Int J Clin Exp Med 2015;8(4):6242-6246
www.ijcem.com /ISSN:1940-5901/IJCEM0004938

Original Article

Randomized study of gefitinib versus pemetrexed as maintenance treatment in patients with advanced glandular non-small cell lung cancer

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Received December 16, 2014; Accepted February 11, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: Gefitinib was compared with pemetrexed as maintenance therapy in Patients with Advanced Glandular Non-small Cell Lung Cancer, mainly regarding clinical effect and side effect. A randomized trial of pemetrexed as study group (500 mg/m^2, dl) versus gefitinib as the control group [250 mg on night 1, 250 mg on morning 2 (every day)] was conducted in 188 patients, 94 cases in each group with a therapy cycle of 21 days. In addition, the study group was also treated with folic acid, vitB12 and dexamethasone. Therapeutic effects and adverse reactions of the two groups were compared. Patients of two groups completed four cycles of chemotherapy mostly, and there was no complete remission (CR) case. The median-cycle of chemotherapy was 2 for the study group, and partial response(PR), stable disease (SD), progressive disease (PD) were observed in 28 (29.8%), 34 (36.2%), 32 (34.0%) cases respectively. The median-cycle was 3 for the control group, PR, SD and PD were observed in 17 (18.1%), 23 (24.5%), 54 (57.4%) cases respectively. The effective rates were 29.8% and 18.1% for pemetrexed (28 cases) and gefitinib (17 cases) respectively ($P > 0.05$). However, there was a statistically significant difference in disease control rates between the 2 groups (65.0% vs 42.6%; $P < 0.05$). Adverse reactions occurred in two groups were mainly mild adverse reactions of 1-2 degree, without renal failure. The study group and control group had three and five cases of mild infection respectively, without statistically significant difference. There was no significant difference in the incidence rate of rash and alopecia between the two groups ($P > 0.05$). However, the number of cases with neutropenia, anemia, thrombocytopenia, gastrointestinal reactions and fatigue in the study group was lower than that of the control group, with a statistically significant difference ($P < 0.05$). Considering the disease control rate and the tolerance of patients with advanced NSCLC, pemetrexed is strongly recommended to be used in clinical.

Keywords: Pemetrexed, gefitinib, non-small cell lung, cancer chemotherapy

Introduction

Lung cancer is one of the most common malignancies in clinical. Non-small cell lung cancer (NSCLC) accounts for about 80%, with a highest mortality in malignant tumors for the 70% to 80% diagnosed advanced patients with poor clinical efficacy, losing the opportunity for surgical treatment [1]. Currently chemotherapy remains the primary treatment for lung cancer and advanced patients. Pemetrexed is a multi-targeted antifolate agent, targeting a variety of enzymes in the synthesis of pyrimidine and purine, also known as multi-target antifolate (MTA). In recent years, it has been used for the treatment of NSCLC, especially in the treatment of lung adenocarcinoma, achieving good efficacy in the first-line, second-line and maintenance treatment with mild adverse reactions [2]. In this study, the short term effects and acute adverse reactions of pemetrexed and gefitinib in patients with advanced NSCLC were compared to evaluate their therapeutic efficacy and safety for advanced NSCLC.

Materials and methods

Patients

188 patients with NSCLC in line with the selection criteria of this study at IIIB and IV stage from august 2011 to May 2012 were selected,

including 98 males and 90 females, aged from 60 to 82 years old with a mean age of 66.2 ± 12.3 years old. The KPS were more than 60. There were 64 cases with the maximum tumor diameter (GTV) of smaller than 3 cm, 85 cases with GTV of 3.1 to 5.0 cm, and 39 cases with GTV of larger than 5 cm. All patients met the diagnostic criteria described in "Chinese common malignancy norms" and were confirmed to be with gland NSCLC by pathology. TNM stages were confirmed through bronchoscopy, mediastinoscopy, chest and brain CT, ultrasound (including the abdomen, neck and supraclavicular area) and whole bone scintigraphy; the detection of electrocardiogram, blood, blood biochemistry and tumor-associated antigens were also carried out. Patients were randomly assigned (1:1) to the study group or control group through random number table. The two groups were comparable in age, sex and TNM stages ($P > 0.05$). Administration, evaluation and case reports of all patients were in accordance with the test program,

Enrolled criteria

Naïve patients in accordance with TNM staging of International Union Against Cancer (UICC), confirmed to be with NSCLC by pathology or cytology, at stages of IIIB and IV, inoperable due to medical reasons or rejecting surgery; or the patients accepting 4 to 8 cycles of first-line chemotherapy and achieving complete remission, partial response and stability. KPS ≥ 60 points; No other disease interfering patients to complete the treatment; enrolled patients without brain metastases, with good compliance and signing informed consent. Review and follow-up after treatment within 2 years.

