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Original Article

Pemetrexed combined with cisplatin for patients with EGFR-TKI resistant advanced lung cancer

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Abstract: Objective: The aim of the current study was to observe the efficacy of pemetrexed combined with cisplatin in patients with advanced lung cancer and EGFR-TKI resistance. Method: A total of 94 patients with advanced lung cancer and acquired resistance to EGFR TKIs were enrolled. They were randomly included in the experimental group (N=47) and control group (N=47). The experimental group was treated with pemetrexed plus cisplatin, while the control group was treated with docetaxel plus cisplatin. Efficacy evaluation criteria of solid tumors were used to compare therapeutic effects at the end of treatment. Chemotherapy toxicity during treatment was compared. Serum vascular endothelial growth factor (VEGF) and carcinoembryonic antigen (CEA) were detected by enzyme-linked immunosorbent assays. Progression-free survival and 3-year survival rates of the two groups of patients after treatment were compared via follow-ups. Finally, the relationship between smoking and efficacy was analyzed. Results: The experimental group showed significantly higher total remission rates, disease control rates, and progression-free survival rates, as well as lower total incidence of toxicity, serum VEGF, and CEA expression, compared to the control group ($P<0.05$). Conclusion: Pemetrexed combined with cisplatin for treatment of advanced lung cancer patients with EGFR-TKI acquired resistance shows better efficacy than docetaxel plus cisplatin.

Keywords: Pemetrexed, cisplatin, lung cancer

Introduction

Lung cancer is a common malignant tumor of the respiratory system, with increasing incidence [1]. Since early symptoms of lung cancer are difficult to detect, many patients are already at advanced stages when diagnosed, missing the chance of surgery [2]. At present, the most appropriate first-line treatment for lung cancer is platinum-based combination therapy. Although it has certain benefits in delaying the progression of the disease, remission rates are not ideal [3]. In recent years, epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) has shown efficacy in treating patients with advanced lung cancer and positive EGFR mutation [4, 5]. One study [6] explored the mechanisms of action of EGFR-TKI, finding that EGFR-TKI inhibits cell signaling and phosphorylation by competing for ATP binding sites in the tyrosine kinase region. This eventually induces cell cycle apoptosis and inhibits the formation of blood vessels. However, if long-term EGFR-TKI treatment is followed, most patients will develop acquired resistance, leading to disease progression [7]. Other studies have shown that, once patients with acquired resistance to EGFR-TKI discontinued EGFR-TKI, rapid progression of the disease was seen [8].

Pemetrexed is a novel multi-target anti-folate drug. It mainly blocks the synthesis of purine and pyrimidines of tumor cells by inhibiting the activity of key enzymes required for folate metabolism. It finally makes the proliferation of tumor cells appear in the S phase, exerting antitumor effects [9]. Other studies have examined the follow-ups of patients with acquired resistance to EGFR-TKI. They found that, after the failure of first-line treatment, if the patient's physical status score was 0 to 2, the platinum-based regimen was more beneficial than other regimens [10, 11]. Pemetrexed and docetaxel are both new chemotherapeutic drugs. Some patients with acquired resistance to EGFR TKIs have been treated with pemetrexed [12]. There was also a study comparing docetaxel monotherapy with optimal support therapy through a randomized phase III clinical trial [13]. Results suggested that docetaxel can significantly

improve survival rates and fitness status scores. However, there is currently no significant data comparing the effects between pemetrexed and docetaxel for treatment of patients with advanced lung cancer after EGFR-TKI acquired resistance.

Therefore, the current study investigated the efficacy and safety of pemetrexed in combination with cisplatin and docetaxel in patients with advanced lung cancer and EGFR-TKI resistance.

Materials and methods

General information

A total of 94 patients with advanced lung cancer and acquired resistance to EGFR TKIs, admitted from January 2013 to March 2014, were enrolled. There were 54 male patients and 40 female patients. There were 68 patients in stage III and 26 patients in stage IV, with an average age of (51.46±6.31) years. The patients were randomly included as the experimental group and control group, with 47 patients in each. The experimental group was treated with pemetrexed plus cisplatin for subsequent treatment. The control group was treated with docetaxel plus cisplatin for subsequent treatment.

