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The effects of pemetrexed combined with gefitinib on the life quality of patients with EGFR-TKI resisted advanced non-small cell lung cancer.

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Abstract

Objective: Our objective is to explore the effects of pemetrexed combined with gefitinib on the life quality of patients with EGFR-TKI resisted advanced Non-Small Cell Lung Cancer (NSCLC).
Methods: 78 advanced NSCLC patients who had EGFR-TKI resistance admitted in our hospital between June 2013-2015 were included and divided into observation group (n=39) and control group (n=39) according to the random number table. The patients in the control group were orally treated with gefitinib and the patients in the observation group were treated with gefitinib combined with pemetrexed. 21 d was set as one cycle and the therapeutic effects were evaluated after 2 cycles.
Results: The short-term effects were not statistically different between two groups (P>0.05). The Quality of Life Questionnaire for Chinese Cancer patients receiving chemobiotherapy (QLQ-CCC) and Karnofsky Performance Status (KPS) scores of the two groups were increased after treatment, which were statistically different (in the control group t=11.0018, 10.3165, 7.0910, 22.0391, 46.4797, in the control group t=5.9088, 4.6628, 4.5348, 11.9525, 24.6582, P<0.05). After treatment, the QLQ-CCC and KPS scores in the observation group were higher than the control group, which were statistically different (t=5.3320, 6.1108, 4.1673, 10.7847, 21.3616, P<0.05). After treatment CD3+, CD4+ and CD4+/CD8+ in the observation group were increased, which were statistically different (t=7.1652, 5.3400, 5.4006, P<0.05). After treatment CD3+, CD4+ and CD4+/CD8+in the observation group were higher than the control group, which were statistically different (t=8.2899, 4.6675, 5.2571, P<0.05). The median survival time and the non-progressive survival time in the observation group were longer than the control group, which were statistically different (P<0.05). The toxic and adverse reaction rates were not statistically different between two groups (P>0.05).
Conclusion: Pemetrexed combined with gefitinib has good effects on EGFR-TKI resisted advanced NSCLC. This may significantly improve the patient life quality, improve the immune function, and prolong the median survival time and progression-free survival time, which is significant in NSCLC patients.

Keywords: Pemetrexed, Gefitinib, EGFR-TKI resistance, Advanced non-small cell lung cancer, Life quality.

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Introduction

Lung cancer is a common malignant cancer, 80% of which is Non-Small Cell Lung Cancer (NSCLC) [1-3]. In the recent years the epidemiological surveys have shown that the morbidity of NSCLC is continuously increasing, significantly affecting the physical and psychological health of patients [4-6]. Several clinical researches have shown that EGFR is overexpressed in 40%-80% NSCLC [7-9]. NSCLC with mutated EGFR kinase domain shows histological characteristics of adenocarcinoma, which is highly sensitive to TKI [10-12]. However, almost all the EGFR mutated patients who are sensitive to EGFR-TKI initial treatment are deteriorated after 1 y. This is defined as EGFR-TKI resistance clinically. Thus, a new therapeutic regimen is urgently needed to solve EGFR-TKI resistance [13-15]. In recent years, the antitumor drugs (such as erlotinib and gefitinib) targeting on EGFR have significantly improved the survival rate of NSCLC and changed the therapeutic pattern of lung cancer [16-19]. This study focus on the effects of pemetrexed combined with

gefitinib on the life quality of patients with EGFR-TKI resisted advanced NSCLC.

Materials and Methods

General data

78 advanced NSCLC patients who had EGFR-TKI resistance admitted in our hospital between June 2013-2015 were included. All the patients were conformed to the acquired resistance criteria made by Jackman and were slowly progressive [20]. The patients were randomly divided into observation group (n=39) and control group (n=39) according to the random number table. In the observation group, there were 24 male patients and 15 female patients, the age was 42-75 y old and the average age was 60.39 ± 4.16 y old, the histological type: 32 cases of adenocarcinoma and 7 cases of squamous carcinoma, the median time of TKI treatment before resistance was 11.64 ± 2.45 months. In the control group, there were 23 male patients and 16 female patients, the age was 40-74 y old and the average age was 59.81 ± 3.79 y old, the histological type: 34 cases of adenocarcinoma and 5 cases of squamous carcinoma, the median survival time of TKI treatment before resistance was 11.43 ± 2.51 months. This study was approved by the Ethics Committee of our hospital, and all the patients signed the informed consent. The general data of two groups were not statistically different (P>0.05), which was comparable, as shown in Table 1.

