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Clinical effectiveness of pemetrexed combined with cisplatin chemotherapy for advanced and maintenance treatment for patients with non-small-cell lung cancer

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Abstract. – OBJECTIVE: To evaluate the clinical effectiveness of pemetrexed combined with cisplatin for the first-line chemotherapy of patients with advanced non-small-cell lung cancer (NSCLC) and maintenance treatment.

PATIENTS AND METHODS: 240 advanced NSCLC patients were randomly divided into either a control group (treated with gemcitabine combined with cisplatin) or an observation group (treated with pemetrexed combined with cisplatin). The primary treatment was defined as first-line chemotherapy, and the maintenance treatment was defined as retreatment. The demographic data from both groups were statistically similar. Patients were treated for 21 days for each cycle and underwent between 4 to 6 treatment cycles.

RESULTS: The mid-and-long term efficacy between groups was compared using efficacy indexes [objective response rate (ORR), disease control rate (DCR), and chemotherapy toxic reaction rate] and progression-free survival (PFS), median survival time, and one-year survival rates. The observation group showed a statically greater ($p<0.05$) ORR and DCR than the control group. Comparison of the prevalence of toxic reaction above level III between the two groups revealed no statistical difference ($p>0.05$). The PFS, median survival time, and one-year survival rate of the observation group were statistically longer ($p<0.05$) than those of the control group.

CONCLUSIONS: Pemetrexed combined with cisplatin was both safe and efficacious for the first-line chemotherapy of NSCLC patients at a progressive stage and for maintenance treatment.

Key Words:
Pemetrexed, Cisplatin, Non-small-cell lung cancer, Progressive stage.

Introduction

Lung cancer is the malignant tumor with the highest prevalence and fatality rate worldwide. More than 85% of lung cancer in China is non-small-cell lung cancer (NSCLC); more than 65% of patients have a progressive stage of lung cancer at diagnosis and are not candidates for surgical excision; and more than 50% patients diagnosed with an early stage of lung cancer will suffer local recurrence or distant metastasis after one year. Chemotherapy is paramount and a first-line treatment for NSCLC at both a progressive stage and treatment maintenance[1,2]. Many lung cancer treatment protocols recommend[3,4] a combined chemotherapy plan with two platinum-based anticancer drugs (e.g., Paclitaxel, docetaxel, or gemcitabine). The progression-free survival (PFS) is approximately four to six months and the median survival time is eight to ten months; the total effective rate is about 25 to 35%. The chemotherapy for NSCLC at progressive stage has reached a therapeutic plateau, and current research is focused on finding more effective and less toxic chemotherapeutics. Pemetrexed (brand name Alimta) is a multitarget antifolate cytotoxic drug. Scagliotti et al[5] have reported that pemetrexed combined with cisplatin is more safe and effective than gemcitabine in the management of non-squamous NSCLC. The purpose of this investigation is to evaluate the clinical effectiveness of pemetrexed combined with cisplatin for the first-line chemotherapy and maintenance treatment of patients with NSCLC at the progressive stage.

Patients and Methods

All patients diagnosed with NSCLC at a progressive stage from the Sixth People's Hospital of Chongqing and China-Japan Friendship Hospital from January 2014 to June 2016 were considered for study inclusion. Inclusion criteria were age 18

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to 75 years old, a pathological diagnosis with Eastern Cooperative Oncology Group (ECOG) score ≤2 points, at least one measurable lesion, chemotherapy completed according to grouping result, completed clinical follow-up material, radiotherapy or surgery at least four weeks prior, an expected survival time of at least 12 weeks and signed an informed consent. Patients were excluded who had lung metastases or other organs' primary malignant tumors, comorbid conditions to preclude treatment, participated in other research protocols or failed to complete the treatment protocol. The study was approved by the Ethics Committee of The Sixth People's Hospital of Chongqing.