Inclusion and exclusion criteria

Inclusion criteria: Patients pathologically diagnosed with advanced lung cancer; Patients pathologically diagnosed as stage III or IV; Patients that met the criteria [8] for acquired EGFR-TKI resistance. Exclusion criteria: Patients with severe liver and kidney dysfunction; Patients with chemotherapy contraindications; Patients with a predicted survival of less than 3 months; Patients with cognitive impairment and communication impairment; Patients unwilling to cooperate with the experiment. All patients and families agreed to participate in the experiment and provided informed consent. This experiment was approved by the hospital Ethics Committee.

Experimental drugs

Pemetrexed was purchased from Qilu Pharmaceutical Co., Ltd. The national drug approval number was H20060672. Docetaxel was purchased from Jiangsu Aosaikang Pharmaceutical Co., Ltd. The national drug approval number was H20064300. Cisplatin was purchased from Jinzhou Jiutai Pharmaceutical Co., Ltd. The national drug approval number was H21020213. Folic acid was purchased from Shandong Luoxin Pharmaceutical Group Co., Ltd. The national drug approval number was H20050740. Dexamethasone was purchased from Guangdong Huanan Pharmaceutical Co., Ltd. The national drug approval number was H44024469. Vitamin B12 (H51023011) was purchased from Sichuan Kangteneng Pharmaceutical Co., Ltd. All chemotherapy methods were in line with clinical lung cancer treatment guidelines [14].

Treatment methods

Patients in the experimental group were treated with pemetrexed plus cisplatin. Specific program: Intramuscular injection of vitamin B12 was performed on patients 7 days before treatment, at 1000 ug per day. They were given 400 ug of folic acid each day until 3 weeks after chemotherapy. Dexamethasone was orally administered on the 1st day before treatment and on the day of treatment. It was also given 1 day after treatment, 2 times/day at 4 mg/time. Pemetrexed was then administered, intravenously, at a concentration of 500 mg/m^2 and a frequency of once per day for more than 10 minutes. At the same time, cisplatin was intravenously instilled at a concentration of 80 mg/m^2 and a frequency of 1 to 2 times per day. One treatment cycle consisted of 3 weeks. The control group was treated with docetaxel and cisplatin. Adjuvant treatment before chemotherapy was the same as that of the experimental group. Docetaxel was intravenously instilled at a concentration of 70 mg/m^2 and a frequency of once a day. The use of cisplatin was the same as that of the experimental group. Appropriate symptomatic treatment was given according to the symptoms of the patient during treatment. Indexes of the two groups were evaluated after 6 cycles of treatment.

Outcome measures

(1) Efficacy evaluation criteria [15] of solid tumors were used to compare therapeutic effects at the end of treatment. The patients were divided into four stages, including complete remission, partial remission, stable condition, and disease progression. Total remission rate of disease = number of complete remissions + number of partial remissions. Control rate of disease = number of complete remissions + number of partial remissions + number