Treatment program

Study Group: From the first 1 to 3 days, pemetrexed (Qilu Pharmaceutical: trade name Race Jane) was dissolved with 20 ml 0.9% NaCl injection at the concentration of 500 mg/m^2. Folic acid was taken seven days before the first administration. 400 μl was taken each time. Folic acid was taken during the treatment cycle and it would not stop until 3 weeks after the last administration. 1000 μg vitamin B12 was injected into intramuscular each time 7 days prior to the first dose and after the first three cycles of treatment. In order to reduce the incidence and severity of skin rash, 4 mg dexamethasone, 2 times each day, was orally taken on the day before, the day and the next day of pemetrexed administration. 5-HT3 receptor antagonists were given in order to prevent vomiting. Control group: patients in this group were treated with 250 mg gefitinib at night in the first day and in the morning after that day. 21 d for a course of treatment in both groups. The next treatment cycle started one week after discontinuation. Tumor imaging was conducted monthly and it will not stop until progression or death.

Efficacy and adverse reactions

The evaluation of solid tumor efficacy was done in accordance with the new standard recist standard judgment [3]. Complete remission: the lesions disappeared completely and maintained more than four weeks; partial remission, lesions narrowed more than 30% and maintained for more than four weeks; stability: the lesions was between complete remission and partial remission; progress: the development of the disease appeared and expanded more than 20 percent scope of lesions, or new lesions appear. Active = complete response + partial response; Disease Control = complete response + partial response + stable [4]. Survival time accumulated from start of treatment to the patient died. Adverse reactions were classified according to World Health Organization chemotherapeutic drug toxicity classification standard [5].

Statistical analysis

SPSS13.0 was used for data analysis and processing. The data was consistent with normal distribution. Measurement data were expressed with the mean ± standard deviation. Two samples were compared by using independent samples t-test, chi-square test was used for count data. If the data do not meet the normal distribution, nonparametric rank sum test was used. $P < 0.05$ was considered significant statistical difference.

Results

Comparisons of the clinical efficacy in the two groups

Two groups of patients completed a maximum of four cycles of chemotherapy and there was no complete remission (CR) case. The median

Table 1. Compares the efficacy of two groups of patients

Group	N	Complete remission (CR)	Partial remission (PR)	Stable (SD)	Progress (PD)	Effective	Disease Control
Research Group	94	0 (0)	28 (29.8)	34 (36.2)	32 (34.0)	28 (29.8)	62 (65.0)
The control group	94	0 (0)	17 (18.1)	23 (24.5)	54 (57.4)	17 (18.1)	40 (42.6)
x^2			3.535	3.046	10.373	3.535	10.373
P			0.06	0.08	0.001	0.06	0.001

Table 2. Compares the two groups were adverse reactions

Adverse reactions	Research Group		The control group		x^2	P
	1~2	3~4	1~2	3~4		
Renal failure	0	0	0	0	0	0
Infection	3	0	5	0	0.522	0.470
Neutropenia	30	2	55	3	14.409	0.0001
Anemia	72	1	89	2	15.476	0.0001
Thrombocytopenia	4	0	23	2	17.980	0.0001
Gastrointestinal reactions	76	0	90	0	10.090	0.001
Rash	35	12	46	8	1.048	0.306
Hair Loss	42	0	48	0	0.767	0.381
Fatigue	66	5	82	7	13.596	0.0001

cycles of chemotherapy for patients in the study group was two, with PR 28 cases (29.8%), SD 34 cases (36.2%), and PD 32 cases (34.0%). In the control group, the median cycles of chemotherapy was three, with PR 17 cases (18.1%), SD 23 cases (24.5%), and PD 54 cases (57.4%). In the study group, 28 cases (29.8%) were effective while 17 cases (18.1%) in the control group, with no significant statistical difference ($P > 0.05$). In the study group, 62 cases (65.0%) were in disease control while 40 cases (42.6%) in the control group, with significant statistical difference ($P < 0.05$, **Table 1**).

