Short-Term and Long-Term Efficacy and Safety of Pemetrexed and Tislelizumab in Advanced Epidermal Growth Factor Receptor Tumor Protein 53 Co-Variant Lung Adenocarcinoma

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We attempt to study the short-term and long-term efficacy and safety of pemetrexed combined with tislelizumab in advanced epidermal growth factor receptor tumor protein 53 co-variant lung adenocarcinoma. The purpose is to explore the application effect of chemotherapy combined with immunotherapy in advanced epidermal growth factor receptor tumor protein 53 co-variant lung adenocarcinoma and provides reference for clinical work. We randomly selected 66 patients with advanced epidermal growth factor receptor+tumor protein 53 co-variant lung adenocarcinoma received from July 2019 to June 2021, then divided them into control group (n=33) and observation group (n=33). Treated control group with chemotherapy alone (pemetrexed), treated observation group chemotherapy combined with immunotherapy (pemetrexed+tislelizumab). Evaluated the short-term and long-term efficacy and safety of both groups, and checked the changes of immune indexes before and after treatment in both groups. In the comparison of short-term efficacy, observation group had higher disease control rate and objective remission rate than control group ($p<0.05$); but in the comparison of long-term efficacy, observation group had remarkably higher median disease progression-free survival than control group ($p<0.05$); both groups had no obvious difference in adverse reactions rate ($p>0.05$); in the comparison of immune indicators, observation group had higher cluster of differentiation 3^+, cluster of differentiation 4^+, cluster of differentiation 4^+/cluster of differentiation 8^+ and natural killer cells activities in T cell subsets than control group, but lower cluster of differentiation 8^+ in T cell subgroup than control group ($p<0.05$). Chemotherapy combined with immunotherapy (pemetrexe+tislelizumab) application is effective and safe in advanced epidermal growth factor receptor+tumor protein 53 co-variant lung adenocarcinoma treatment, can prolong the survival period of patients, has good safety and will not have a great impact on immune indicators level.

Key words: Pemetrexed, tislelizumab, epidermal growth factor receptor, tumor protein 53, lung adenocarcinoma, efficacy, chemotherapy

Lung adenocarcinoma is the commonest type of non-small cell lung cancer which tends to occur in the elderly. About 30 % of them are in the advanced stage when they are diagnosed, so they have missed the best surgical treatment time, the 5 y survival rate is low[1]. Especially in lung adenocarcinoma patients with genetic mutations, multiple gene mutations will further affect the patient's treatment effect, resulting in an unsatisfactory prognosis[2]. Epidermal Growth Factor Receptor (EGFR)+Tumor Protein 53 (TP53) covariation lung adenocarcinoma is one of the most common types of gene mutation, after chemotherapy for advanced EGFR+TP53 co-mutated lung adenocarcinoma patients, conventional doses cannot achieve satisfactory therapeutic effects. Although increasing the dose can improve the efficacy, it will aggravate the toxic and side effects and cannot guarantee the safety of the treatment[3]. With the development of medical technology, currently Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 (PD-1/PD-L1) inhibitors have achieved good results in lung adenocarcinoma treatment, PD-1 inhibitors block the interaction between PD-1 and PD-L1 by binding to PD-1 on the surface of T lymphocytes, allowing T lymphocytes to kill cancer cells, tislelizumab,