Table 1. Baseline data

Factor	Test group n=47	control group n=47	t/X^2	P
Sex			0.091	0.764
male	27 (57.45)	25 (53.19)		
female	20 (42.55)	21 (44.68)		
Age			0.043	0.836
≥50	25 (53.19)	24 (51.06)		
<50	22 (46.81)	23 (48.94)		
BMI			0.171	0.679
≥23	23 (48.94)	21 (44.68)		
<23	24 (51.06)	26 (55.32)		
TNM by stages			0.054	0.815
III	35 (74.47)	34 (72.34)		
IV	12 (25.53)	13 (27.66)		
Pathological type				
Squamous cell carcinoma	9 (19.15)	9 (19.15)		
Non-small cell carcinoma	31 (65.96)	30 (63.83)		
Adenocarcinoma	7 (14.89)	8 (17.02)		
Nutritional status				
Excellent	7 (12.28)	6 (10.53)		
General	31 (54.39)	30 (52.63)		
Bad	19 (33.33)	21 (36.84)		
Latency from diagnosis to current	7.15±0.59	7.16±0.61	0.189	0.842
Smoking			0.047	0.829
yes	31 (65.96)	30 (63.83)		
no	16 (34.04)	17 (36.17)		
EGFR Mutagenesis			0.045	0.833
19 Exon deletion	29 (61.70)	28 (75.68)		
L858R mutation	18 (38.30)	19 (40.43)		
Coagulation function				
APTT s	28.12±2.83	29.01±2.71	1.557	0.123
PT s	11.97±1.03	12.06±1.05	0.420	0.676
FIB g/l	3.31±0.25	3.32±0.26	0.190	0.850
TT s	14.15±1.35	14.47±1.41	1.124	0.264
Liver function index				
Serum total protein g/L	68.24±2.71	69.33±2.83	1.907	0.060
Glutamic pyruvic transaminase μmol/L	27.71±4.15	27.54±4.21	0.197	0.844
total bilirubin μmol/L	11.45±2.06	11.43±2.11	0.047	0.963

of stable patients; (2) The chemotherapy toxicity was compared, including nausea and vomiting, constipation, anemia, and leukopenia; (3) Venous blood of patients was taken before and after chemotherapy. Serum vascular endothelial growth factor (VEGF) and carcinoembryonic antigen (CEA) were detected by enzyme-linked immunosorbent assays; (4) Progression-free survival and 3-year survival rates, after treatment, were recorded via follow-ups with Wechat (2 times/month), telephone questionnaires (1 time/month), and onsite visits (1 time/month); and (5) Correlation levels between smoking and total remission rates, progression-free survival, and 3 year survival rates were analyzed.

Statistical methods

SPSS 19.0 software (Bizinsight (Beijing) Information Technology Co., Ltd.) was used for statistical analysis of experimental data. Count data was analyzed by Chi-square tests. Measurement data are expressed using mean ± standard deviation and independent t-tests were used to compared the two groups. Comparisons before and after treatment were performed using paired t-tests. Survival analysis was performed with Kaplan-Meier estimation. $P<0.05$ indicates statistical differences.

Results

Comparison of general data between the two groups of patients

No significant differences were shown regarding gender, age, BMI, latency from diagnosis to current therapy, nutrition status, and pathological types between the two groups ($P>0.05$), which were comparable (**Table 1**).

Comparison of treatment effects between the two groups of patients

The number of patients with complete remission, partial remission, stable disease, and progression of the disease in the experimental

Table 2. Comparison of therapeutic effects between the two groups of patients [n (%)]

Treatment effect	Test group n=47	Control group n=47	X^2	P
complete remission	0	0	-	-
Partial remission	20 (42.55)	11 (23.40)		
Stability of the disease	17 (36.17)	14 (29.79)		
Progress of the disease	10 (21.28)	22 (46.01)		
Total effective rate	20 (42.55)	11 (23.40)		
Disease control rate	37 (78.72)	25 (53.19)	6.823	<0.050

Table 3. Toxicity of chemotherapy in two groups of patients [n (%)]

Toxic reaction	Test group n=47	Control group n=47	X^2	P
Nausea and vomiting	3 (6.38)	5 (10.64)	0.547	0.460
constipation	3 (6.38)	6 (12.77)	1.106	0.293
anemia	2 (4.26)	5 (10.64)	1.389	0.239
Leukocyte reduction	4 (8.51)	7 (14.89)	0.927	0.336
Total incidence	12 (25.53)	23 (48.94)	5.508	<0.050

group were 0, 20, 17, and 10, respectively. The total effective rate was 42.55%, while the disease control rate was 78.72%. The number of patients with complete remission, partial remission, stable disease, and disease progression were 0, 11, 14, and 22, respectively. The total effective rate was 23.40%, while the disease control rate was 53.19%. The total effective rate and disease control rate of the experimental group was significantly higher than those of the control group (P<0.05) (**Table 2**).

