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Clinical Study of Recombinant Human Endostatin Combined with Iressa in Targeted Treatment of Patients with Lung Adenocarcinoma with Pleural Metastasis

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Abstract: ***Objective:*** To evaluate and comprehensively analyze the clinical efficacy of recombinant human endostatin combined with Iressa targeted therapy in patients with pleural metastasis of lung adenocarcinoma. ***Methods:*** The interval of the selected study period span was from January 2017 to April 2021. The sample source of the study was 42 patients with lung adenocarcinoma admitted to hospital. The random number table method was used for study grouping, and they were further divided into study groups (n = 21, 14 cases with pleural metastasis) and control group (n=21, 13 cases with pleural metastasis), all patients received systemic chemotherapy with pemetrexed and cisplatin. Patients with pleural metastases in the control group were injected with 60 mg cisplatin into the thoracic cavity. Patients in the study group were treated with Iressa (gefitinib) targeted therapy if genetic testing showed epidermal growth factor receptor (EGRF) mutations, and patients with pleural metastases were treated with pleural metastasis with Endo (recombinant human endostatin YH-16) to control pleural effusion. Two sets of related indicators were compared and analyzed. ***Results:*** Comparing the short-term disease control rate, treatment effectiveness and long-term survival rate between the two groups shows that the study group has more advantages ($P<0.05$). In the comparison between the two groups of serum markers and related indicators, the study group has more advantages ($P<0.05$), whereas in the comparison between the two groups in the incidence of adverse reactions, there is no significant difference ($P>0.05$). Based on statistics of the recurrence rate of pleural fluid in the two groups, the study group is significantly lower than the control group ($P<0.05$). ***Conclusion:*** Recombinant human endostatin combined with Iressa targeted therapy for patients with lung adenocarcinoma with pleural metastasis has significant short-term and long-term effects without serious adverse reactions. It can be fully promoted in medical institutions at all levels.

Keywords: Recombinant human endostatin; Iressa; Pleural metastasis of lung adenocarcinoma

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1. Introduction

Lung adenocarcinoma is a multiple malignant tumor with a high degree of malignancy and the prognosis effect is poor after targeted treatment intervention [1]. Most patients with lung adenocarcinoma have no typical clinical symptoms at the initial stage of onset, and pleural metastasis has occurred at the stage of diagnosis, and increased the difficulty of treatment significantly. The routine clinical treatment of lung adenocarcinoma pleural metastasis is cisplatin combined with pemetrexed first-line chemotherapy, which is prone to adverse reactions such as abnormal liver function and bone marrow suppression. Most patients need to stop treatment after a 6-month course of chemotherapy [2]. For patients who cannot complete the first-line chemotherapy treatment, clinical maintenance treatment is often used to control disease progression and to prolong their survival time. Recombinant human endostatin combined with Iressa

targeted therapy is the main maintenance treatment for patients with lung adenocarcinoma with pleural metastasis. Its main advantage is that it has mild side effects, can effectively control the progression of the disease, and help improve the quality of life of the patients [3]. Further study and analysis of effective treatment options for lung adenocarcinoma pleural metastasis are investigated in this study. Admitted patients were recruited as a study subjects to explore the related issues of recombinant human endostatin combined with Iressa targeted therapy.

2. Materials and methods

2.1. General information

The duration of the study was from January 2017 to April 2021. The study sample is 42 patients with lung adenocarcinoma admitted to this hospital. The random number table method was used for study grouping, and they were further divided into study groups (n=21) and control group (n=21). Demographic data of the two study groups were summarized and analyzed. The study group has 12 males and 9 females with the age range of 54-75 years and an average age of 64.58±2.73 years old. Among them, 14 patients are with pleural metastasis (all belong to stage IV cancer). In the control group, there were 11 males and 10 females, age range from 56 to 76 years old, with an average age of 64.72±2.88 years. Among them, 13 patients with pleural metastasis (all belong to stage IV cancer) had no significant difference in baseline data ($P>0.05$). The inclusion criteria for this study is based on comprehensive examination that consistent with the diagnostic criteria for lung adenocarcinoma pleural metastasis in the 2015 Lung Cancer Diagnosis and Treatment Guidelines. On the other hand, the exclusion criteria is underlying psychiatric diseases and organic critical diseases, combined with other malignant tumors. Informed consent was obtained from subjects who fulfilled the inclusion criteria.

