma	53	25	28
Squamous carcinoma	13	8	5
Clinical stage			
IIIb	34	16	18
IV	32	17	15
ECOG score			
0–1	31	16	15
2–3	35	17	18

ment detection of an *EGFR* gene mutation was made in all 66 patients, of which 42 patients had exon 19 mutations and 24 patients had exon 21 mutations. The patients signed informed consent forms before treatment. Routine blood tests and liver and kidney functions results of the patients were all within the normal range. The 66 patients were equally randomized into 2 groups; the clinical characteristics of the patients in each group were not statistically different ($P > 0.05$; Table 1).

Therapeutic methods

In the control group, 250 mg gefitinib was administered orally once a day. In the observation group, a venous blood sample was collected on the first day of gefitinib administration, and mononuclear cells were separated and cultured for 14 days in the lab. The concentration of cells was adjusted to 2×10^6 /mL using serum-free medium; 1000 U/mL IFN-gamma was added and the cells were cultured at 37 ℃ with 5% CO_2 for 24 h. A total of 1000 U/mL IL-2 and 50–100 ng/mL anti-CD3 monoclonal antibody were then added. On day 14, the CIK cells were collected and suspended in physiological saline containing 1% albumin. The suspension was then re-infused intravenously in 2 fractions. This was the protocol for CIK treatment. Patients in the observation group underwent 1 CIK treatment per month, more than 3 consecutive times. In both groups, gefitinib was used continuously until disease progression or an intolerable adverse reaction occurred. No other systemic anti-tumor treatment was conducted at the same time. The patients were followed-up every 2 months after treatment. Clinical information, including symptoms, signs, and the Eastern Cooperative Oncology Group (ECOG) score were recorded. The results were assayed, including routine blood examination, liver and kidney function measurements, urinalysis, electrocardiography, ultrasonic cardiography, abdominal ultrasonography, and lung computed tomography (CT). Cerebral CT and bone emission computed tomography (ECT) were performed every 3–6 months.

Table 2 The objective response rate (ORR) and disease control rate (DCR) of patients (*n*)

	CR	PR	SD	PD	ORR (%)	DCR (%)
Control group	1	20	5	7	63.6	78.8
Observation group	1	21	5	6	66.7	84.5

Therapeutic effect evaluation and adverse reactions

The short-term therapeutic effects were evaluated by using Response Evaluation Criteria in Solid Tumors (RECIST). The effects were classified as complete remission (CR), partial response (PR), stable disease (SD), or progression of disease (PD). The objective response rate (ORR) was the percentage of CR + PR in all patients, and the disease control rate (DCR) was the percentage of CR + PR + SD in all patients. The improvement of clinical symptoms and the ECOG score was evaluated to determine the quality of life. The criteria of the WHO was used to evaluate adverse reactions.

Statistical methods

SPSS 17.0 software was used for the statistical analyses. The Chi-square test was used to analyze the short-term therapeutic effect and adverse reactions. $P < 0.05$ was considered to have statistical significance.

Results

Therapeutic effect evaluation

The median follow-up time was 12.3 months (6–41 months). None of the patients were lost to follow-up. Therapeutic effects and adverse reactions were evaluated, and at least 2 evaluations were performed for all patients. CIK treatments were administrated 5 times for the patients in the observation group. As shown in Table 2, the ORR of the observation group was slightly higher than that of the control group, but no statistical difference was found between the 2 groups ($\chi^2 = 0.0667$, $P = 0.7962$). The DCR of the observation group was also slightly higher than that of the control group, but no statistical difference was found between the 2 groups ($\chi^2 = 0.0958$, $P = 0.7569$).

