Cite as: Wang F, Liu P, Pu JZ, et al. Effects of tislelizumab combined with platinum-containing dual-drug regimen in elderly patients with advanced lung adenocarcinoma [J]. Chin J Clin Res, 2024, 37(1): 29-33.
DOI: 10.13429/j.cnki.cjcr.2024.01.007

Effects of tislelizumab combined with platinum-containing dual-drug regimen in elderly patients with advanced lung adenocarcinoma

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Abstract: Objective To explore the efficacy of tislelizumab combined with pemetrexed and carboplatin in elderly patients with advanced lung adenocarcinoma (LUAD) and its effects chemotherapy on serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels. **Methods** Ninety-four driver gene-negative elderly patients with advanced LUAD admitted to the Fourth Affiliated Hospital of Nanjing Medical University from July 2021 to December 2022 were selected as the study subjects. They were divided into chemotherapy group (pemetrexed combined with carboplatin, n=48) and tislelizumab group (pemetrexed+carboplatin+tislelizumab, n=46) by the random number table method, and both groups were treated for 4 cycles, with 21 days as a cycle. The clinical efficacy, immune function [T lymphocyte subsets ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$)] and serum indicators (IGF-1, IGFBP-3) before and after treatment were recorded in both groups, and the adverse reactions were assessed. **Results** The clinical efficacy and objective response rate (58.70% *vs* 29.17%, χ^2=8.329, P<0.01) in tislelizumab group were significantly higher than that in chemotherapy group. After 4 cycles of treatment, the $CD4^+$, $CD4^+/CD8^+$ ratio and IGFBP-3 levels in both groups were significantly increased compared with those before treatment (P<0.05), and the indicators in tislelizumab group were higher than those in chemotherapy group (P<0.05); $CD8^+$ and IGF-1 levels were significantly decreased in both groups compared with those before treatment (P<0.05), and the indicators in tislelizumab group were lower than those in chemotherapy group (P<0.05). Adverse reactions were mainly 1-2 grade in both groups, and there was no significant difference in the incidence of adverse reactions between two groups (P>0.05). **Conclusion** The first-line therapy of tislelizumab combined with platinum-containing dual-drug for elderly advanced LUAD can improve the clinical efficacy, improve the balance of $CD4^+/CD8^+$, regulate the expression of serum IGF-1 and IGFBP-3 levels. The adverse reactions are controllable, and the treatment regimen is safe and reliable.

Keywords: Lung adenocarcinoma, advanced; Tislelizumab; Carboplatin; Pemetrexed; Immune function; Insulin-like growth factor 1; Insulin-like growth factor binding protein 3
Fund program: Medical Research Project of Jiangsu Provincial Health Commission (ZD2021012)

Lung adenocarcinoma (LUAD) is the most common histological type of lung cancer, and the elderly are the high-risk population. Due to lacking typical symptoms, most patients are in the medium or advanced stage when diagnosed and miss the best time for surgical treatment. The overall 5-year survival rate of LUAD is low[1]. Platinum-containing dual-drug is the first-line chemotherapy regimen for advanced non-small cell lung cancer (NSCLC), and pemetrexed is sensitive to adenocarcinoma. Hence, pemetrexed plus carboplatin is a typical regimen for the clinical treatment of advanced LUAD. However, the effect of platinum-containing dual-drug chemotherapy is limited, making it difficult to improve the patients' survival significantly[2]. It has been found that programmed cell death protein 1 (PD-1) inhibitors can inhibit the tumor cell-mediated reduction of effector T-cell activation to reduce immune evasion. PD-1 inhibitors, such as sindilizumab and tislelizumab, have been gradually applied to treat advanced lung cancer which can improve tumor control probability and prolong survival[3]. Tislelizumab has specific binding sites compared with other PD-1 inhibitors, which can modify the structure of the Fc segment, which can avoid the phagocytic response of macrophages, reduce T-cell damage, and perform a better immunotherapy effect[4]. Tislelizumab has a short time to market. It was approved by the Chinese Medical Products Administration in June 2021 as the first-line treatment of advanced non-squamous NSCLC with driver gene-negative[5]. However, the reports of application effects and safety are still rare on tislelizumab. In this study, a randomized controlled trial was adapted to analyze the efficacy and safety of tislelizumab plus pemetrexed and carboplatin in the first-line treatment of advanced LUAD in elderly patients, and provide data support for the clinical application of tislelizumab.

1 Data and methods

1.1 general data

Ninety-four elderly patients with advanced driver gene-negative LUAD admitted to The Fourth Affiliated

Hospital of Nanjing Medical University from July 2021 to December 2022 were selected as the study subjects. The inclusion and exclusion criteria for the study were as follows.

