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Original Article

Effect of pemetrexed on the efficacy, toxic reaction, and survival rate of patients with EGFR-TKI resistant moderate and advanced lung cancer

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Abstract: Objective: To explore the effect of pemetrexed on the efficacy, toxic reaction, and survival rate of patients with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistant moderate to advanced lung cancer. Methods: A total of 86 patients with EGFR-TKI resistant moderate and advanced lung cancer in our hospital were divided by therapeutic drugs into a control group (39 patients) and pemetrexed group (47 patients). Differences in general data, clinical efficacy, immunoglobulin expression, tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) levels, tumor markers, toxic reaction, and survival rate between the two groups were analyzed. Results: Similar expression levels of carcinoembryonic antigen, IL-6, carbohydrate antigen 125, TNF-α, carbohydrate antigen 153 and immunoglobulin were found in the control group and pemetrexed group before treatment (all $P>0.05$). Expression levels of the above indicators in all patients decreased one month after the end of treatment, and levels of immunoglobulin, inflammatory factors, and tumor markers in the control group were higher than those in the pemetrexed group (all $P<0.05$). Similar incidence rates of toxic reactions were shown in the two groups ($P>0.05$). Twelve months after the end of treatment, one-year survival rate was significantly higher in the pemetrexed group than in the control group ($\chi^2=3.332$, $P=0.042$). Conclusion: Pemetrexed can significantly improve the clinical efficacy in patients with EGFR-TKI resistant lung cancer, decrease the expression of inflammatory factors, tumor markers, and immunoglobulin in serum, has few side effects on the body, and prolongs the long-term survival rate.

Keywords: Pemetrexed, EGFR-TKI resistant, lung cancer, toxic reaction, survival rate

Introduction

The incidence of lung cancer remains high in China and shows an upward trend [1]. A survey by experts in 2013 showed that about 30% of males that died from a tumor died from lung cancer, which is significantly higher than the proportion in females [2]. The specific pathogenesis of lung cancer is still unclear [3, 4].

Lung cancer is difficult to distinguish from common lung diseases, resulting in the missing of an optimal treatment period in many patients [5]. Clinical methods for the treatment of lung cancer mainly include surgery and chemotherapy. Various chemotherapeutic drugs have been developed for the treatment of lung cancer, with different therapeutic effects and toxic and side effects. Therefore, the optimal chemotherapeutic drug to select during the treatment of lung cancer is the key factor to improve patients' survival and prognosis. At present, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) used for first-line treatment versus chemotherapy produces better remission rate in epidermal growth factor receptor (EGFR)-sensitive mutant lung adenocarcinoma (exons 19 and 21). However, the vast majority of patients will acquire resistance to tyrosine kinase inhibitor. After EGFR-TKI failure, it is recommended to use pemetrexed as the first choice for second-line treatment [6, 7].

Pemetrexed as an antifolate, decreases the activity of multiple folic acid related enzymes to inhibit folic acid synthesis, resulting in the inhibition of the folic acid-dependent metabolic pathway in tumor cells, the arrest of cell cycle in

Table 1. Diagnostic criteria for short-term efficacy

Efficacy	Abbreviation	Clinical manifestation
Complete remission	CR	The lesion disappeared completely and lasted for at least 1 month.
Partial remission	PR	The volume of lesion decreased by more than 30% and lasted for at least 1 month.
Stable disease	SD	The volume of lesion decreased by less than 30% or increased by less than 25%.
Progression of disease	PD	The volume of lesion increased by more than 25%.

Note: Total effective rate (%) = (Number of patients with CR + number of patients with PR + number of patients with SD)/total number of patients. CR: complete remission; PR: partial remission; SD: stable disease; PD: progression of disease.

the S phase, the interference of normal DNA synthesis of tumor cells, the blocking of cell duplication, and the inhibition of cell proliferation [8, 9]. Recently, pemetrexed has been applied in the treatment of lung cancer effectively. However, the effect of the mechanism of action of pemetrexed on the immune function and survival rate of patients with lung cancer is still unknown. Therefore, in this study, differences in general data, clinical efficacy, immunoglobulin expression, tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) levels, tumor markers, toxic reaction, and survival rate between the control group and pemetrexed group were analyzed.