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a domestic original PD-1 inhibitor, has been used in the first-line treatment of Non-Small-Cell Lung Cancer (NSCLC)[4]. This study investigated the short-term and long-term efficacy and safety of pemetrexed+ tislelizumab in advanced EGFR+TP53 covariant lung adenocarcinoma. We randomly selected 66 patients with advanced EGFR+TP53 co-variant lung adenocarcinoma received from July 2019 to June 2021, then divided them into control group (n=33) and observation group (n=33). After lung Computed Tomography (CT) and pathological cytology examinations, diagnosed as lung adenocarcinoma; EGFR gene test results are positive; estimated lifetime >6 mo; with complete clinical data; knowing the purpose, significance and risks of this research and expressing willingness to participate in the research. Combined with abnormal blood routine, abnormal liver and kidney function or other malignant tumors; poor physical fitness; those who have undergone major surgery or the surgical wound has not healed within 1 mo before enrollment; with mental disorders or a history of taking psychotropic drugs. Control group included 14 males and 19 females, ages were from 58 y to 78 y old, average were about (65.58±2.49) y old; The course of disease is 1 y to 4 y, average were about (2.31±0.56) y; tumor metastasis site has 9 cases abdominal metastasis, 11 cases bone metastasis, 10 cases central nervous system liver metastasis and 3 cases other metastasis. Observation group included 15 males and 18 females, ages were from 59 y to 78 y old, average were about (65.74±2.36) y old; the course of disease is 1 y to 5 y, average were about (2.58±0.52) y; tumor metastasis site has 10 cases abdominal metastasis, 12 cases bone metastasis, 8 cases central nervous system liver metastasis and 3 cases other metastasis. After comparison, general data of both groups had no obvious difference ($p>0.05$). The control group adopted chemotherapy treatment alone and the specific methods were as follows, mixed 500 mg/m^2 pemetrexed disodium (Yangzijiang Pharmaceutical Group Co., Ltd., national medicine permission number H20143379, size: 0.1 g) with 100 ml of normal saline and then inject it into the patient by intravenous drip, took 21 d as a cycle, only 1 intravenous infusion on the 1 d of each cycle, the infusion time was 30 min; mixed 25 mg/m^2 of cisplatin (Jiangsu Hansoh Pharmaceutical, national medicine permission number H20040813, size: 30 mg) with 250 ml of normal saline and then give it to the patient by intravenous drip, took 21 d as a cycle, only 1 intravenous infusion was given on the 1st to 3rd d of each cycle and the infusion time was 2 h, continuous treatment for 6 cycles. The observation group adopted chemotherapy combined with immunotherapy, the specific methods are as follows, adopted the same chemotherapy method as control group in terms of medication, usage and dosage, at the same time, intravenously infused 200 mg tislelizumab into the patient (Guangzhou BeiGene Bio-Pharmaceutical Co., Ltd., national medicine permission number S20190045, size 10 ml: 100 mg), took 21 d as a cycle, only 1 intravenous infusion was given on the 1 d of each cycle. The first infusion time was 60 min. If the patient tolerated it well, the subsequent infusion time can be changed to 30 min, continuous treatment for 6 cycles. After 6 consecutive cycles of treatment, assess the patient's short-term effects. The patient's lesions have completely disappeared and the disappearance time can be maintained for more than 4 w, it means Complete Remission (CR); the sum of the lesion diameter is reduced by more than 30 % compared before treatment, and it can be maintained for more than 4 w, it means Partial Remission (PR); the patient's lesion diameter increased within 20 % or decreased within 30 %, it means Stable Disease (SD); the patient's total lesion diameter increased by more than 20 % or new lesions appeared, it means Progression Disease (PD)[5]. CR+PR+SD=Disease Control Rate (DCR), CR+PR=Objective Response Rate (ORR). After the patients finished 6 cycles of treatment, followed up the patients by means of telephone and outpatient review, the follow-up deadline was February 2022 and the focus of follow-up was Progression-Free Survival (PFS), i.e. time from initiation of chemotherapy or immunotherapy until disease progression or patient death[6]. Evaluate and record adverse reactions of patients during treatment, common adverse reactions include leukopenia, anemia, thrombocytopenia, rash, mouth ulcer, alopecia and weakness. Before treatment and after 6 cycles of treatment, collected 5 ml of patient's fasting venous blood, adopted monoclonal antibody technology to detect T cell subsets (Cluster of Differentiation (CD) 3^+, $CD4^+$, $CD8^+$) numbers, then calculated $CD4^+/CD8^+$ and adopted external isotope method to detect Natural Killer (NK) cells activities. Adopted Statistical Package for Social Sciences (SPSS) 20.0 software to process the data. Used $\bar{x}\pm s$ to represent measurement data that conform to a normal distribution and t test to compare both groups; used percentage (%) to express enumeration data, Chi-square (χ^2) test to compare both groups, test results are $p<0.05$, it indicated difference possessed statistical significance. In the comparison of short-term effects, observation group