240 patients met the inclusion criteria and were randomly and equally divided (120 cases per group) into either the control or observation group. The control group was treated with gemcitabine combined with cisplatin. Gemcitabine was given by intravenous drip at 1000 mg/m^2 for 30 min on treatment days 1 and 8. Cisplatin was given by intravenous drip at 75 mg/m^2 for 30-120 min on treatment day 1. The observation group was given pemetrexed (Eli Lilly & Co, Overland Park, KS, USA) combined with cisplatin. Pemetrexed was given by intravenous drip at 500 mg/m^2 for >10 min on treatment day 1. Cisplatin was given by intravenous drip at 75 mg/m^2 for 30-120 min on treatment day 1; One week before administration of pemetrexed, vitamin B_{12} was administered by intramuscular injection at 1000 μg/time and repeated every nine weeks. Oral administration of folic acid (400 μg/d) was given and discontinued after treatment day 21. Patients were given oral dexamethasone at 8 mg/per day (separated into two doses) on the day before, on the day of, and one day after the administration of pemetrexed. Before chemotherapy, patients were given 5-HT receptor antagonists to prevent vomiting. Patients suffering myelosuppression above level II were treated with G-CSF. If patients suffered above a level III adverse reaction, the amount of pemetrexed and platinum-based medicine during next circle was reduced 25% or held. Patients were treated for 21 days for each cycle and underwent between 4 to 6 treatment cycles. Efficacy was evaluated at the end of every two cycles.

The mid-and-long term efficacy between groups was compared using efficacy indexes (objective response rate (ORR), disease control rate (DCR), and chemotherapy toxic reaction rate) and progression-free survival (PFS), median survival time, and one-year survival rates. According to RECIST 1.0, the efficacy evaluation is divided into CR (complete response), PR (partial response), SD (stable disease) and PD (progression disease). ORR=(CR=PR)/total case number×100%. DCR=(CR+PR+SD)/total case number×100%; the toxic reaction was evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 3 of the National Cancer Institute (NCI).

Statistical Analysis

SPSS20.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed by mean ± standard deviation. Comparison among groups adopted independent sample *t*-test. Enumeration data were expressed by case number of (%). Comparison among groups adopted χ^2-test; the survival period adopted Kaplan-Meier model. Comparison adopted log-rank χ^2-test; $p<0.05$ was statistically significant.

Results

The average follow-up time of the control group was 20.5±5.6 months, and the observation group was 22.5±6.8 months; demographic data (Table I) of the two groups were comparable ($p>0.05$).

The observation group had a statistical significance ($p<0.05$) greater ORR and DCR than the control group (Table II). Comparison of the prevalence of toxic reactions above level III between the two groups revealed no statistical difference ($p>0.05$) (Table III). The PFS, median survival time and the one-year survival rate of the observation group were statistically significantly ($p<0.05$) longer than the control group (Table IV and Figure 1).

Discussion

Pemetrexed has a strong inhibition effect on many important nucleic acids synthesizing enzymes and has been highly effective in the management of pleural mesothelioma[6]. Hanna et al[7] reported that pemetrexed had better safety than docetaxel in the second-line treatment of NSCLC and was more efficacious in adenocarcinoma patients. Scagliotti et al[5] reported superior safety of pemetrexed combined with cisplatin than a control group for the first-line treatment of NSCLC at an advanced stage. Both the National Comprehensive Cancer Network (NCCN) and the Amer-

Table I. Comparison of demographic data between groups.

Grouping	Control group (n=120)	Observation group (n=120)	t/χ^2	*p*
Male/female	80/40	75/45	0.455	0.500
Age (years)	52.6±9.3	54.3±8.7	0.265	0.678
Primary treatment/retreatment	76/44	74/46	0.071	0.790
Tumor TNM staging			0.308	0.579
III stage	84 (70.0)	80 (66.7)		
IV stage	36 (30.0)	40 (33.3)		
Largest tumor diameter (cm)	3.6±1.1	3.7±1.2	0.162	0.932
Pathological type [case (%)]			1.437	0.488
Squamous cell carcinoma	66 (55.0)	75 (62.5)		
Adenocarcinoma	46 (38.3)	39 (32.5)		
others	8 (6.7)	6 (5.0)		

Table II. The mid-and-long term efficacy between groups were compared using efficacy indexes.