Comparison of chemotherapy toxicity in the two groups of patients

Patients in the experimental group with nausea, vomiting, constipation, anemia, and leukopenia were 3, 3, 2, and 4, respectively. Total incidence of toxicity was 25.53%. Patients in the control group with nausea, vomiting, constipation, anemia, and leukopenia were 5, 6, 5, and 7 respectively. Total incidence of toxicity was 48.94%. Total incidence of toxicity in the experimental group was significantly lower than that in the control group. Differences were statistically significant (P<0.05) (**Table 3**).

Comparison of VEGF and CEA before and after treatment in both groups

Serum VEGF and CEA expression levels in the experimental group, before treatment, were (748.11±65.32) ng/L and (23.89±3.81) ug/L. Serum VEGF and CEA expression levels in the control group, before treatment, were (751.23±66.29) ng/L and (24.11±3.92) ug/L. There were no significant differences in serum VEGF and CEA expression levels between the two groups before treatment (P>0.05). Serum VEGF and CEA expression levels in the experimental group were (279.25±41.62) ng/L and (8.76±1.27) ug/L. Serum VEGF and CEA expression levels in the control group were (487.61±46.81) ng/L and (15.42±2.46) ug/L. Serum VEGF and CEA expression levels of the two groups were lower than those before treatment. However, serum VEGF and CEA expression levels in the experimental group were significantly lower than those in the control group. Differences were statistically significant (P< 0.05) (**Table 4, Figures 1**, **2**).

Progression-free survival and 3-year survival rates in both groups

The progression-free survival time of the experimental group was (9.12±1.31) months. The progression-free survival time of the control group was (5.23±1.06) months. The experimental group showed significantly higher progression-free survival than the control group (P<0.05). In the experimental group, 24 patients died within 3 years and the 3-year survival rate was 48.94%. In the control group, 35 patients died within 3 years and the 3-year survival rate was 25.53%. The 3-year survival rate of the experimental group was significantly higher than that of the control group (P<0.05) (**Table 5** and **Figure 3**).

Comparison of clinical features between smokers and non-smokers

Therapeutic efficiency, progression-free survival, and 3-year survival rates of the smokers were 24.59%, (5.01±1.25) months, and 21.31%, respectively. Therapeutic efficiency, progression-free survival, and 3-year survival rates of the non-smokers were 54.55%, (9.32±1.17) months, and 54.55%. Treatment efficiency, progression-free survival, and 3-year survival rates of smokers were significantly lower than those of non-smokers. Differences were statistically significant (P<0.05) (**Table 6** and **Figure 4**).

Table 4. Comparison of VEGF and CEA between the two groups before and after treatment

Index	VEGF (ng/L)		t	p	CEA (ug/L)		t	P
	Pre chemotherapy	After chemotherapy			Pre chemotherapy	After chemotherapy		
Test group n=47	748.11±65.32	279.25±41.62	3.50	<0.001	23.89±3.81	8.76±1.27	5.83	<0.001
Control group n=47	749.23±66.29	487.61±46.81	5.10	<0.001	24.11±3.92	15.42±2.46	2.87	<0.001
t	0.083	22.81			0.276	16.49		
P	0.934	<0.001			0.783	<0.001		

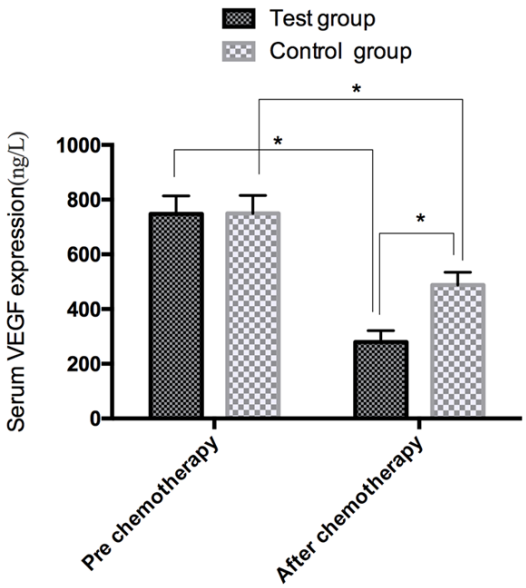

Figure 1. VEGF expression in the two groups of patients before and after treatment. Serum VEGF expression in both groups, after treatment, was lower than that before treatment. However, serum VEGF of the experimental group was significantly lower than that of the control group and the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