Adverse reactions

Adverse reactions occurred in two groups are mainly 1 to 2 degree mild adverse reactions. There was no renal failure in the two groups. Three cases of mild infection occurred in the study group, while the control group had five cases of mild infection with no significant statistical difference. Besides the incidence of rash and alopecia also showed no significant statistical difference ($P > 0.05$) in the two groups. But the study group of patients with neutropenia, anemia, thrombocytopenia, the number of cases of gastrointestinal reactions, fatigue and other patients were lower than the control group with significant statistical difference ($P < 0.05$). But in the study group, patients with neutropenia, anemia, thrombocytopenia, gastrointestinal reactions, fatigue were less than that in the control group with significant statistical difference ($P < 0.05$, **Table 2**).

Discussion

Lung cancer is a common malignancy in clinical. With the development of society, the worsening environmental pollution and the accelerated pace of life, the incidence of lung cancer has gradually increased. The incidence of male lung cancer incidence ranked first (21.91%) and the female (13.73%) ranked second while the morbidity ranked first [6]. Most patients with advanced lung cancer have immune dysfunction. If inappropriate chemotherapy is applied, adverse drug reactions will directly lead to the decrease of compliance. The chemotherapy will not be carried out successfully. The prognosis of patients will be affected. Patients with advanced lung cancer are commonly treated with chemotherapy-based methods. Although the effective rate of first-line combination chemotherapy is 44.6~67.8% [7-10], the remission of the disease is short. However, combined chemotherapy brought more serious adverse drug reactions, and the patient cannot tolerate. Therefore, it is very necessary to find an efficient and low toxicity maintenance treatment program to extend the time to progression of disease, and improve patient survival and quality of production for patients with advanced gland lung cancer.

Pemetrexed is a new emerging anticancer drug in recent years. It has a multi-targeted antifolate activity and mainly plays a wide range of

anti-tumor effect on tumor cells by interfering with the replication process folate metabolism. Clinical studies have shown that the current pemetrexed for mesothelioma, gastric cancer, lung cancer, breast cancer, pancreatic cancer, colon cancer and other types of diseases have a certain anti-cancer activity [11]. In vitro studies have shown that pemetrexed inhibit the activity of varieties of enzyme, such as thymidylate synthase, dihydrofolate reductase and glycinamide nucleoside acyltransferase. The pemetrexed can suppress several key enzymes so that it could reduce the incidence of drug-resistant tumors. This advantage makes it have better prospects than traditional antifolate drugs. FDA approved pemetrexed as a second-line drug for the treatment of locally advanced or metastatic non-small cell lung cancer.

Gefitinib is a targeted therapy drug based on epidermal growth factor receptor (EGFR). By inhibiting tumor cell signaling, the proliferation of tumor cell will be inhibited and the apoptosis will be promoted. Clinical studies have shown that gefitinib have a certain therapeutic effect on the failure treatment of chemotherapy in advanced NSCLC and have a better effect on the quality of life and tolerability than chemotherapy. Large-scale clinical studies in Europe showed that low-dose (250 mg/d) and high dose (500 mg/d) of gefitinib have the same curative effect in patients with advanced NSCLC and the adverse reactions reduced significantly. Therefore, 250 mg/d was used in the present study [12].

This study shows that, by using the pemetrexed in patients with advanced glandular NSCLC, the effective rate was 29.8%, and the disease control rate was 65%, which were significantly higher than that in the control group (18.1% and 42.6%, relatively). The study show no significant statistical difference in effective rate between the study group and the control group, but the disease control rate in the study group were significantly higher, with significant statistical difference ($P < 0.05$).

Adverse reactions showed there were no serious adverse reactions in the two groups. But in the study group, patients with neutropenia, anemia, thrombocytopenia, gastrointestinal reactions, fatigue were less than that in the control group with significant statistical difference ($P < 0.05$) while there was no significant statistical difference ($P > 0.05$) in infections, skin rashes and hair loss.

The results revealed that the pemetrexed for the maintenance treatment of advanced non-small cell glandular carcinoma showed better disease control and higher patient tolerance. It can be widely used in clinical practice.

Disclosure of conflict of interest

None.

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