Grouping	CR	PR	SD	PD	ORR	DCR
Control group (n=120)	32 (26.7)	46 (38.3)	17 (14.2)	25 (20.8)	78 (65.0)	95 (79.2)
Observation group (n=120)	40 (33.3)	53 (44.2)	14 (11.7)	13 (10.8)	93 (77.5)	107 (89.2)
χ^2					4.577	4.502
p					0.032	0.034

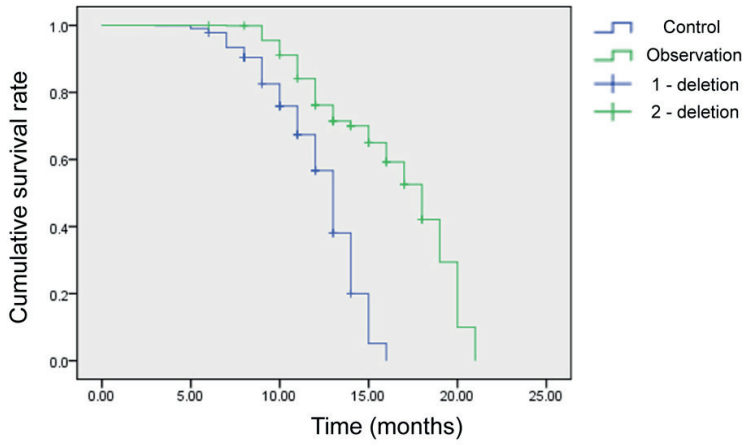

Figure 1. Kaplan Meier survivorship between groups.

ican Society of Clinical Oncology (ASCO) have recommended pemetrexed combined with platinum as the first treatment for non-squamous NSCLC patients[8].

Results from this investigation have shown that the ORR and DCR of the observation group were greater than the control group. The prevalence of toxic reaction above level III between the two groups revealed no difference. The PFS and median survival time of the observation group were longer than the control group. The one-year survival rate of the observation group was also increased. These findings show promising safety and efficacy results for pemetrexed combined with cisplatin for the first-line chemotherapy of NSCLC at a progressive stage and for maintenance treatment. The PFS of advanced NSCLC treated by pemetrexed combined with cisplatin was 12.5 months and the median survival time was 18.6 months. These survivorship results are longer than that has been previously reported by Gronberg et al[9] in their phase III study by the Norwegian lung cancer study group. This may be due to a greater percentage of initial treatment pa-

Table III. Comparison of toxic reactions between the two groups [(%)].

Grouping	Myelosuppression	Liver and kidney dysfunction	Gastrointestinal reaction	Total prevalence
Control group (n=120)	3 (2.5)	5 (4.2)	7 (5.8)	15 (12.5)
Observation group (n=120)	2 (1.7)	3 (2.5)	7 (5.8)	12 (10.0)
χ^2				0.376
p				0.540

Table IV. Comparison of follow-up indexes between the two groups.

Grouping	PFS (month)	Median survival time (month)	One-year survival rate [case (%)]
Control group (n=120)	8.2	13.5	65 (54.2)
Observation group (n=120)	12.5	18.6	82 (68.3)
χ^2	19.352	32.625	5.074
p	0.000	0.000	0.024

tients, early tumor clinical staging, low-grade malignancy, better overall patient health and a longer chemotherapy treatment course.

Esteban et al[10] reported that first-line treatment of NSCLC by pemetrexed has a total effective rate of 11.6 -23.3%, median survival time of 7.2-9.2 months, and one-year survival rate of 25.3-32.0%; these results demonstrated similar efficacy as Taxanes with less adverse reactions and better tolerance in elder patients[11]. The FDA has approved pemetrexed as a first-line treatment of NSCLC at an advanced stage but does not recommend application in squamous cell carcinoma (since the histology characteristics of squamous cells do not appear to be sensitive to pemetrexed)[12]. In this investigation, there were more cases of squamous cell carcinoma than adenocarcinoma, and the results have demonstrated that pemetrexed is still effective. There may exist differences in sensitivity to pemetrexed-based on race. Zheng et al[13] pointed out that the expression level of tumour thymidylate synthase (TS) in tumor tissues may be associated with sensitivity to pemetrexed. Tissues with high expression of TS are poorly sensitive to pemetrexed and expression levels of TS in lung squamous cell carcinoma, and small cell lung cancer are higher than those in the lung adenocarcinoma and large cell carcinoma.

Conclusions

Pemetrexed combined with cisplatin showed both good safety and efficacy for the first-line chemotherapy of NSCLC at a progressive stage and maintenance treatment. Further research is necessary to confirm and define which pathological type of tumors, the conditions of initial treatment, or retreatment, are best suitable for this treatment.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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