Short-Term Efficacy of Tislelizumab with Carboplatin/ Cisplatin Pemetrexed in Advanced Lung Adenocarcinoma and its Effect on Tumor Markers

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We attempt to study the short-term efficacy of tislelizumab+carboplatin/cisplatin+pemetrexed in advanced lung adenocarcinoma and its effect on tumor markers. Retrospectively analyzed the clinical data of 68 advanced lung adenocarcinoma patients admitted to our hospital from May 2019 to June 2021 and divided them into control group (n=34) and study group (n=34). Treated control group with carboplatin or cisplatin+pemetrexed, while treated study group with tislelizumab+carboplatin or cisplatin+pemetrexed. Compared both groups on total clinical response rate, serum tumor marker levels and immune function indexes before treatment and after 6 mo treatment. Study group had higher total effective rate than control group ($p<0.05$); after 6 mo treatment, study group had lower serum carbohydrate antigen 125, carbohydrate antigen 199 and carcinoembryonic antigen levels than control group ($p<0.05$). Meanwhile, study group had higher cluster of differentiation 3, cluster of differentiation 4 and cluster of differentiation 4/cluster of differentiation 8 than control group, while lower cluster of differentiation 8 than control group ($p<0.05$). Tislelizumab plus carboplatin or cisplatin plus pemetrexed therapy in advanced lung adenocarcinoma can improve short-term efficacy, reduce serum tumor marker levels and improve immune function.

Key words: Advanced lung adenocarcinoma, tislelizumab, carboplatin, cisplatin, pemetrexed, tumor markers

Lung cancer is one malignant tumor originating from the trachea, bronchi and lungs, it has high morbidity and mortality in China[1,2]. Lung adenocarcinoma is one main lung cancer and belongs to non-small cell lung cancer. Such patients mainly present with cough, expectoration, hemoptysis, weight loss, dyspnea and chest pain[3]. Since lung adenocarcinoma often has no obvious symptoms in the early stage, most patients are already in the advanced stage when they are diagnosed and lost the opportunity for surgical treatment at this time. Chemotherapy is the treatment method for advanced lung adenocarcinoma and platinum drugs (carboplatin/cisplatin)+pemetrexed are the conventional chemotherapy regimens[4]. However, after long-term clinical practice, it has been found that the simple conventional chemotherapy regimen can improve the curative effect at an increased dose, but it has large toxic and side effects on patients, and is prone to treatment interruption, resulting in unsatisfactory treatment effects[5,6]. With the further deepening of clinical research, it is found that the occurrence and development of cancer cells are closely related to the immune mechanism. As a humanized Immunoglobulin G4 (IgG4) anti-Programmed Cell Death 1 (PD-1) monoclonal antibody, tislelizumab has immunomodulatory effects. This study attempts to further discuss the short-term efficacy of tislelizumab+carboplatin/cisplatin+pemetrexed in advanced lung adenocarcinoma and its impact on tumor markers, retrospectively analyzed the clinical data of 68 advanced lung adenocarcinoma patients in our hospital from May 2019 to June 2021. Retrospectively analyzed the clinical data of 68 advanced lung adenocarcinoma patients admitted to our hospital from May 2019 to June 2021, divided them into control group (n=34) and study group (n=34). This study has gotten approval from the ethics committee of our hospital. Inclusion criteria includes lung adenocarcinoma confirmed by biopsy and in advanced stage; completes clinical data; expected survival ≥6 mo; all patients were treated for the first time and there was no history of chemotherapy and with indications for chemotherapy. Exclusion criteria has combined multiple or distant metastases; combined with other