2.2. Method

Both groups of lung adenocarcinoma patients were given oral folic acid (400μg/d) before chemotherapy, and the drug administration was stopped 3 weeks after the end of chemotherapy. In order to improve patients' tolerance to chemotherapy, vitamin B12 is injected before chemotherapy. All patients were treated with pemetrexed and cisplatin systemic chemotherapy. The drug administration mode selection plan was intravenous infusion of pemetrexed (specification: 200mg) on the first day of treatment, with a dosage of 500mg/m2, and intravenous infusion of cisplatin on the first day of treatment. Daily 30mg, (specification: 10mg), the dosage is 25mg/m2.Patients in the control group with pleural metastases received 60 mg cisplatin injection into the chest cavity.

Patients in the study group showed epidermal growth factor receptor (EGRF) mutations through genetic testing. Gefitinib was used for targeted therapy. Gefitinib 250mg was taken orally at a fixed time every day. It can be consumed with meals or on an empty stomach. A single course of treatment lasts for 21 days. If the patient's condition progresses or the drug cannot be tolerated, the drug should be stopped. Patients with pleural metastases were treated with 45 mg of Endo in the chest on the 1st, 4th, and 7th day of treatment, and 30 mg of cisplatin was injected into the chest on the 2nd, 5th, and 8th day of treatment. Dexamethasone was taken orally 1 day before chemotherapy, on the day of chemotherapy, and 1 day after chemotherapy, 4 mg/time. If patients have adverse reactions during chemotherapy, symptomatic treatments such as Shengbaixin and Ondansetron can be used to improve the efficacy of chemotherapy and reduce the incidence of adverse reactions.

2.3. Evaluation criteria

The recent disease control rate and total effective rate of treatment were compared between the two groups, and evaluated according to the relevant standards according to 2015 Lung Cancer Diagnosis and Treatment

Guidelines. The specific criteria include: (i) CR (complete remission): tumor lesions disappeared and no new lesions were found for more than 1 month; (ii) PR (partial remission): the tumor volume has been reduced by more than 50%, and there is no new lesion for more than 1 month; (iii) SD (stable): the tumor volume is reduced by 25-50%; PD (progress): the tumor volume increases by more than 25%, and new lesions are generated, the total effective rate of disease treatment = (CR+PR)/21, disease control rate = (CR+PR+SD)/21. After treatment, the two groups of patients were followed up and the long-term survival rate was calculated.

2.4. Statistical methods

SPSS software version 23.0 was used for data analysis. In this study, the measurement data is expressed as mean±SD. The *t* test was used for analyzing measurement data. The count data is expressed as percentage, and was analyzed using Chi-squared test. If $P<0.05$, there are differences between groups.

3. Results

3.1. Comparison of short-term disease control rate, total effective rate of treatment, and long-term survival rate between the two groups

In the comparison of short-term disease control rate, total effective rate of treatment, and long-term survival rate between the two groups, the study group has more advantages ($P<0.05$) (**Table 1**).

Table 1. Comparison of the short-term disease control rate, total effective rate of treatment, and long-term survival rate (n/%) between the two groups

Group	CR	PR	SD	PD	Total effective rate	Disease control rate	Long-term survival rate
Research group (n=21)	2	7	8	4	9 (42.9)	17 (80.9)	13 (61.9)
Control group (n=21)	0	3	8	10	3 (14.3)	11 (52.4)	6 (25.6)
χ^2 value					4.200	3.857	4.709
P value					0.040	0.049	0.029

3.2. Comparison of serum markers between the two groups after treatment

In the comparison of the serum markers between the two groups after treatment, the study group had more advantages ($P<0.05$) (**Table 2**).

Table 2. Comparison of serum markers (mean±SD, ng/ml) and CA125 after treatment between the two groups

Group	CYFRA-21	NSE	CEA	CA125
Research group (n=21)	3.11±1.74	10.38±1.65	9.29±1.74	8.48±1.19
Control group (n=21)	5.29±1.86	16.44±1.57	15.58±1.79	22.63±4.88
X value	3.922	12.192	11.546	12.909
P value	0.000	0.000	0.000	0.000

3.3. Comparison of the incidence of adverse reactions and the recurrence rate of pleural fluid between the two groups

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). After comparison between the two groups, we found that the recurrence rate of pleural fluid of the study group was lower than that of the control group (P<0.05) (**Table 3**).