Clinical symptoms improvement

The clinical symptoms of the 2 patients who showed a CR completely disappeared, and the ECOG scores were 0. The clinical symptoms of the PR and SD patients improved significantly, such as cough, chest tightness, fatigue, and abdominal pain and distension. There was

Table 3 Incidence of adverse reactions in two groups [*n* (%)]

	Control group				Observation group				χ^2	*P*
	I	II	III	IV	I	II	III	IV		
Rash	15 (45.5%)	10 (30.3%)	1 (3.0%)	0	16 (48.9%)	10 (30.3%)	1 (3.0%)	0	0.096	0.757
Diarrhea	10 (30.3%)	5 (15.2%)	0	0	4 (12.1%)	1 (3.0%)	0	0	7.174	0.007
Anorexia	6 (18.2%)	0	0	0	1 (3.0%)	0	0	0	3.995	0.046
Fatigue	6 (18.2%)	0	0	0	2 (6.1%)	0	0	0	2.276	0.131
Oral mucositis	11 (33.3%)	0	0	0	3 (9.1%)	0	0	0	4.442	0.035
Nausea/vomit	3 (9.1%)	0	0	0	2 (6.1%)	0	0	0	NA	NA
Myelosuppression	2 (6.1%)	0	0	0	2 (6.1%)	0	0	0	NA	NA

no significant difference in the improvement of clinical symptoms between the observation and control groups ($P > 0.05$).

Adverse reactions

The main adverse reactions found in the patients were grade I–II skin rash and diarrhea. One case of grade I skin rash was observed in both groups, and the symptom was alleviated after symptomatic treatment. The other adverse reactions were anorexia, fatigue, nausea, vomiting, oral mucositis, itchy skin, xeroderma, and paronychia. No obvious myelosuppression or abnormality of liver and kidney functions occurred. Low fever occurred in 2 patients in the observation group. The incidences of diarrhea, fatigue, anorexia, oral mucositis, and myelosuppression in the observation group were much lower than those in the control group ($P < 0.05$; Table 3).

Discussion

Lung cancer is a malignant tumor with the highest morbidity and mortality in the world. One-third of lung cancer patients have no opportunity for surgical treatment and even show metastasis at the time of diagnosis [5]. Human epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), the first targeted drugs in the field of lung cancer, have opened a new way for the treatment of advanced cancer, and have become a standard treatment strategy in lung cancer [6].

EGFR is a type of a transmembrane protein that is related to the activation of intracellular tyrosine kinase domains. Gefitinib can combine with EGFR-tyrosine kinase competitively, block the downstream signal transduction, and inhibit the proliferation of tumor cells [5]. In 2003, gefitinib was approved by the State Food and Drug Administration (SFDA) as the second-line treatment for local or metastatic NSCLC. At present, gefitinib has become the primary treatment of choice for NSCLC patients with *EGFR* mutations, according to the NCCN guidelines. In this study, the 66 subjects were all NSCLC patients with *EGFR* mutations, and gefitinib was used for their second-line treatment. Irrespective of whether CIK treatment was used, the objective efficacy and DCR have been consistent with the data of clinical researchers in China and abroad [2, 6–7].

CIKs are polyclonal effector cells that are stimulated by a variety of cytokines. $CD3^+CD56^+$ cells are the main effectors, and can exert MHC-unrestricted killing ability through large-scale expansion *in vitro* [3–4]. CIK cells can regulate the host's immune function *in vivo*, directly or indirectly [8–10]. It is uncertain whether the combined application of CIK treatment can increase antitumor efficacy of gefitinib in NSCLC. In this study, no statistical differences in the ORR or DCR were found between the observation and control groups. This may be due to the fact that CIK treatment was only added in the early stage of gefitinib administration, and there were relatively few CIK treatments. In future studies, CIK treatment would be administrated during the entire process of gefitinib use. In addition, it will be more valuable to evaluate its efficacy after increasing the number of CIK treatments.

Liang's study [11] on 122 patients with postoperative breast cancer showed that CIK cell therapy could significantly improve T-lymphocyte subsets distribution, the host's immune functions, and the quality of life of breast cancer patients. In our study, patients in the 2 groups had gefitinib-induced adverse reactions of diarrhea and skin toxicity, such as skin rashes, itching, xeroderma, and acne. When CIK treatment was combined with gefitinib, the incidence of grade 3 or 4 diarrhea was significantly lowered, which was related to an increase in mucosal repair. It was also found that the incidences of anorexia, fatigue, and nausea were significantly reduced. This was speculated to be relevant to the improvement of patients' immune function by CIK treatment [12–13].

In summary, CIK treatment cannot increase the objective efficacy of gefitinib in advanced NSCLC, but it can lower the adverse reactions, elevate the safety of gefitinib, and improve the patients' quality of life. The clinical value of the treatment model should be confirmed by large-scale studies in the future.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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