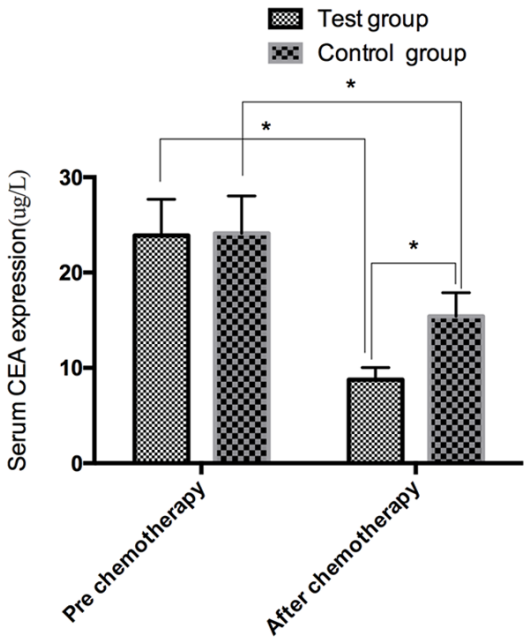

Figure 2. CEA expression in the two groups of patients before and after treatment. Serum CEA expression after treatment was lower in both groups than that before treatment. However, serum CEA expression of the experimental group was significantly lower than that of the control group and the difference was statistically significant (P<0.05).

Discussion

Although EGFR-TKI therapy can result in significantly higher tumor response, most will experience drug resistance [7]. It is also mentioned in the National Comprehensive Cancer Network (NCCN) [16] that "TKI" addiction in cells after treatment with EGFR-TKI may be the cause of accelerated tumor growth after drug withdrawal.

Clinically, acquired resistance is one of the leading causes of failure in targeted therapy [17]. Therefore, it is particularly important to find a better subsequent therapy regimen for treatment of lung cancer. The anti-tumor mechanisms of action of pemetrexed are by inhibiting enzyme activity during folate metabolism. This has a great advantage in chemotherapy for non-squamous cell lung cancer. Some scholars have found that pemetrexed has advantages in the treatment of advanced non-squamous and non-small cell lung cancer patients [18, 19].

In the current study, efficacy and safety levels of pemetrexed in combination with cisplatin and docetaxel were investigated. Results showed that the treatment efficiency of the experimental group was higher than that of the control group. However, incidence of toxicity was significantly lower than that of the control group. This result indicates that pemetrexed can improve the treatment efficiency of patients

Table 5. Disease progression free survival and 3 year survival rates in the two groups of patients

	Test group n=47	Control group n=47	X^2/t	P
Progression free survival/month	9.12±1.31	5.23±1.06	15.83	<0.001
3-year survival rate	18 (38.30)	8 (17.02)	5.32	<0.050

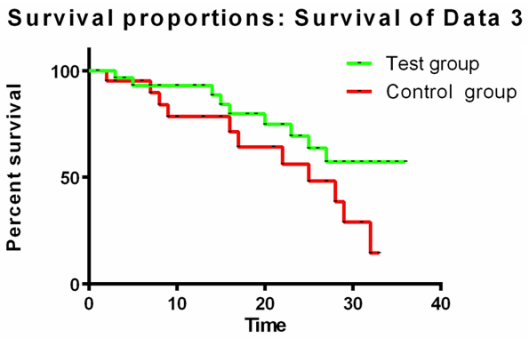

Figure 3. Comparison of 3-year survival rates between the two groups of patients. The 3-year survival rate of the experimental group was significantly higher than that of the control group and the difference was statistically significant (P<0.05).

better than docetaxel, with less toxicity and higher safety. Docetaxel inhibits cell division and proliferation by blocking the formation of mitotic spindles during mitosis [20]. Studies have compared the efficacy of pemetrexed in combination with cisplatin and docetaxel in combination with cisplatin in elderly patients with non-small cell lung cancer [21]. It has been found that the efficacy of pemetrexed plus cisplatin was more effective than that of docetaxel plus cisplatin.