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malignant tumors; intolerance to the study regimen; severe mental illness or cognitive and communication impairments. Control group have 22 males and 12 females included, ages were from 45 y to 73 y old, average was about (60.78±11.21) y old; clinical stage has 9 cases stage IIIB, 11 cases stage IIIC, 14 cases stage IV; smoking history in 25 cases and not in 9 cases. Observation group have 21 males and 13 females included, ages were from 48 y to 72 y old, average were about (60.03±11.05) y old; clinical stage in 8 cases stage IIIB, 11 cases stage IIIC, 15 cases stage IV; smoking history in 22 cases and not in 12 cases. General data of both groups had no obvious significant difference ($p>0.05$). Treated control group with carboplatin or cisplatin+pemetrexed, cisplatin (manufacturer: Guangdong Lingnan Pharmaceutical Co., Ltd., national medicine permission number H20183341, the dosage is 75 mg/m^2, intravenous drip, d1); carboplatin (manufacturer: Hyacrono Pharmaceutical Co., Ltd., national medicine permission number H20203353, dosage=blood concentration-area under the time curve=5, d1) and pemetrexed (manufacturer: Sichuan Huiyu Pharmaceutical Co., Ltd., national medicine permission number H20173301, the dosage is 500 mg/m^2, intravenous drip, d1). Chose carboplatin or cisplatin according to the actual situation of the patient and the degree of tolerance to the drug. Took 21 d as a treatment cycle, 6 cycles totally. Study group adopted the same medication method of carboplatin or cisplatin+pemetrexed as control group, tislelizumab (manufacturer: Boehringer Ingelheim Biopharmaceuticals (China) Co., Ltd., national medicine permission number S20190045, the dosage is 200 mg, intravenous drip, d1). Took 21 d as a treatment cycle, 6 cycles totally. Efficacy criteria, after 6 cycles treatment, the re-examination found that the patient's tumor tissue disappeared and the maintenance time was >1 mo, it means complete remission; tumor tissue shrinkage >30 % and maintained for >1 mo, it means partial remission; tumor tissue is between a shrinkage of ≤30 % and an increase of <20 %, it means stable disease; tumor tissue increased by ≥20 % or new tumor tissue appeared, it means disease progression. Total clinical efficacy=(Complete remission+partial remission+stable disease)/cases×100 %. Before treatment and after 6 mo treatment, collected 5 ml of fasting venous blood from patients in the morning and centrifuged the samples at 3500 r/min for 15 min, the effective centrifugation radius was 12 cm and the supernatant is collected and divided into 2 parts. Took 1 part of the supernatant, detected serum Carbohydrate Antigen (CA) 125, CA199 and Carcinoembryonic Antigen (CEA) levels by electrochemiluminescence immunoassay. The same time as the detection time of serum tumor marker levels, took the remaining 1 supernatant, measured Cluster of Differentiation ($CD3^+$), $CD4^+$, $CD8^+$ with a loss cytometer and calculated the $CD4^+/CD8^+$ ratio. Adopted Statistical Package for Social Sciences (SPSS) 20.0 software to process the data. Used $\bar{x}\pm s$ to represent measurement data such as serum tumor marker levels, immune index and tested by t; use percentage (%) to express enumeration data such as total clinical efficacy, tested by Chi-square (χ^2), $p<0.05$ mean comparison differences possessed statistical significance. Table 1 shows study group had higher total clinical efficacy than control group ($p<0.05$). Table 2 shows that, before treatment, both groups had no significant difference in serum tumor marker levels; after 6 mo treatment, study group had lower serum tumor marker levels than control group ($p<0.05$). Table 3 shows that, before treatment, both groups had no statistically significant difference in immune function indicators; after 6 mo treatment, study group had higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$, but lower $CD8^+$ ($p<0.05$). Lung adenocarcinoma is one type common non-small cell lung cancer. Currently, there is no unified clinical conclusion on the etiology of the disease, but it is mostly related to environmental, genetic and other factors[7,8]. Advanced lung adenocarcinoma patients are seriously ill and have missed the opportunity for surgery, so chemotherapy is the main clinical treatment. Carboplatin or cisplatin+pemetrexed are conventional chemotherapy regimens for advanced lung adenocarcinoma patients. Although they can control the patient's disease progression to a certain extent, it is difficult to achieve the desired effect in prolonging the survival period[9,10]. In recent years, with the deepening of clinical research, the immunotherapy proposed for advanced cancer patients has brought a new direction to advanced lung adenocarcinoma treatment. In general, the immunosuppression of cancer cells is mainly achieved by expressing the immune check molecule PD-Ligand 1 (PD-L1), and completes immune escape, resulting in the malfunction of the "radar" function of the human immune system and the inability to complete the capture of cancer cells[11]. It is difficult to obtain an ideal therapeutic effect if the growth of cancer cells is inhibited and killed by chemotherapy alone. Tislelizumab is a novel PD-L1 inhibitor that can bind to PD-1 on the surface of T lymphocytes in patients after administration, block the interaction between PD-1 and PD-L1, restore T lymphocyte function, and kill cancer

