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Research Article

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Pharmacodynamic comparison of gefitinib plus carboplatin versus gemcitabine plus carboplatin in the treatment of advanced non-small-cell lung carcinoma

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ABSTRACT

The aim of this study was to explore the clinical efficacy and safety of two different dosage regimens, gefitinib plus carboplatin versus gemcitabine plus carboplatin in the treatment of advanced non-small-cell lung carcinoma (NSCLC). The control group received gemcitabine plus carboplatin treatment while the experimental group received gefitinib plus carboplatin. The result demonstrated that gefitinib plus carboplatin in the treatment of patients with advanced NSCLC was effective and safe, while further clinical investigation should be warranted.

Key words: Pharmacodynamics; Lung cancer; Gefitinib; Carboplatin; Drug therapy; Adverse drug reaction (ADR)

INTRODUCTION

Recently, the environmental pollution became even worse than ever before, lung cancer has became one of worldwide cancer with the highest morbidity and mortality. The prognosis of lung cancer is very poor. More than 80% of lung cancer were non-small cell lung cancer (NSCLC)[1-2]. Herein, 137 patients of advanced non-small-cell lung carcinoma NSCLC were randomly divided into the experimental group (71 cases) and the control group(66 cases). The evaluation of the therapeutic effect as well as quality of life indicated that the total effective rate of experimental group and the control group were 77.5% versus 47.0%($P<0.05$), while the disease control rates was 88.7% versus 78.8% ($P>0.05$). Compared with the control group, the median survival time of experimental group is 14.5 months. Additionally, the major adverse drug reactions (ADR) in the experimental group were erythra, nausea, vomiting and alopecia, in contrast, myelo suppression and gastrointestinal reaction in the control group.

EXPERIMENTAL SECTION

1. General Information：From May 2011 to May 2013，137 cases of initially treated patients with advanced NSCLC were randomly divided into experimental group and control group. The experimental group has 71 patients (male 40 cases, female 31 cases); the median age was 62.3 years; 39 cases of adenocarcinoma, 21 cases of squamous cell carcinoma, 11 cases of pathological type is unknown; 11 cases in IIIa stage, 21 cases in IIIb, 39 cases in IV. The control group has 66 patients (36 males, 30 females); median age 61.5 years; 34 cases of adenocarcinoma, 19 cases of squamous cell carcinoma, 13 cases of pathological type is unknown; 9 cases in IIIa stage, 20 cases in IIIb stage, 37 cases in IV. Comparing the generally data of the two groups, the difference was not statistically significant ($P > 0.05$).

2. Inclusion criteria：The Karnofsky score (KPS) before chemotherapy ≥ 70；The expected survival > 4 months; at least one measurable lesion; before treatment were confirmed by pathology or cytology diagnosis of advanced NSCLC, Histological staging using the American Joint Committee on Cancer staging system：the heart, liver, kidney and blood (including coagulation) function is normal, can be evaluated. Exclusion criteria: to give a operation, radiotherapy or platinum containing preparation for treating in 30 days; obvious systemic chemotherapy contraindication.

3. Treatment: the experimental group were treated with 250 mg gefitinib (AstraZeneca company, State Medical Permitment No.J20100014), fasting or with food once a day . while the first day a week for 130 mg/m^2 carboplatin, temporary use , put this product into 5% Glucose Injection 250mL intravenous injection, continuous 3 weeks for 1 cycles. Patients in the control group first days a week for 800 mg/m2 gemcitabine (Nanjing Chia Tai Tianqing Pharmaceutical Co. Ltd., State Medical Permitment No. H20093404), Physiological saline 250 ml intravenous drip infusion of 30min. Before and after, applying 100 ml of normal saline infusion +5 mg of dexamethasone intravenously washing the blood vessels, while giving carboplatin (same test group). Two groups of patients during treatment can be given analgesia and nutritional support or other symptomatic treatment. When there is disease progression or intolerance of adverse reactions, discontinue the medication.

4. Outcome measures: Imaging study evaluated the efficacy of two cycles after treatment, continue to give drug treatment if effective, a total of 3 to 5 cycles, every 3 months to review a chest and abdomen B ultrasound CT. The recent efficacy was evaluated by the response evaluation criteria in solid tumors(RECIST).divide into complete remission(CR), partial remission(PR), progression of disease(PD) and stable disease(SD). CR: The known lesions disappeared and maintained for at least 4 weeks. PR: The maximum diameter of the tumor decreased by 30%, and maintained for more than 4 weeks. PD: The largest single size increase of 20% or a new lesions appear. SD: All other lesions. Total disease control rate = (CR+PR+SD) / total number X 100%, total disease efficiency = (CR+PR) / total number x 100%. Evaluation of the adverse reactions with USA NCI toxicity criteria, Follow up as of the date of January 30, 2014, follow-up for the telephone follow-up.

5. Statistical methods: Statistical analysis was performed using SPSS13.0 software, count data were compared by using χ 2 test, with P <0.05 was considered statistically significant.