Table 1. Comparison of baseline data between two groups.

Group	Case number	Male/Female	Average age (y)	Histological type		Median application time of TKI before resistance (month)
				Adenocarcinoma	Squamous cell carcinoma	
Observation group	39	24/15	60.39 ± 4.16	32	7	11.64 ± 2.45
Control group	39	23/16	59.81 ± 3.79	34	5	11.43 ± 2.51
X^2/t	-	0.0535	0.699	0.3939		0.4061
P	-	>0.05	>0.05	>0.05		>0.05

Definition of slow progression

Cancer is controlled by EGFR-TKI for more than 6 months, and the original lesion is slightly enlarged or there were 1-2 non-targeted lesions.

Therapeutic regimen

Control group: Oral administration of 250 mg gefitinib once per day (AstraZeneca Pharmaceutical Co., Ltd. London, UK).

Observation group: 4 drops of 500 mg/m^2 pemetrexed (Hansoh Pharmaceutical Co., Ltd. Lianyungang, China) for every 21 d combined with gefitinib. 21 d was set as one cycle and the therapeutic effect was evaluated after 2 cycles.

Evaluation criteria of short-term therapeutic effects

Complete remission (CR): The legion is gone for more than 4 weeks.

Partial remission (PR): The lesion size is decreased by more than 30% for more than 4 weeks.

Progressive disease (PD): The lesion size is increased by more than 20% or there is new lesion.

Stable (SD): The status between PR and PD.

Observation indexes

The Quality of Life Questionnaire for Chinese Cancer patients receiving chemobiotherapy (QLQ-CCC) and Karnofsky Performance Status (KPS) in two groups before and after the treatment were evaluated. QLQ-CCC includes somatic, physical, social and overall scores. The higher QLQ-CCC or KPS scores suggest better life quality; the change of immune indexes, including CD3+, CD4+, CD4+/CD8+ in two groups before and after treatment was evaluated. 3 ml venous blood was collected from the patients before and after the treatment, and 50 μl completely mixed anticoagulated whole blood was added in. Then 20 μl CD3/CD4/CD8 antibodies were added and kept in the darkness for 15 min. 450 μl 1 × FACS hemolysin was added in the sample and thoroughly mixed, kept in the darkness for 15 min, at last the samples was detected by flow cytometer within 24 h. The median survival time and non-progressive survival time of two groups were evaluated. The toxic and adverse reactions of two groups were observed.

Statistical analysis

The data was analyzed by SPSS19.0 (International Business Machines Corp., New York, USA). The measurement data were analyzed by t-test and the enumeration data were analyzed by Chi-squared test. Kaplan-Meier survival analysis was applied and the survival was compared by Log-rank test, P<0.05 was defined as statistically significant.

Results

Comparison of short-term therapeutic effects between two groups

As shown in Table 2, the short-term effects were not statistically different between two groups (P>0.05).

Comparison of QLQ-CCC and KPS between two groups before and after treatment

As shown in Table 3, before treatment QLQ-CCC and KPS scores were not statistically different between two groups (t=0.5285, 0.8463, 1.6256, 0.8360, 0.5916, P>0.05). QLQ-CCC and KPS scores of the two groups were increased after treatment, which were statistically different (in the control group t=11.0018, 10.3165, 7.0910, 22.0391, 46.4797, in the control group t=5.9088, 4.6628, 4.5348, 11.9525, 24.6582, P<0.05).

After treatment the QLQ-CCC and KPS score in the observation group were higher than the control group, which were statistically different (t=5.3320, 6.1108, 4.1673, 10.7847, 21.3616, P<0.05).