Inclusion criteria:

(1) aged from 60 to 70 years old;
(2) diagnosed as LUAD by pathological examination, and combined with advanced stage (IIIB to IV) with imaging;
(3) Epidermal growth factor receptor (EGFR) mutation negative sensitivity and anaplastic lymphoma kinase (ALK) fusion mutation negative;
(4) no systemic anti-tumour therapy for advanced LUAD previously;
(5) expected survival time > 3 months;
(6) full understanding of possible adverse effects caused by the treatment and precautions; signing of an informed consent form.

Exclusion criteria:

(1) elective surgery is proposed;
(2) had a transplantation treatment history of previous organ or blood system;
(3) had symptomatic central nervous metastasis or history of Parkinson's disease, epilepsy or other neuropsychiatric disorders;
(4) require long-term systemic glucocorticoid treatment;
(5) comorbid immunodeficiency diseases;
(6) comorbid severe hepatic and renal dysfunction, or coagulation dysfunction.

All patients were informed consent. The research was reviewed by the Medical Ethics Committee of the hospital (approval number: IIT-IRB-2023-003). The 94 patients were divided into chemotherapy group (n=48) and tislelizumab group (n=46) by random number table method, and the general data of the two groups were compared **[Table 1]**.

Tab.1 Comparison of general data between the two groups [case(%)]

Item	Tislelizumab group (n=46)	Chemotherapy group (n=48)	χ^2 value	P value
Sex				
Male	31（67.39）	34（70.83）	0.131	0.718
Female	15（32.61）	14（29.17）		
Age				
<65	26（56.52）	30（62.50）	0.349	0.555
65-70	20（43.48）	18（37.50）		
Smoking history				
Smoking	29（63.04）	26（54.17）	0.763	0.383
Non-smoking	17（36.96）	22（45.83）		
ECOG* performance status score				
0-1	39（84.78）	41（85.42）	0.008	0.931
2	7（15.22）	7（14.58）		
Clinical staging				
IIIB	10（21.74）	13（27.08）	0.835	0.659
IIIC	5（10.87）	7（14.58）		
IV	31（67.39）	28（58.33）		
Brain metastases	9（19.57）	7（14.58）	0.413	0.521
Liver metastases	5（10.87）	4（8.33）	0.005	0.946

* ECOG, Eastern Cooperative Oncology Group

1.2 Methods

The chemotherapy group was treated with a platinum-containing dual-drug regimen: pemetrexed (H20133215, 0.1 g, Nanjing Sincere Dongyuan) was used at a dose of 500 mg/m^2, d1, *ivgtt.* Carboplatin (H10950273, 50 mg, Yunnan Phytopharmaceutical) was used at a dose of AUC 5, d1, *ivgtt.* The dose of carboplatin was calculated by the area under the concentration-time curve (AUC) and myohepatic clearance, and the AUC [mg/(mL·min)] was taken as 5. The treatment was carried out with 21 days as 1 cycle, and 4 cycles of treatment. The blood routine, liver and kidney functions were monitored on time during the chemotherapy period. Tislelizumab group referred to the tislelizumab treatment on the basis of chemotherapy group: tislelizumab injection (S20190045, 100 mg, Guangzhou BeiGene) was used at a dose of 200 mg, *ivgtt*, with 21 days as 1 cycle, and 4 cycles of treatment.

1.3 Observation indexes

(1) Clinical efficacy: Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1) was used after 4 cycles of treatment[6]. The clinical efficacy was classified into complete remission, partial remission, stability and progression. The objective response rate (ORR) and disease control rate (DCR) were calculated. ORR was the proportion of complete remission + partial remission cases, and DCR was the proportion of complete remission + partial remission + stablility cases.

(2) Immune function indexes: Fasting peripheral median cubital vein blood was collected in 3-4 mL before and after 4 cycles of treatment, and peripheral blood T-lymphocyte subpopulations $CD4^+$ and $CD8^+$ were detected by a fully automated flow cytometer (B.D. Company, USA, model: FACSCalibur), and $CD4^+/CD8^+$ ratio was calculated.

(3) Serum indexes: The collected peripheral median cubital vein blood was centrifuged at 3 500 r/min for 10

min (radius 8 cm) to obtain the serum specimen, and the enzyme-linked immunoassay (kit purchased from Shanghai Beyotime Biotechnology) was used to detect levels of insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3).
(4) Adverse reactions: NCI-CTACE (Version 4.0) [7] were referred to assess the grade of adverse reactions.