had higher DCR and ORR than control group ($p<0.05$), as shown in Table 1. The median PFS in control group was 7.65 mo (95 % confidence interval 3.88-10.52), the median PFS in observation group was 12.12 mo (95 % confidence interval 8.50-13.91), compared long-term effects of both groups, observation group had bigger median PFS than control group ($p<0.05$). After comparison, adverse reactions rate between both groups had no obvious difference ($p>0.05$), as shown in Table 2. In the comparison of immune indicators, after treatment, observation group had higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK cell activities in T cell subsets than control group, but lower $CD8^+$ than control group ($p<0.05$), as shown in Table 3. Early stage lung adenocarcinoma patients have no obvious symptoms, so it is not easy to detect, usually diagnosed by the presence of a round or oval mass on chest X-ray, the disease develops slowly, but some patients have metastases in the early stages of the disease[7]. Surgical resection of patients in the early stage of the disease is the first choice for the treatment of the disease, while in the advanced stage, chemotherapy; immunotherapy and targeted therapy are mainly used[8]. Chemotherapy is the main treatment for advanced EGFR+TP53 co-mutation lung adenocarcinoma patients with gene mutation, but chemotherapy cannot prolong their survival and gene mutation patients may develop primary resistance to chemotherapy drugs, resulting in poor prognosis[9,10]. Studies have confirmed that adding PD-1/PD-L1 inhibitors to patients for immunotherapy on the basis of chemotherapy can reduce the impact of the disease on the immune function of the body and effectively improve the patients short-term and long-term effects[11]. Tislelizumab is a monoclonal antibody against PD-1, during the research and development, the drug has been modified and optimized the Fragment crystallizable (Fc) segment and it is not easy to be captured by macrophages after entering the human body, which can reduce the phagocytosis effect, promotes the maintenance of T lymphocyte activity and attack tumor cells to enhance anti-cancer activity[12]. In this study, observation group had higher DCR and ORR

TABLE 1: COMPARISON OF SHORT-TERM EFFECTS BETWEEN BOTH GROUPS (n %)

Group	CR	PR	SD	PD	DCR	ORR
Control group (n=33)	4 (12.12)	7 (21.21)	8 (24.24)	14 (42.42)	19 (57.58)	11 (33.33)
Observation group (n=33)	8 (24.24)	12 (36.36)	7 (21.21)	6 (18.18)	27 (81.82)	20 (60.61)
χ^2					4.591	4.927
p					0.032	0.026

TABLE 2: COMPARISON OF ADVERSE REACTIONS RATE BETWEEN BOTH GROUPS (n %)

Group	Neutropenia	Anemia	Thrombocytopenia	Rash	Mouth ulcer	Alopecia	Weakness
Control group (n=33)	11 (33.33)	6 (18.18)	7 (21.21)	13 (39.39)	12 (36.36)	18 (54.55)	13 (39.39)
Observation group (n=33)	12 (36.36)	5 (15.15)	6 (18.18)	14 (42.42)	14 (42.42)	15 (45.45)	15 (45.45)
χ^2	0.067	0.109	0.096	0.063	0.254	0.545	0.248
p	0.796	0.741	0.757	0.802	0.614	0.46	0.618

TABLE 3: COMPARISON OF IMMUNE INDEXES BETWEEN BOTH GROUPS BEFORE AND AFTER TREATMENT ($\bar{x}\pm s$)