Table 2. *Comparison of short-term therapeutic effects between two groups.*

Group	Case number	CR	PR	SD	PD	RR (%)
Observation group	39	5 (12.82)	16 (41.03)	12 (30.77)	6 (15.38)	21 (53.85)
Control group	39	2 (5.13)	14 (35.89)	16 (41.02)	7 (17.95)	16 (41.03)
X^2	-	-	-	-	-	1.2854
P	-	-	-	-	-	>0.05

Table 3. *Comparison of QLQ-CCC and KPS between two groups before and after treatment ($\bar{x} \pm s$).*

Group	Time	QLQ-CCC (point)				KPS (point)
		Somatic score	Physical score	Social score	Overall score	
Observation group (n=39)	Before treatment	25.73 ± 3.14	13.24 ± 1.76	7.73 ± 1.22	46.70 ± 2.35	32.45 ± 4.13
	After treatment	34.36 ± 3.76*#	17.83 ± 2.15*#	9.83 ± 1.39*#	62.02 ± 3.65*#	71.29 ± 3.19*#
Control group (n=39)	Before treatment	26.09 ± 2.87	12.89 ± 1.89	7.29 ± 1.17	46.27 ± 2.19	31.87 ± 4.52
	After treatment	30.15 ± 3.19*	14.95 ± 2.01*	8.56 ± 1.30*	53.66 ± 3.18*	54.76 ± 3.63*

Note: *P<0.05 compared with before treatment in the same group; #P<0.05 compared with the control group after treatment.

Comparison of immune function indexes between two groups before and after treatment

As shown in Table 4, before treatment CD3+, CD4+ and CD4+/CD8+ were not statistically different between two groups (t=0.2895, 0.5194, 0.8327, P>0.05). After treatment CD3+, CD4+ and CD4+/CD8+ in the control group were not statistically different from before treatment (t=0.3099, 0.7856, 0.9591, P>0.05). After treatment CD3+, CD4+ and CD4+/CD8+ in the observation group were increased, which were statistically different (t=7.1652, 5.3400, 5.4006, P<0.05). After treatment CD3+, CD4+ and CD4+/CD8+ in the observation group were higher than the control group, which were statistically different (t=8.2899, 4.6675, 5.2571, P<0.05).

Comparison of median survival time and non-progressive survival time between two groups

As shown in Table 5 and Figures 1-2, the median survival time and the non-progressive survival time in the observation group were longer than the control group, which were statistically different (P<0.05).

Comparison of toxic and adverse reaction between two groups

As shown in Table 6, the toxic and adverse reaction rates were not statistically different between two groups (P>0.05).

Table 4. *Comparison of immune function indexes between two groups before and after treatment ($\bar{x} \pm s$).*

Group	Time	CD3+	CD4+	CD4+/CD8+
Observation group (n=39)	Before treatment	54.37 ± 4.36	34.36 ± 3.67	0.94 ± 0.18
	After treatment	61.30 ± 3.28*#	38.49 ± 3.14*#	1.25 ± 0.31*
Control group (n=39)	Before treatment	54.09 ± 4.18	34.80 ± 3.81	0.98 ± 0.24
	After treatment	53.81 ± 3.79	34.17 ± 3.25	0.93 ± 0.22

Note: *P<0.05 compared with before treatment in the same group; #P<0.05 compared with the control group after treatment.

Table 5. Comparison of median survival time and non-progressive survival time between two groups.

Group	Case number	Median survival time (month)	Non-progressive survival time (month)
Observation group	39	15.83 ± 3.29	6.47 ± 0.61
Control group	39	12.84 ± 2.10	5.38 ± 0.48
t	-	4.784	8.7696
P	-	<0.05	<0.05

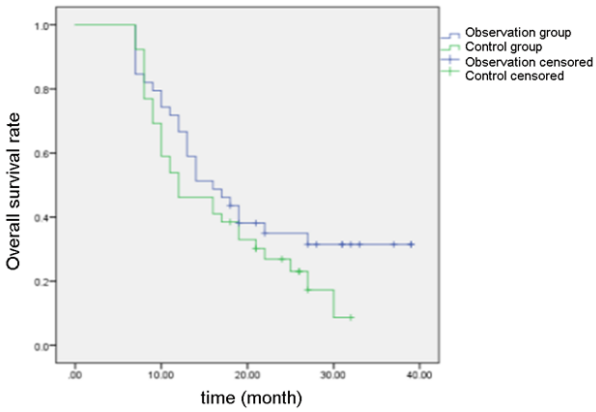

Figure 1. The overall survival of two groups.