1.4 Statistical methods

SPSS 24.0 software was used for data processing. Continuous data in accordance with normal distribution were expressed by independent samples *t*-test between two groups, and paired samples *t*-test before and after treatment within a group. Discrete data were expressed by cases (%), and Chi-square test was used. Mann-Whitney *U* test was used for ordinal data. P <0.05 was regarded as the difference was statistically significant.

2 Results

2.1 Comparison of clinical efficacy between the two groups

The clinical efficacy of the tislelizumab group was significantly higher than that of the chemotherapy group (P<0.05), and the ORR was significantly higher than that of the chemotherapy group (P < 0.05) **[Table 2]**.

2.2 Comparison of immune function indexes between the two groups

The peripheral blood $CD4^+$ and levels of $CD4^+/CD8^+$ ratio in both groups all increased compared with those before treatment after 4 cycles of treatment and the levels of these indexes in the tislelizumab group were higher than those in the chemotherapy group (P<0.05). The peripheral blood $CD8^+$ levels of the two groups were reduced compared with those before treatment, and the levels of $CD8^+$ in the tislelizumab group were lower than those in the chemotherapy group after treatment (P < 0.05) **[Table 3]**.

2.3 Comparison of serum indexes between the two groups

After 4 cycles of treatment, the serum IGF-1 level of both groups was lower than that before treatment, and the IGF-1 level of the tislelizumab group was lower than that of the chemotherapy group after treatment (P <0.05); the serum IGFBP-3 level of both groups was higher than that before treatment, and the IGFBP-3 level of the tislelizumab group was higher than that of the chemotherapy group after treatment (P <0.05) **[Table 4]**.

2.4 Comparison of adverse reactions between the two groups

There were no fatal events of adverse reactions in the two groups. The adverse reactions were mainly of grade 1 to 2, and the difference between the adverse reactions of the two groups was not statistically significant (P>0.05) **[Table 5]**.

Tab.2 Comparison of clinical efficacy between the two groups

Group	Case	Efficacy (cases)				ORR	DCR
		Complete remission	Partial remission	Stability	Progression	Case (%)	Case (%)
Tislelizumab group	46	2	25	11	8	27 (58.70)	38 (82.61)
Chemotherapy group	48	0	14	19	15	14 (29.17)	33 (68.75)
Z / χ^2 value			2.787			8.329	2.441
P value			0.005			0.004	0.118

Tab.3 Comparison of immune function indicators between the two groups ($\bar{x} \pm s$)

Group	Case	$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$ ratio	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Tislelizumab group	46	30.79±5.04	39.36±4.13[a]	30.05±3.82	23.46±2.97[a]	1.09±0.21	1.82±0.35[a]
Chemotherapy group	48	31.85±4.38	35.27±4.22[a]	29.13±3.15	25.73±3.04[a]	1.15±0.24	1.59±0.31[a]
t value		1.097	4.747	1.554	3.660	1.288	3.376
P value		0.275	<0.001	0.124	<0.001	0.201	0.001

Tab. 4 Comparison of serum indicators between the two groups (ng/mL, $\bar{x} \pm s$)

Group	Case	IGF-1		IGFBP-3	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Tislelizumab group	46	290.42±45.12	227.96±34.35[a]	3349.41±328.49	4315.85±387.22[a]
Chemotherapy group	48	283.79±37.45	249.28±32.48[a]	3297.05±297.25	4117.08±368.45[a]
t value		0.777	3.093	0.811	3.550
P value		0.439	0.003	0.420	0.012

Note: Compared with the same group before treatment, [a]P<0.05.

Tab. 5 Comparison of adverse reactions between the two groups [case(%)]

Adverse Reactions	Tislelizumab group（*n*=46）	Chemotherapy group（*n*=48）	χ^2 value	*P* value
Leukopenia	19（41.30）	18（37.50）	0.142	0.706
Anemia	25（54.35）	21（43.75）	1.056	0.304
Neutropenia	11（23.91）	9（18.75）	0.374	0.541
Thrombocytopenia	11（23.91）	9（18.75）	0.374	0.541
Nausea and vomiting	19（41.30）	15（31.25）	1.029	0.311
Loss of appetit	5（10.87）	4（8.33）	0.005	0.946
Diarrhea	10（21.74）	9（18.75）	0.130	0.718
Fatigue	4（8.70）	4（8.33）	0.094	0.759
Rash	6（13.04）	1（2.08）	2.658	0.103
Liver Function Abnormalities	6（13.04）	7（14.58）	0.047	0.829
Kidney Function Abnormalities	4（8.69）	3（6.25）	0.003	0.953
Hypothyroidism	6（13.04）	3（6.25）	0.590	0.442