cells. Based on conventional chemotherapy, tislelizumab is mainly used as immunotherapy in treating advanced lung adenocarcinoma patients. Fan[12] conducted a similar study, the study proposed a treatment regimen of tislelizumab combined with pemetrexed disodium and cisplatin, The results found that the program can improve clinical efficacy and prolong the median overall survival advanced wild-type lung adenocarcinoma patients. It can be seen that tislelizumab+platinum drugs (carboplatin/cisplatin)+pemetrexed have a certain research basis in advanced lung adenocarcinoma patients. In this study, tislelizumab+carboplatin or cisplatin+pemetrexed was applied to advanced lung adenocarcinoma patients and checked the changes in immune function indexes of patients after 6 mo treatment, the results shows that study group had higher $CD3^+$, $CD4^+$, $CD4^+/CD8^+$, but lower $CD8^+$ ($p<0.05$). The results suggest that tislelizumab+carboplatin or cisplatin+pemetrexed can effectively improve patient's immune function. During the research and development of tislelizumab, the Fragment crystallizable (Fc) segment was modified and optimized, so that it is not easy to be captured by macrophages in patients after using the drug, reducing the effect of phagocytosis, enhancing T lymphocyte activity and having a powerful attack on cancer cells, improving anti-cancer activity. The combination of tislelizumab and PD-1 on the surface of T lymphocytes can promote the recovery of patient's "radar" function immune system, activate T cells, and improve patient's immune function. According to this study, in terms of serum tumor markers, after 6 mo treatment, study group had lower CA125, CA199 and CEA levels than control group ($p<0.05$). The results suggest that tislelizumab+carboplatin or cisplatin+pemetrexed can effectively reduce tumor marker levels in advanced lung adenocarcinoma patients. CA125 and CA199 are CA, and their content is low in healthy humans. When cancer cells are generated and develop further, they will cause damage to human tissues, causing CA125 and CA199 to enter the blood and make them in a state of high expression[13,14]. CEA is an acidic glycoprotein that is highly expressed in cancer tissues[15]. The above tumor markers are commonly used clinical indicators to evaluate the growth of tumor tissue. However, after treatment with tislelizumab+carboplatin or cisplatin+pemetrexed in advanced lung adenocarcinoma patients, chemotherapy can kill cancer cells and release antigens while activating T cells, enhance the ability of T cells to recognize cancer cells and their ability to kill cancer cells. Meanwhile, regulating the patient's immune function by tislelizumab can not only promote the recovery of immune system function and further kill cancer cells, but also improve the patient's tolerance to chemotherapy, avoid chemotherapy interruption and improve the effect of inhibiting and killing cancer cells[16]. When cancer cells in advanced lung adenocarcinoma patients are effectively inhibited and killed, serum tumor marker levels can be effectively reduced. Moreover, this study evaluated the short-term efficacy of tislelizumab+carboplatin or cisplatin+pemetrexed and found that study group had higher total clinical efficacy than control group ($p<0.05$). The above combination therapy can further improve the short-term efficacy of advanced lung adenocarcinoma, which is mainly related to the further reduction of tumor markers levels in patients and the effective improvement of immune function. In summary, tislelizumab+carboplatin or cisplatin+pemetrexed application in advanced lung adenocarcinoma treatment can improve patient's short-term efficacy, reduce serum tumor marker levels and improve immune function. However, in this study, the shortcomings were less samples and lack of long-term efficacy observation, resulting in certain limitations in the research data. Follow-up research needs to be strengthened to address the above shortcomings.

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

Group (n=34)	Complete remission	Partial remission	Stable disease	Disease progression	Total effective
Control group	0 (0.00)	10 (29.41)	8 (23.53)	16 (47.06)	18 (52.94)
Study group	2 (5.88)	15 (44.12)	9 (26.47)	8 (23.53)	26 (76.47)
χ^2	--	--	--	--	4.121
p	--	--	--	--	0.042

TABLE 2: COMPARISON OF SERUM TUMOR MARKER LEVELS BETWEEN BOTH GROUPS (x̄±s)

Group (n=34)	CA125 (U/ml)		CA199 (U/ml)		CEA (ng/ml)	
	Before treatment	After 6 mo treatment	Before treatment	After 6 mo treatment	Before treatment	After 6 mo treatment
Control group	275.18±38.67	101.04±21.16*	233.75±30.17	102.51±20.53*	130.47±25.48	50.81±15.37*
Study group	272.46±37.92	85.99±19.63*	236.19±32.01	87.66±19.78*	133.19±26.05	43.66±12.82*
t	0.293	3.041	0.323	3.037	0.435	2.803
p	0.771	0.003	0.747	0.003	0.665	0.041

Note: Compared with the group before treatment, *p<0.05

TABLE 3: COMPARISON OF IMMUNE FUNCTION INDICATORS BETWEEN BOTH GROUPS (x̄±s, %)