Materials and methods

General data

A total of 86 patients with EGFR-TKI resistant moderate and advanced lung cancer in our hospital from August 2018 to August 2019 were retrospectively analyzed and divided by therapeutic drugs into the control group (39 patients, treated with gefitinib only) and pemetrexed group (47 patients, treated with gefitinib combined with pemetrexed). All enrolled patients were informed of this study and signed the informed consent. This study was approved by the Ethics Committee of the hospital.

Inclusion and exclusion criteria

Inclusion criteria: The patient met the diagnostic criteria for moderate to advanced lung cancer [10]. The patient was resistant to EGFR-TKI; The patient was not allergic to drugs used in this study. Exclusion criteria: The patient had chronic infectious disease or malignant tumor; The patient had mental retardation; The patient withdrew without reason during the study.

Treatment methods

Patients in the control group took 0.25 g gefitinib tablets (Hubei Widely Chemical Technology Co., Ltd., China, article number: 12303-11863) orally before or during meals, once a day. Patients in the pemetrexed group were injected with 500 mg/m^2 pemetrexed disodium (Dezhou Deyao Pharmaceutical Co., Ltd., China, article number: 14207857313) besides taking gefitinib tablets, with a duration of intravenous drip of over 30 min/d, for 21 days per cycle, for 2 cycles.

Outcome measures

One month after the end of treatment, therapeutic efficacy in the two groups was evaluated. Specific diagnostic criteria are shown in **Table 1** [11].

Expression levels of immunoglobulins (immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG)) in serum were detected by immunoturbidimetry method with a BN100 protein analyzer made in Germany (Shanghai Kehua Bio-Engineering Co., Ltd., China).

TNF-α and IL-6 levels in serum were detected by the ELISA method. The test was completed within 20 min, and the average value was obtained.

Tumor markers were detected using an automatic chemiluminescence immunoassay analyzer made in ABBO TT Corporation, America (Suzhou Hybiome Biomedical Engineering Co., Ltd., China, model number: AXS YM) and the auxiliary reagents (Tellgen Corporation, China, article number: EIA5071). The automatic chemiluminescence immunoassay analyzer measured the content of the detected substance at

Table 2. Comparison of general data (n/$\bar{x}$ ± sd)

Item	Control group (n=39)	Pemetrexed group (n=47)	χ^2/t	P
Gender			0.348	0.555
Male	21	25		
Female	18	22		
Tumor stage			0.321	0.571
III	23	27		
IV	16	20		
Lymph node metastasis			0.111	0.739
Yes	17	19		
No	22	28		
Type			0.926	0.335
Squamous cell carcinoma	11	16		
Adenocarcinoma	13	15		
Other	15	16		
Age (years)	55.3±8.4	54.1±8.6	0.487	0.626

Table 3. Comparison of clinical efficacy (n, %)

Group	n	CR	PR	SD	PD	Efficacy
Control group	39	11 (28.20)	19 (48.72)	4 (10.26)	5 (12.82)	34 (87.18)
Pemetrexed group	47	21 (44.68)	18 (38.30)	7 (14.89)	1 (2.13)	46 (97.87)
χ^2						0.136
P						0.711

Note: CR: complete remission; PR: partial remission; SD: stable disease; PD: progression of disease.

each wavelength furthest and diluted the serum automatically. After the completion of detection, the content was calculated using micro-particle enzyme immunoassay.

The incidence rates of drug toxic reactions during treatment were compared between the two groups.

Patients were followed up for 12 months after treatment, and the number of survivals and survival rates in the two groups were recorded.

Statistical analysis

Data were analyzed using SPSS 23.00. General data, clinical efficacy and toxic reactions were expressed as n/% and analyzed by chi-square test. The data of levels of immunoglobulins, inflammatory factors and tumor markers conformed to normal analysis and were expressed as $\bar{x}$ ± sd; the data were analyzed by LSD t test or Bonferroni test. Log-rank test was used to compare the differences in survival curves and survival rates. P< 0.05 was considered a significant difference.

Results

Comparison of general data

No significant differences existed in general data between the control group and pemetrexed group (P>0.05, **Table 2**).

Comparison of clinical efficacy

More patients with complete remission and fewer patients with progression of disease were observed in the pemetrexed group than in the control group. Patients in the pemetrexed group had better clinical efficacy than those in the control group, but without a significant difference (P>0.05, **Table 3**).