3 Discussion

PD-1 is an immunosuppressive transmembrane protein on the surface of T-lymphocytes, which can bind to ligands expressed by tumor cells, leading to tyrosine phosphorylation of the intracellular structural domain of PD-1, inducing dephosphorylation of T-lymphocyte receptor signaling molecules, inhibiting their downstream signaling pathways, and restricting the proliferation activation of T-lymphocytes and the cytokine production, so that the tumor cells can escape from the killing activity of the body[8-9]. Tislelizumab and other PD-1 inhibitors can block the above pathway and reduce the immune invasion of tumor cells. Tislelizumab has specific binding epitopes such as aspartic acid Asp77 and arginine Arg86 residues, which have strong targeting affinity, and modify the structure of the Fc segment. It reduces phagocytosis effect-mediated T-cell damage, and has an excellent anti-tumor activity[10].

Balance of $CD4^+/CD8^+$ ratio is an important indicator for assessing the effect of immunotherapy for malignant tumors, $CD4^+$ T lymphocytes can not only promote immune response, but also promote B lymphocytes to produce specific antibodies and enhance the killing activity of tumor cells of humoral immunity[11]; CD8+ T lymphocytes have a negative feedback inhibitory effect on CD4+ T lymphocytes[12]; if the $CD4^+/CD8^+$ ratio becomes more extensive, the balance will shift to the left, suggesting that the body's cellular and humoral immunity is strengthened and the immune escape of tumor cells is inhibited[13]. In this study, at the end of 4 cycles of treatment, the peripheral blood $CD4^+/CD8^+$ ratio of both groups increased compared with that before treatment, and it was higher in the tislelizumab group than in the chemotherapy group, suggesting that tislelizumab combined with platinum-containing double-drug first-line treatment can regulate immune function effectively. The immune evasion in advanced LUAD can be prevented, which benefits the enhancement of anti-tumor effect. This study also showed that the ORR of the tislelizumab group was significantly higher than that of the chemotherapy group, confirming that the immunotherapeutic effect of tislelizumab was significant and could enhance the anti-tumor effect. The phase 3 open-label randomized controlled trial by Zhou *et al*[14] also showed that tislelizumab was effective in immunotherapy for progressive NSCLC, which could benefit patients in the long term and prolong survival. However, due to the short period that tislelizumab has been approved for the first-line treatment of advanced LUAD in China and the small sample size in the study, the survival of the two groups has not been analyzed. The two groups should be followed up and observed in the long term to evaluate the effect of tislelizumab on the survival of elderly patients with advanced LUAD.

It has also been reported that IGF-1 is a mitogen, which is an essential factor for the transition of cells from the G1 phase to the S phase, and the up-regulation of IGF-1 suggests an enhanced role in cell growth. More than 90% of IGF-1 binds explicitly to IGFBP-3 in the peripheral blood circulation[15-16]. It has been suggested that monitoring changes in patients' serum IGF-1 and IGFBP-3 levels are beneficial to assessing tumor cell growth[17]. In this study, serum IGF-1 levels decreased, and IGFBP-3 levels increased in both groups after treatment compared with those before treatment. The magnitude of change in the tislelizumab group was greater than that in the chemotherapy group, suggesting that tislelizumab can down-regulate serum IGF-1 levels, inhibit tumor cell growth and proliferation, and that combined treatment can enhance the anti-tumor effect. The safety of immunotherapy and chemotherapy, keeping consistent, is the focus of clinical concern. Hematologic toxicity and gastrointestinal reactions are common adverse reactions of platinum-containing chemotherapy [18-19]. PD-1 inhibitors, like tislelizumab, can lead to adverse reactions include hypothyroidism, rash, etc.[20-22]. In this study, although the incidence of hypothyroidism and rash in the tislelizumab group was slightly higher than that in the chemotherapy group, the difference between the two groups was not statistically significant. This result may be related to the fact that there are not many adverse reactions to tislelizumab on the one hand, and the small sample size and low test efficacy of this study may cause bias in the results on the other hand. However, the adverse reactions in both groups mainly belonged to grades 1-2, and no fatal severe events occurred. This suggests that the safety of tislelizumab

combined with pemetrexed and carboplatin regimen is good.

In conclusion, the anti-tumor effect of tislelizumab combined with platinum-containing double-drug in elderly patients with advanced LUAD is remarkable, which can improve the balance of $CD4^+/CD8^+$ ratio and regulate the expression of serum IGF-1 and IGFBP-3 levels. The adverse reactions are controllable, and the treatment protocol is safe and reliable.