Group (n=34)	$CD3^+$		$CD4^+$		$CD8^+$		$CD4^+/CD8^+$	
	Before treatment	After 6 mo treatment	Before treatment	After 6 mo treatment	Before treatment	After 6 mo treatment	Before treatment	After 6 mo treatment
Control group	40.63±7.45	55.48±8.13*	28.91±6.47	39.32±7.11*	29.36±6.72	22.45±6.28*	0.95±0.22	1.72±0.68*
Study group	41.83±7.69	60.37±9.52*	29.56±6.71	45.69±7.84*	30.11±6.92	17.42±6.03*	0.96±0.23	2.64±0.75*
t	0.654	2.278	0.407	3.509	0.453	3.369	0.183	5.299
p	0.516	0.026	0.687	0.001	0.652	0.001	0.855	0

Note: Compared with the group before treatment, *p<0.05

Author's contributions:

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

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Rocco D, Della Gravara L, Battiloro C, Maione P, Gridelli C. The treatment of advanced lung adenocarcinoma with activating EGFR mutations. Expert Opin Pharmacother 2021;22(18):2475-82.
2. Ma CF. Effect of pemetrexed combined with cisplatin chemotherapy on serum tumor markers and KPS score in patients with advanced non-small cell lung cancer. J Rare Uncommon Dis 2022;29(4):30-1.
3. Xu Y, Yang J, Li N. Effects of tarceva targeted therapy combined with pemetrexed and cisplatin on serum tumor markers, immunoglobulin and T-lymphocyte subsets in patients with non-small cell lung cancer. Prog Mod Biomed 2021;21(17):3264-335.
4. Fu MY, Lei KJ, Jia YM. Clinical efficacy of docetaxel combined with cisplatin in the treatment of advanced lung adenocarcinoma and the impact on immune function of patients. Pract J Cardiac Cerebral Pneumal Vascular Dis 2021;29(8):48-53.
5. Yin Y, Han T, Li HQ. Effect of pemetrexed chemotherapy on serum tumor markers and cellular immune function in patients with non-small cell lung cancer. Int J Pathol Clin Med 2021;41(7):1490-4.
6. Zhang YH, Lan F, Cheng SQ. Clinical efficacy of different platinum drugs combined with pemetrexed in treatment of patients with pul-monary adenocarcinoma and its effects on serum tumor markers and toxic and side reactions. Clin Misdiagn Misther 2021;34(7):45-50.
7. Yanarateş A, Yazici B. Volumetric PET parameters can predict overall survival in advanced lung adenocarcinoma. Rev Esp Med Nucl Imagen Mol 2020;39(1):3-8.
8. Luo GJ. Efficacy of camrelizumab combined with cisplatin+pemetrexed chemotherapy in the treatment of advanced NSCLC and its effect on serum tumor markers. Jiangxi Med J 2021;56(7):1012-4.
9. Li Q, Wang XP, Du WF. Clinical study on recombinant human endostatin combined with pemetrexed and cisplatin on advanced lung adenocarcinoma. J Med Res 2021;50(4):78-81.
10. Jia J, Xue YJ, Wu Y. Effect of combination chemotherapy of afatinib, pemetrexed and gemcitabine on advanced non-small cell lung cancer and its influence on tumor markers, immune function and quality of life. Clin Misdiagn Misther 2020;33(10):53-7.
11. Chen H, Xu HX, Hu Q. Clinical efficacy of different regimens in the treatment of advanced lung adenocarcinoma and its effect on tumor marker levels. Clin J Med 2020;48(9):1066-8.

12. Fan RL. Clinical efficacy and side effects of tislelizumab combined with pemetrexed disodium and cisplatin in advanced gene wild-type lung adenocarcinoma. Strait Pharm J 2021;33(11):136-40.
13. Liu HN, Cai ZR, Shan GQ. The effect of different medications on the short-term efficacy and levels of serum tumor markers in patients with advanced non-small cell lung cancer. Oncol Prog 2020;18(3):282-5.
14. Deng JL, Zhong JH. Effect of hyperthermia combined with pemetrexed and cisplatin on CYFRA 21-1, CA199 and TPS in patients with advanced lung adenocarcinoma. J Clin Pulm Med 2020;25(1):117-21.
15. Chang YW, Wang X. Efficacy and safety of pemetrexed combined with etoposide combined with cisplatin concurrent thoracic radiotherapy in the treatment of locally advanced lung adenocarcinoma. Guizhou Med J 2020;44(7):1089-90.
16. Wang WY, Li DM, Zeng C. Effects of PD-1 inhibitors pembrolizumab combined with pemetrexed and carboplatin on T lymphocyte subsets and serum tumor markers in patients with NSCLC. Prog Mod Biomed 2021;21(23):4509-13.

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