Comparison of immunoglobulin expression

Similar expression levels of IgA, IgM, and IgG were measured in the control group and pemetrexed group before treatment (all P>0.05). The expression levels of IgA, IgM, and IgG decreased significantly one month after the end of treatment (all P<0.01) and were significantly higher in the control group than in the pemetrexed group (all P<0.01, **Table 4** and **Figure 1**).

Comparison of TNF-α and IL-6 levels

Similar expression levels of inflammatory factors were detected in the control group and pemetrexed group before treatment (all P> 0.05). The expression levels of inflammatory factors decreased significantly one month after the end of treatment (all P<0.01), and the

Table 4. Comparison of immunoglobulin expression ($\bar{x} \pm sd$)

Group	IgA (g/L)	IgM (g/L)	IgG (g/L)
Before treatment			
Control group (n=39)	1.28±0.28	0.96±0.22	8.68±1.32
Pemetrexed group (n=47)	1.31±0.29	0.95±0.23	8.66±1.09
t	0.485	0.204	0.076
P	0.628	0.838	0.938
One month after the end of treatment			
Control group (n=39)	1.12±0.23##	0.85±0.21##	8.08±1.15##
Pemetrexed group (n=47)	0.96±0.21##	0.70±0.19##	7.08±0.96##
t	3.369	3.475	4.396
P	0.001	<0.001	<0.001

Note: Compared with before treatment in the group, ##P<0.01. IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G.

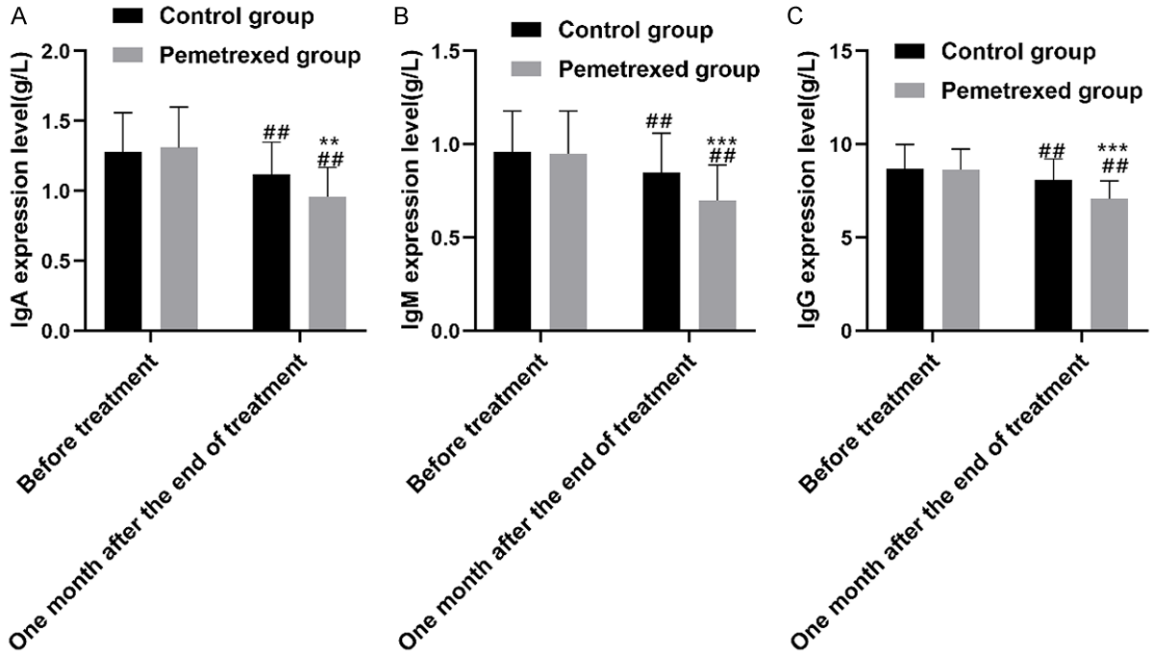

Figure 1. Immunoglobulin expression level before treatment and one month after the end of treatment. A: IgA expression level before treatment and one month after the end of treatment; B: IgG expression level before treatment and one month after the end of treatment; C: IgM expression level before treatment and one month after the end of treatment. Compared with before treatment in the group, ##P<0.01; compared with after the treatment in the control group, **P<0.01, and ***P<0.001. IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G.

expression levels of TNF-α and IL-6 in the control group were higher than those in the pemetrexed group (all P<0.001, **Table 5** and **Figure 2**).