Table 3. Comparison of the incidence of adverse reactions between the two groups (n/%)

Group	Diarrhea	Rashes	Nausea	Elevated transaminase	Recurrence rate of pleural fluid
Research group (n=21)	7 (33.3)	6 (28.6)	6 (28.6)	5 (23.8)	0 (0.0)
Control group (n=21)	6 (28.6)	4 (19.0)	5 (23.8)	4 (19.0)	4 (19.0)
X value	0.111	0.525	0.123	0.141	4.421
P value	0.738	0.468	0.725	0.706	0.035

4. Discussion

Lung adenocarcinoma belongs to the category of non-small cell lung cancer, and the site of incidence originates from bronchial mucosal epithelial tissue. Lung adenocarcinoma has no typical clinical symptoms in the early stage, and the patient's condition progresses rapidly. Advanced lung adenocarcinoma can induce symptoms such as dyspnea, hemoptysis, and coughing. Most patients with lung adenocarcinoma have developed pleural metastasis at the diagnosis stage, and the difficulty of treatment is significantly increased [4]. Clinical treatment of lung adenocarcinoma mostly adopts single-drug or multi-drug combination chemotherapy. The side effects caused by the drugs are serious. Most patients cannot tolerate it after 6 courses of standard treatment. It is necessary to implement maintenance treatment intervention before the disease progresses significantly. Progression-free survival time, improve patients' quality of life [5].

Gefitinib belongs to the aniline quinoline compound. The drug attribute is a small molecule EGFR-TKI (small molecule epidermal growth factor receptor tyrosine kinase inhibitor). It is a molecular targeted drug with a wide range of clinical applications. The Mg-ATP binding in the EGFR-TK catalytic site on the cell surface blocks EGFR signal transmission, inhibits receptor phosphorylation caused by ligand binding to EGFR, reduces the amount of hetero-homodimer synthesis, and triggers a variety of downstream areas down-regulation of signal pathway activation can effectively inhibit tumor angiogenesis, control tumor growth and metastasis, and accelerate tumor cell apoptosis [6]. Gefitinib is administered orally. It can also be administered via a gastric tube after dissolution. The drug is metabolized by the liver, with high bioavailability, and no serious adverse reactions after administration. It can be used as a metastatic lung adenocarcinoma as a first-line, second line and third-line treatment drugs for locally advanced lung cancer [7].

Endo, which is recombinant human endostatin YH-16 is an endogenous anti-angiogenic factor. After administration, it can interact with neovascular endothelial cells, control the range of endothelial migration, and induce apoptosis of neovascularization, thereby inhibiting angiogenesis effect. Endo drug is mildly toxic. Combination of Endo with gefitinib can inhibit tumor cells through different pathways of action, thereby inducing and controlling the progression of the patient's condition. This can prolong the survival time also the toxic effect of the combined drug regimen is not significantly enhanced and its application value is better than single chemotherapy treatment [8]. In summary, the total effective rate of treatment in

the study group was 42.9%, the disease control rate was 80.9%, and the long-term survival rate was 61.9%. All of them were significantly better than the control group. The serum markers were better than the control group. The incidence of such adverse reactions was not significantly different from that of the control group, and the recurrence rate of pleural effusion was lower than that of the control group. It can be considered that Endu combined with gefitinib targeted therapy has significant efficacy and safety.

Based on the above analysis, it can be seen that the use of recombinant human endostatin combined with Iressa targeted therapy for patients with lung adenocarcinoma and pleural metastasis has significant short-term and long-term effects without serious adverse reactions and can be fully practice in medical institutions at all levels. At the same time, the sample size of patients in this study is small, there is a lack of analysis and comparison of the same type of data, and the process design needs to be completed. The clinical value of recombinant human endostatin combined with Iressa targeted therapy still needs to be continuously studied.

Disclosure statement

The author declares that there is no conflict of interest.

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