The current study then compared VEGF and CEA, before and after treatment, in both groups. Results showed that serum VEGF and CEA expression levels of the two groups were lower than those before treatment. However, serum VEGF and CEA expression levels in the experimental group were significantly lower than those in the control group. VEGF is closely related to tumor cell proliferation and metastasis. An elevation of serum VEGF will lead to accelerated angiogenesis in tumor tissues and promote tumor recurrence and metastasis [22]. CEA is one of the commonly used tumor markers in clinic. An increase of CEA suggests that the proliferation of tumor cells is more active [23]. Present experimental results suggest that pemetrexed has good effects in inhibiting tumor cell proliferation. Finally, progression-free survival and 3-year survival rates of the two groups of patients, as well as disease progression-free survival and 3-year survival rates of smokers and non-smokers, were compared. Results showed that disease progression-free survival and 3-year survival rates of the experimental group were significantly higher than those of the control group, suggesting that, compared with cisplatin plus docetaxel, pemetrexed plus cisplatin can prolong progression-free survival and 3-year survival, as well as inhibit tumor progression.

In a study [24] in patients with acquired EGFR-TKI treated with pemetrexed, the disease control rate was found to be 77.8%. The median progression-free survival was up to 7 months. Although this study did not combine pemetrexed with cisplatin, current conclusions were confirmed from the side. Moreover, the current study found that treatment efficiency, progression-free survival, and 3-year survival rates of smokers were significantly lower than those of non-smokers, suggesting that smoking may be an important reason for different sensitivity levels to treatment. Some studies have suggested that the reason why smokers are less effective than non-smokers may be related to the presence of TP53 mutations in smokers [25].

In summary, pemetrexed in combination with cisplatin for treatment of advanced lung cancer patients with EGFR-TKI acquired resistance shows better efficacy. It can effectively improve patient conditions, prolong survival times, and has less toxicity and higher safety. However, no single drug trials were set up in this study, mainly for the combination of drugs. Therapeutic mechanisms of pemetrexed plus cisplatin in patients with advanced lung cancer with EGFR-TKI acquired resistance were not explored. The current study did not perform outcome measurements at multiple time points. Thus, this study was unable to assess whether pemetrexed had stable effects in the long-term. Moreover, this study did not assess quality of life before and after treatment. The purpose of cancer treatment is to improve the quality of life of patients. However, this study did not evaluate patient treatment effects in a comprehen-

Table 6. Comparison of treatment efficiency, progression free survival, and 3-year survival rates between smokers and non-smokers

	Smokers n=61	Non-smokers n=33	X^2/t	P
Total effective rate of treatment	15 (24.59)	18 (54.55)	8.435	<0.050
Progression free survival	5.01±1.25	9.32±1.17	17.26	<0.001
3-year survival rate	13 (21.31)	18 (54.55)	10.70	<0.050

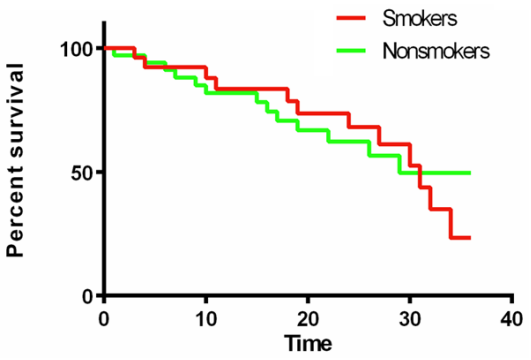

Figure 4. Comparison of 3-year survival rates between smokers and non-smokers. The 3-year survival rate of the smokers was significantly lower than that of the non-smokers and the difference was statistically significant (P<0.05).

sive manner. The above issues will be explored in future research.

Disclosure of conflict of interest

None.

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