Comparison of tumor markers

Similar expression levels of carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA) and carbohydrate antigen 153 (CA153) were detected in the control group and pemetrexed group before treatment (all P>0.05). The expression levels of CA125, CEA, and CA153 decreased significantly one month after the end of treatment (all P<0.01) and were significantly higher in the control group than in the pemetrexed group (all P<0.001, **Table 6** and **Figure 3**).

Table 5. Comparison of TNF-α and IL-6 levels ($\bar{x} \pm sd$)

Group	TNF-α (U/mL)	IL-6 (g/L)
Before treatment		
Control group (n=39)	1.23±0.21	171.51±18.26
Pemetrexed group (n=47)	1.22±0.19	172.62±18.01
t	0.231	0.282
P	0.817	0.778
One month after the end of treatment		
Control group (n=39)	0.72±0.09##	146.19±19.61##
Pemetrexed group (n=47)	0.51±0.10##	127.25±18.12##
t	10.240	4.614
P	<0.001	<0.001

Note: Compared with before treatment in the group, ##P<0.01. TNF-α: tumor necrosis factor α; IL-6: interleukin-6.

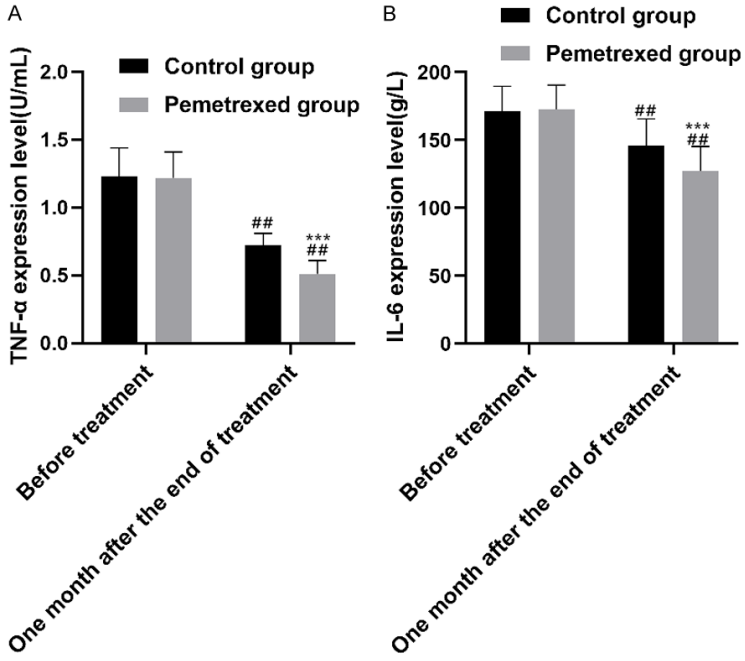

Figure 2. TNF-α and IL-6 expression levels before treatment and one month after the end of treatment. A: TNF-α expression level before treatment and one month after the end of treatment; B: IL-6 expression level before treatment and one month after the end of treatment. Compared with before treatment in the group, ##P<0.01; compared with after the treatment in the control group, ***P<0.001. TNF-α: tumor necrosis factor α; IL-6: interleukin-6.

Comparison of toxic reactions

Similar incidence rates of toxic reactions were found in the control group and pemetrexed group (P>0.05, **Table 7**).

Comparison of survival rate

Patients were followed up for 12 months after the end of treatment. There were 42 (89.36%) survivals in the pemetrexed group and 29 (74.36%) survivals in the control group. The short-term survival rate was significantly higher in the pemetrexed group than in the control group (χ^2=3.332, P=0.042, **Figure 4**).