Discussion

The EGFR mutated site in NSCLC is mainly located at the intracellular coding domain, including deletion mutation of exon 19 and point mutation of exon 21, which are 90% of all the EGFR kinase mutation [21,22]. It is also related to the sensitivity of EGFR tyrosine-kinase inhibitor. Generally speaking, the sensitivity of EGFR mutated NSCLC patients to TKI is high. Furthermore, EGFR tyrosine-kinase inhibitor can block the tyrosine autophosphorylation in EGFR molecule to inhibit the formation of EGFR homo-dimer by competitively combining the extracellular ligand-binding site against ATP or substrate. This can further inhibit EGFR activation, block the downstream signal transduction, inhibit angiogenesis and metastasis, accelerate cell apoptosis and inhibit cell cycle progress [23-25]. However, in the clinical practice, most of patients are not sensitive to EGFR-TKI, or there is resistance after a period. Some scholars have shown that stopping EGFR-TKI in EGFR-TKI acquired resistance patients will cause aggressive progress of the cancer [26]. Thus, taking effective measures to treat the patients with EGFR-TKI resistance is very important.

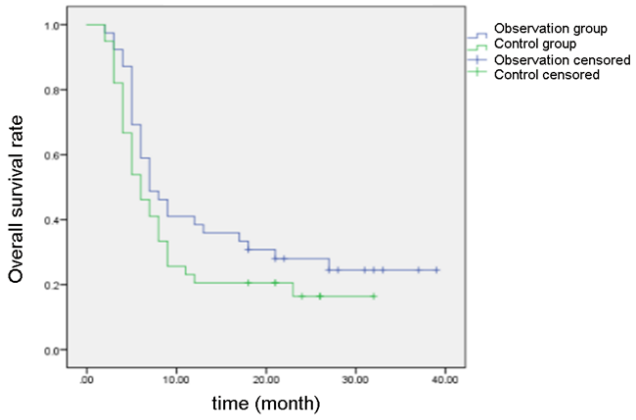

Figure 2. The overall non-progressive survival time of two groups.

As the approval of pemetrexed and gefitinib application, it brings a new hope for the NSCLC patients after the failure of first-line treatment [27]. Pemetrexed has good therapeutic effects on various cancers especially NSCLC, and the effects are better in adenocarcinoma than squamous carcinoma in the first-line treatment. The anti-tumor effect of pemetrexed is mainly through interfering the metabolic pathway of folic acid during cell replication, and it can also obviously inhibit the activity of folic acid dependent coenzyme [28,29].

Table 6. Comparison of toxic and adverse reaction between two groups.

Group	Case number	Bone marrow suppression	White blood cell decrease	Platelet decrease	Nausea, vomiting	Diarrhoea
Observation group	39	9 (23.08)	6 (15.38)	10 (25.64)	16 (41.03)	3 (7.69)
Control group	39	7 (17.95)	6 (15.38)	6 (15.38)	17 (17.95)	2 (5.13)
X^2	-	0.3145	0	1.2581	0.0525	0
P	-	>0.05	>0.05	>0.05	>0.05	>0.05

Gefitinib a second line chemotherapy drug approved for lung cancer treatment, which is an EGFR tyrosine-kinase inhibitor. It can competitively combines with the ATP binding site against EGFR tyrosine-kinase inhibitor and inhibit autophosphorylation, which further blocks the downstream signal transduction to inhibit cancer cell proliferation and promote cancer cell apoptosis to exert anticancer effects [30-32]. In this study, the results showed that the short-term effective rate was 53.85%, suggesting that the short-term therapeutic effect of pemetrexed combined with gefitinib is significant. In the observation group, after treatment the QLQ-CCC and KPS scores were both higher than the control group,

suggesting pemetrexed combined with gefitinib can improve the life quality of patients. After treatment the CD3+, CD4+ and CD4+/CD8+ in the observation group were higher than the control group, suggesting that pemetrexed combined with gefitinib can improve the immune function of patients. The median survival time and non-progressive time in the observation group were longer than the control group, suggesting that pemetrexed combined with gefitinib can prolong the median survival time and non-progressive time.

In conclusion, pemetrexed combined with gefitinib has good effects on EGFR-TKI resisted advanced NSCLC. This may significantly improve the patient life quality, improve the immune function, and prolong the median survival time and progression-free survival time, which is significant in NSCLC patients.

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