Group	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$		NK cells activities (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=33)	59.51±15.24	51.69±13.21	42.79±12.63	35.67±10.79	28.72±7.87	32.63±8.79	1.23±0.42	0.91±0.40	23.58±3.87	20.35±3.66
Observation group (n=33)	58.88±15.52	57.28±5.89	42.46±12.59	40.23±5.25	28.87±7.72	28.22±4.77	1.25±0.45	1.13±0.22	23.60±3.79	22.69±1.47
t	0.166	2.22	0.106	2.183	0.078	2.533	0.187	2.768	0.021	3.408
p	0.868	0.03	0.916	0.033	0.938	0.014	0.853	0.007	0.983	0.001

than control group ($p<0.05$), it shows that pemetrexed+tislelizumab can improve the short-term effects of advanced EGFR+TP53 covariant lung adenocarcinoma. Compared with similar drugs, tislelizumab has a lower Half-maximal Inhibitory Concentration (IC_{50}) value, so its antitumor activity is stronger than other PD-1 inhibitors, which can improve the patient's short-term effects. Although chemotherapy can control the patients local lesions, long-term disease metastasis will still occur, which shortens the patient's median PFS[13]. In this study, observation group had bigger median PFS than control group ($p<0.05$), it shows that pemetrexed+tislelizumab can prolong patients survival. The reason is that tislelizumab blocks the PD-1/PD-L1 signaling pathway through its Fragment antigen-binding (Fab) segment, which relieves T cell immunosuppression, at the same time, the Fc segment is not easily captured by macrophages, which can reduce its phagocytosis by macrophages, thus reducing the consumption of T cells and effectively improving the killing effect of T cells on tumor cells, to a certain extent, the control of tumor metastasis can effectively prolong patients survival[14,15]. In this study, adverse reactions in observation group had no significant difference with control group during the treatment ($p>0.05$), it shows that the addition of immunotherapy at the same time of chemotherapy will not increase the treatment risk of advanced EGFR+TP53 covariant lung adenocarcinoma and it is safety. Common adverse reactions include leukopenia, anemia, thrombocytopenia, rash, mouth ulcers, alopecia and weakness, most of which are caused by chemotherapy. The adverse reactions caused by immunotherapy are different from chemotherapy[16], the adverse reactions caused by immunotherapy include skin rash, diarrhea, thrombocytopenia, abnormal thyroid function, etc., it is pervasive in all systems of the body. If effective intervention measures are not taken in time, it may cause adverse consequences[17]. Therefore, when treating patients, medical staff should observe the occurrence of adverse reactions of patients and intervene in patients with adverse reactions as soon as possible to reduce their impact on the treatment effect and ensure the safety of treatment. In this study, after treatment, observation group had higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK cell activities in T cell subsets than control group, but lower $CD8^+$ than control group ($p<0.05$), it indicates that pemetrexed+tislelizumab has little effect on the immune function of patients with advanced EGFR+TP53 covariant lung adenocarcinoma. Because tislelizumab can bind to PD-1 on the surface of T cells, block the interaction between PD-L1 and PD-1 on the surface of cancer cells and restore the body's immune system function[18]. Combined immunotherapy and chemotherapy can produce synergistic effects in advanced EGFR+TP53 covariant lung adenocarcinoma patients, chemotherapy can kill tumor cells, release antigens, activate T cells and then stimulate human T cells to recognize and kill tumor cells[19]; the PD-inhibitor tislelizumab can regulate the immune function of cells in the body and reduce the impact of chemotherapy on the immune function of the body, contribute to the recovery of the body's anti-tumor immunity and further strengthen the killing effect of immune cells on tumor cells[20,21]. In summary, pemetrexed+tislelizumab applications in treating advanced EGFR+TP53 covariant lung adenocarcinoma patients can improve their short-term effects, prolong their survival, and will not affect the body's immune function and it is safe.

Authors' contributions:

Li Li and Yanxing Zhu have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interest.

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