Discussion

Non-small cell lung cancer, especially lung adenocarcinoma, is a malignant tumor due to mutations in multiple types of genes. With the development and widespread application of gene detection technology, targeted drugs have been used for the individual treatment of lung adenocarcinoma [12, 13]. Since gefitinib, an EGFR-TKI, was applied in clinical practice in 2000, three generations of EGFR-TKIs have been approved for marketing. More and more targeted drugs will be used in clinical practice, which will greatly improve the progression-free survival and overall survival of patients having lung cancer with a driver mutation [14, 15]. However, drug resistance, targeted drug insensitivity and other ubiquitous problems have become difficult points in the treatment of lung cancer, especially moderate to advanced lung cancer [16, 17]. It is controversial whether continuous oral administration of targeted drugs or systemic chemotherapy should be performed after drug resistance. Increasing studies support that continuous administration of targeted drugs prolongs the survival time of patients with oligometastatic or slow-progression tumor [18, 19]. Targeted drugs combined with local treatment including surgery, radiotherapy, and local ablation have been confirmed to lengthen the progression-free survival and overall survival [20].

In this study, patients in the pemetrexed group had better clinical efficacy than those in the

Table 6. Comparison of tumor markers ($\bar{x} \pm sd$)

Group	CEA (ng/mL)	CA125 (U/mL)	CA153 (U/mL)
Before treatment			
Control group (n=39)	13.30±2.53	45.24±6.43	51.28±8.24
Pemetrexed group (n=47)	13.28±2.48	46.19±6.09	50.28±8.75
t	0.036	0.702	0.541
P	0.970	0.484	0.589
One month after the end of treatment			
Control group (n=39)	10.28±1.89##	38.28±5.15##	48.46±7.35##
Pemetrexed group (n=47)	7.28±1.34##	31.28±4.64##	40.45±7.23##
t	8.591	6.626	5.076
P	<0.001	<0.001	<0.001

Note: Compared with before treatment in the group, ##P<0.01. CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CA153: carbohydrate antigen 153.

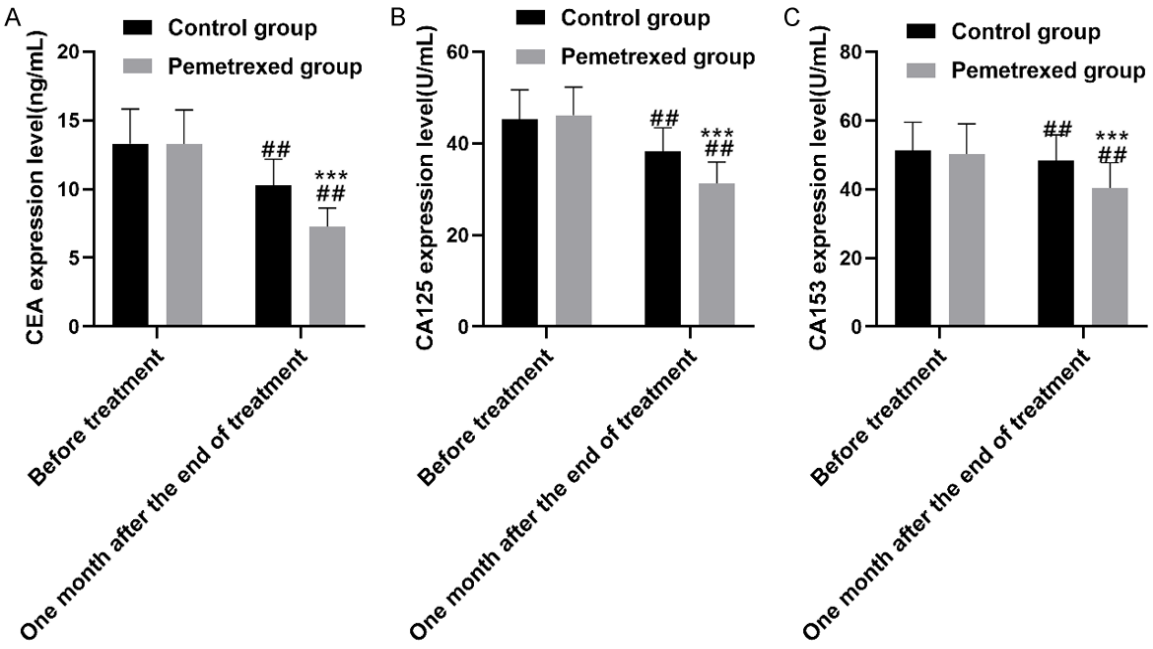

Figure 3. Expression levels of tumor markers before treatment and one month after the end of treatment. A: CEA expression level before treatment and one month after the end of treatment; B: CA125 expression level before treatment and one month after the end of treatment; C: CA153 expression level before treatment and one month after the end of treatment. Compared with before treatment in the group, ##P<0.01; compared with after the treatment in the control group, ***P<0.001. CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CA153: carbohydrate antigen 153.