RESULTS

1. Comparison of the therapeutic effect：The test group CR + PR patients with a total of 55 cases, SD 8 cases, PD 8 cases, the median time to progression was 6.5 months, the median survival time was 14.5 months. The test group and the control group the total effective rate was 77.5% and 47% (P < 0.05), the total disease control rates were 88.7% and 78.85 (P > 0.05), the 1 year survival rates were 66.9% and 47.6% (P < 0.05, table 1).

Table 1. Comparison of the therapeutic effect (%)

Outcome measures	Experimental group（n=71）	Control group（n=66）	P
Total disease efficiency（%）	77.5	47.0	0.009
Total disease control rate（%）	88.7	78.8	0.117
Median time of progression（month）	6.5	6.1	0.217
Median survival time（month）	14.5	11.8	0.034
1-year survival rate（%）	66.9	47.6	0.015

Table 2 Adverse reactions of the two groups of patients (cases (%))

ADR	Experimental group（n=71）			Control group（n=66）			P
	Class I	Class II	Class III～IV	Class I	Class II	Class III～IV	
Acne-like rash	13 (18.3)	25 (35.2)	14 (19.3)	3 (4.5)	7 (10.6)	1 (1.5)	0.009
Neutropenia	3 (4.2)	7 (9.8）	1 (1.4）	4 (6.0）	7 (10.6）	3 (4.5）	0.017
Anemia	2 (2.8)	3 (4.2)	1 (1.4)	4 (6.0)	5 (7.6)	2 (3.0)	0.021
Thrombocytopenia	4 (5.6)	6 (8.4）	2 (2.8)	2 (3.0)	9 (13.6）	2 (3.0）	0.340
Nausea, vomiting, diarrhea	18 (25.3)	11 (15.5)	6 (8.4)	24 (36.4）	15 (22.7)	7 (10.6)	0.016

2. Comparison of ADR: experimental group patients with acne like rash in 53 cases (74.7%), 35 cases of gastrointestinal reaction (49.3%), including diarrhea, nausea, vomiting, loss of appetite and so on。The control group of patients with hematological adverse reaction in 38 cases (74.6%), Including anemia, neutropenia and thrombocytopenia. After oral administration of leucogen and Batilol, the situation improves. Gastrointestinal

reactions in 46 cases (69.7%, Table 2). Two groups of patients have one case of phlebitis, Control group had 2 cases of mild liver function damage, all the adverse reactions of patients can be tolerated, no treatment-related deaths.

DISCUSSION

The advanced NSCLC patients(Class III~IV), totally more than 60% of lung caner patients, achieved 40% ~ 50% effective rate of chemotherapy [3]. Epithelial growth factor receptor(EGFR) is the epidermal growth factor receptor family member. EGFR are exist in specific mutation glioblastoma and most epithelial cancer[4]. Recent research indicated that EGFR-positive cancer patients with EGFR inhibitors achieved over 60% therapeutic efficiency, both of the response rate and effective rate were better than that of conventional chemotherapy [5]. Gefitinib is the first selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain. Thus gefitinib is an EGFR inhibitor, it is only effective in cancers with mutated and overactive EGFR. gefitinib has been used for certain breast, lung and other cancers[6-9]. In May 2003, the FDA approved gefitinib for NSCLC treatment. Currently, gefitinib has been marketed in more than 64 countries and regions. Iressa Pan-Asia Study is a randomized, double-blind study of large-scale. Comparing the efficacy of gefitinib plus carboplatin and (or) paclitaxel first-line treatment of advanced NSCLC, phase III clinical trials of it's first four stages were confirmed gefitinib therapy in NSCLC patient population in advantage.

We conducted a comparative analysis about the efficacy and safety of gefitinib plus carboplatin versus gemcitabine plus carboplatin curative effect in treatment of advanced NSCLC. The results showed that the efficiency of experimental group（74.6%）was better than the control group (47.0%, P = 0.009), median survival time compared with control group was extended (14.50 vs 11.80, P = 0.034), 1-year survival rate was also higher (66.9% vs 47.6%, P = 0.015). However, the disease control rate and median time to disease progression were almost the same, the difference was not statistically significant (P> 0.05). EGFR mutations are more common in Asians, women, and non-smoking patients [10-11]. Therefore, in Chinese NSCLC patients, gefitinib therapy improves the sensitivity to chemotherapy and targeted, to prolong the median survival time and improve the survival rate. Adverse drug reactions in the control group mainly for neutropenia and anemia, this may be related to the effects of gemcitabine on hematopoietic function. The experimental group mainly for acne-like rash, rash severity over time gradually reduced, consistent with the literature [12]. In addition, the occurrence of gastrointestinal reaction in the experimental group（ClassIII～IV）were higher than control group. (8.4% vs 10.6%，P = 0.016).

CONCLUSION

In summary, gefitinib plus carboplatin in the treatment of advanced NSCLC have better clinical results and less side effects. The dosage regimen is expected to play an important role in the treatment of NSCLC, but still need further clinical practice and observation due to the limited number of clinical cases.

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