Table 7. Comparison of toxic reactions (n, %)

Group	Gastrointestinal reaction	Myelosuppression	Injury of liver and kidney function	Hand foot syndrome	Oral mucositis
Control group (n=39)	2 (5.13)	1 (2.56)	1 (2.56)	1 (2.56)	1 (2.56)
Pemetrexed group (n=47)	2 (4.26)	2 (4.26)	0 (0.00)	1 (2.13)	2 (4.26)
χ^2	0.169				
P	0.680				

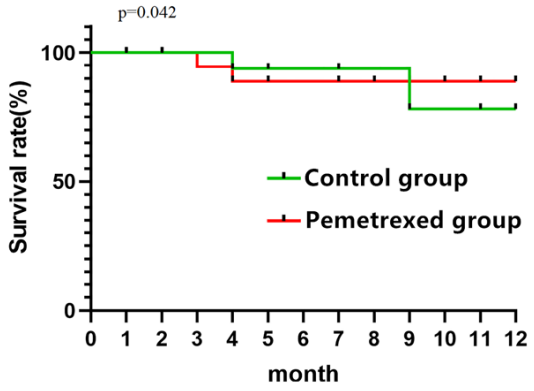

Figure 4. Survival rate.

control group. The expression levels of CEA, IL-6, CA125, TNF-α, CA153 and immunoglobulins before treatment in the pemetrexed group were similar to those in the control group. One month after the end of treatment, the levels of inflammatory factors and tumor markers in the control group were higher than those in the pemetrexed group, and similar incidence rates of toxic reactions were found in the two groups. Six months after the end of treatment, pemetrexed for the treatment of moderate to advanced lung cancer effectively eliminated inflammatory factors, improved body immunity, and decreased the expression levels of tumor markers in serum, showing superiority to gefitinib alone. A study has proved that pemetrexed shows a synergistic effect as a clinical adjuvant drug and better antitumor effect [21]. Pemetrexed can decrease the stability of tumor cell membrane, inhibit the activity of drug resistance proteins such as multidrug resistance-associated protein and p-glycoprotein, and promote the absorption of chemotherapy drugs by tumor cells [20]. Pemetrexed can increase the activity of tumor cell apoptosis channels to influence normal metabolism and promote apoptosis, and also improve the activity of pharmaceutical molecules to reverse drug resistance of tumor cells, thus forming a good complementary action with chemotherapy [22]. Cancer patients with EGFR mutation who developed resistance to gefitinib due to the administration of gefitinib then received the combination treatment with gefitinib and pemetrexed. Cancer patients with EGFR mutation had significantly severer and more frequent adverse reactions such as rash, nausea, and bone marrow suppression compared with patients without mutation [23]. Patients without EGFR mutation after the treatment with EGFR-TKI had some drug resistance phenomena and received pemetrexed to further explore the superiority of pemetrexed in patients with EGFR-TKI resistant moderate and advanced lung cancer and to improve the prognosis [24]. The study showed that the efficacy of pemetrexed in lung adenocarcinoma was not significantly correlated to age, gender, or tumor stage and had a correlation with the type of gene mutation in tissues [25]. The above results might be related to the drug-resistance mechanism of EGFR-TKI or directly related to different mutation sites. Further clinical and basic studies are needed due to small sample size and the lack of relevant research literature.

In this study, one month after the end of treatment, the expression levels of IgA, IgM, and IgG in the two groups decreased significantly and were significantly higher in the control group than in the pemetrexed group. The occurrence and development of cancer brought about immune imbalance, which increased immune escaping of cancer cells, further induced cancer cells spread, and worsened the condition. Immunoglobulins (IgA, IgG, and IgM) are indicators of the body's immune response. The mucosa needs IgA to play an anti-infection effect. IgM is the first immunoglobulin in the body to play an anti-infection effect. The content of IgG is the highest in the body [26]. If bacteria and viruses invade the body in the normal body state, immunoglobulins will eliminate these viruses in a timely manner. However, the immune system will still be affected by partial pathogens and be in an abnormal state, which will decrease immunoglobulin content and induce illness. Chemotherapy can damage immunoglobulins and reduce the activity of immunoglobulins to injure body immune function besides inhibiting gene duplication of cancer cells. A previous study indicated that after patients with lung cancer were treated with pemetrexed, the content of immunoglobulin in serum decreased, and immune function declined gradually [27]. Therefore, patients should be given adequate nutrition to enhance body immunity when treated with pemetrexed.

There were some shortcomings in the study. Comprehensive physical examination was not performed on all subjects in this retrospective

study, and thus the effect of other factors could not be excluded. The small sample size might bias the results to some extent. In addition, there were few types of chemotherapeutic drugs in this study, causing limitations. Therefore, more experimental methods should be used in future studies to provide more favorable experimental evidence for the treatment of EGFR-TKI resistant middle and advanced lung cancer.

In conclusion, pemetrexed can significantly improve the clinical efficacy of patients with EGFR-TKI resistant moderate and advanced lung cancer, decrease the expression levels of inflammatory factors, tumor markers and immunoglobulins in serum, have few side effects on the body, and prolong the long-term survival rate.

Disclosure of conflict of interest

None.

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References

[1] Schiller JH. A new standard of care for advanced lung cancer. N Engl J Med 2018; 378: 2135-2137.

[2] Moya-Horno I, Viteri S, Karachaliou N and Rosell R. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). Ther Adv Med Oncol 2018; 10: 1758834017745012.

[3] Listed NA. Gefitinib (iressa) for advanced non-small cell lung cancer. Med Lett Drugs Ther 2018; 44: 77-78.

[4] Sim EH, Yang IA, Wood-Baker R, Bowman RV and Fong KM. Gefitinib for advanced non-small cell lung cancer. Cochrane DB Syst Rev 2018; 1: CD006847.

[5] Fan F and Wang ZQ. Detection of circulating tumor cells in peripheral blood of patients with advanced non-small cell lung cancer and its clinical significance. J Chin Oncol 2018; 24: 463-478.

[6] Wang Y, Li Y, Xia L, Niu K, Chen X, Lu D, Kong R, Chen Z and Sun J. Continued EGFR-TKI with concurrent radiotherapy to improve time to progression (TTP) in patients with locally progressive non-small cell lung cancer (NSCLC) after front-line EGFR-TKI treatment. Clin Transl Oncol 2018; 20: 366-373.

[7] Tian R, Guo W, Guo Y, Zhang X, Zhu H, Shen F, Xu J, Zhang X, Wang R and Ren X. Apatinib combined with EGFR-TKI in treating advanced non-small cell lung cancer with EGFR-TKI resistance - sciencedirect. Ann Oncol 2019; 30: 46-59.

[8] Lu YM, Ji XL and Zhang JW. Therapeutic effect of single-agent pemetrexed second-line therapy for advanced non-small cell lung cancer. China Foreign Med Treat 2018; 37: 134-135.

[9] Pang J, Chen Y and Hao GY. Clinical analysis of whole body Γ-knife combined with pemetrexed concurrent chemoradiotherapy for the elderly patients with locally advanced lung adenocarcinoma. Chin J Cancer Prev Treat 2018; 27: 3532-3540.

[10] Tomita M, Ayabe T and Nakamura K. The advanced lung cancer inflammation index is an independent prognostic factor after surgical resection in patients with non-small-cell lung cancer. Interact Cardiovasc Thorac Surg 2018; 26: 288-292.

[11] Zhang XW, Liu W, Jiang HL and Mao B. Chinese herbal medicine for advanced non-small-cell lung cancer: a systematic review and meta-analysis. Am J Chin Med 2018; 46: 923-952.

[12] Kawachi H, Fujimoto D, Morimoto T, Ito M, Teraoka S, Sato Y, Nagata K, Nakagawa A, Otsuka K and Tomii K. Clinical characteristics and prognosis of patients with advanced non-small-cell lung cancer who are ineligible for clinical trials. Clin Lung Cancer 2018; 19: e721-e734.

[13] Akamatsu H, Katakami N, Okamoto I, Kato T, Kim YH, Imamura F, Shinkai M, Hodge RA, Uchida H and Hida T. Osimertinib in Japanese patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial. Cancer Sci 2018; 109: 1930-1938.

[14] Kobayashi K, Nakachi I, Naoki K, Satomi R, Nakamura M, Inoue T, Tateno H, Sakamaki F, Sayama K, Terashima T, Koh H, Abe T, Nishino M, Arai D, Yasuda H, Kawada I, Soejima K and Betsuyaku T. Real-world efficacy and safety of nivolumab for advanced non-small-cell lung cancer: a retrospective multicenter analysis. Clin Lung Cancer 2018; 19: e349-e358.

[15] Xu H, Qin WJ and Guo RX. Concurrent radiotherapy and chemotherapy combined with endostar for locally middle and advanced non-small cell lung cancer. Pract J Cancer 2018; 33: 450-453.

[16] Lin L, Zhao HT and Hong LH. Curative effect of pemetrexed and gefitinib in the treatment of EGFR-TKI resistant advanced non-small cell lung cancer. J China PS Drug 2018; 53: 68-79.

[17] Nishikawa S, Kimura H, Koba H, Yoneda T, Watanabe S, Sakai T, Hara J, Sone T, Kasahara K and Nakao S. Selective gene amplification to detect the T790M mutation in plasma from patients with advanced non-small cell lung cancer (NSCLC) who have developed epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance. J Thorac Dis 2018; 10: 1431-1439.

[18] Liu YX, Guo LH and Yang QL. Effects of pemetrexed combined with cisplatin in treatment of patients with non-small cell lung cancer and influence on their quality of life. Chin J Disast Med 2020; 8: 443-445.

[19] Wang Y, Wei Y, Ma X, Ma X and Gong P. Association between advanced NSCLC T790 M EGFR-TKI secondary resistance and prognosis: a observational study. Medicine (Baltimore) 2018; 97: e11346.

[20] Calvo E, Lee JS, Kim SW, Moreno V, deCastro Carpeno J, Weilert D, Laus G, Mann H and Vishwanathan K. Modulation of fexofenadine pharmacokinetics by osimertinib in patients with advanced EGFR-mutated non-small cell lung cancer. J Clin Pharmacol 2019; 59: 1099-1109.

[21] Fu Z. Effects of pemetrexed combined with cisplatin on clinical symptoms and serum tumor markers in patients with advanced non-small cell lung cancer. J Med Forum 2018; 39: 136-137.

[22] Xue YJ, Jia J, Wu Y, Shao D, Zhao MZ and Xue YC. Clinical research of afatinib + pemetrexed and afatinib + gemcitabine in the treatment of NSCIC. Med J Air Force 2019; 35: 28-31.

[23] Jiao L, Xu J, Sun J, Chen Z, Gong Y, Bi L, Lu Y, Yao J, Zhu W, Hou A, Feng G, Jia Y, Shen W, Li Y, Zhang Z, Chen P and Xu L. Chinese herbal medicine combined with EGFR-TKI in EGFR mutation-positive advanced pulmonary adenocarcinoma (CATLA): a multicenter, randomized, double-blind, placebo-controlled trial. Front Pharmacol 2019; 10: 732.

[24] Tong X, Tanino R, Sun R, Tsubata Y, Okimoto T, Takechi M and Isobe T. Protein tyrosine kinase 2: a novel therapeutic target to overcome acquired EGFR-TKI resistance in non-small cell lung cancer. Respir Res 2019; 20: 270.

[25] Cheng LL, Gao EM, Zhu FX, Wang YY, Zhong J and An TT. A case report on successful third challenge to the pemetrexed-based regimen for advanced non-small cell lung cancer. Zhongguo Fei Ai Za Zhi 2019; 22: 395-400.

[26] Fang P, Zhang L, Zhang X, Yu J, Sun J, Jiang QA, Zha M, Nesterova AP and Cao H. Apatinib mesylate in the treatment of advanced progressed lung adenocarcinoma patients with EGFR-TKI resistance -a multicenter randomized trial. Sci Rep 2019; 9: 14013.

[27] Pasquini G and Giaccone G. C-MET inhibitors for advanced non-small cell lung cancer. Expert Opin Investig Drugs 2018; 27: 363-375.