Conflict of Interest None

References

[1] Chen GY, Ma JX, Hu Y. Value of DNA repair gene and TP53 co-mutation in predicting effect of immunotherapy on lung adenocarcinoma[J]. Cancer Res Prev Treat, 2021, 48(7): 704-708. [In Chinese]

[2] Guan YL, Hu HL, Jin Y, et al. Pembrolizumab in combination with pemetrexed and carboplatin versus pemetrexed plus carboplatin for the first-line treatment of advanced, non-squamous NSCLC: interpretation of data from the phase II, randomized, open study KEYNOTE-021G cohort study and long-term follow up[J]. J Chin Oncol, 2022, 28(9): 786-796. **[In Chinese]**

[3] Xu L, Huang LY, Wang YH, et al. Efficacy and safety of PD-1 inhibitor combined with brain radiotherapy for brain metastases in patients with pan-negative non-small cell lung cancer[J]. J Pract Med, 2022, 38(24): 3100-3105. [In Chinese]

[4] Chen MY, Shen HL, Tong X, et al. Efficacy and safety of tislelizumab in the treatment of locally advanced or metastatic urothelial carcinoma[J]. Oncol Prog, 2022, 20(20): 2095-2097, 2101. **[In Chinese]**

[5] Liu Y, Liu Q, Huang L, et al. A programmed death receptor-1 inhibitor—Tislelizumab[J]. Clin Med J, 2022, 20(1): 37-42. **[In Chinese]**

[6] Sun JM, Ahn MJ, Park MJ, et al. Accuracy of RECIST 1.1 for non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors[J]. Lung Cancer, 2010, 69(1): 105-109.

[7] Liu YJ, Zhu GP, Guan XY. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma[J]. Oral Oncol, 2012, 48(6): 554-559.

[8] Zucali PA, Lin CC, Carthon BC, et al. Targeting CD38 and PD-1 with isatuximab plus cemiplimab in patients with advanced solid malignancies: results from a phase I/II open-label, multicenter study[J]. J Immunother Cancer, 2022, 10(1): e003697.

[9] Zheng Y, Patiguli Aerxiding.CTLA-4 and PD-1/ PD-L1 immune checkpoint inhibitors in extensive stage small cell lung cancer[J].Chin J Clin Res, 2023,36(6):805-809.

[10] Zhu LK, Li ZJ, Wang ZB, et al. A rare case of bladder cancer that metastasized to brain, heart, and lung lymph nodes benefited from immunotherapy[J]. World J Surg Oncol, 2022, 20(1): 1-8.

[11] Hoek KL, Greer MJ, McClanahan KG, et al. Granzyme B prevents aberrant IL-17 production and intestinal pathogenicity in CD4+ T cells[J]. Mucosal Immunol, 2021, 14(5): 1088-1099.

[12] Ba W, Yang HH, Wang WJ, et al. CD8 + mycosis fungoides with ichthyosiform clinical presentation and angiocentric feature[J]. J Cutan Pathol, 2022, 49(5): 487-490.

[13] Zhu Y, Zhu YQ, Zhang XJ, et al. Correlation of cancer-associated fibroblasts, CD4+ and CD8+T lymphocytes with development and lymph node metastasis of breast carcinoma[J]. J Nanjing Med Univ Nat Sci, 2021, 41(4): 575-579. **[In Chinese]**

[14] Zhou CC, Huang DZ, Fan Y, et al. Tislelizumab versus docetaxel in patients with previously treated advanced NSCLC (RATIONALE-303): a phase 3, open-label, randomized controlled trial[J]. J Thorac Oncol, 2023, 18(1): 93-105.

[15] Haldrup D, Wei CS, Holland-Fischer P, et al. Effects of lifestyle intervention on IGF-1, IGFBP-3, and insulin resistance in children with obesity with or without metabolic-associated fatty liver disease[J]. Eur J Pediatr, 2023, 182(2): 855-865.

[16] Kim M, Kim EY, Kim EY, et al. Investigating whether serum IGF-1 and IGFBP-3 levels reflect the height outcome in prepubertal children upon rhGH therapy: LG growth study database[J]. PLoS One, 2021, 16(11): e0259287.

[17] Ouyang CL, Li ZY, Li HC. Expression and clinical significance of IGF-1 and IGFBP-3 in serum and tissues of non-small cell lung cancer[J]. Chin Clin Oncol, 2022, 27(6): 522-526. **[In Chinese]**

[18] Li W, Yang YL, Hu JJ, et al. Efficacy of Shenqi Fuzheng injection combined with platinum-based dual-drug chemotherapy for advanced non-small-cell lung cancer[J]. Chin J Hosp Pharm, 2022, 42(3): 299-303. **[In Chinese]**

[19] Feng CJ,Zhang RG,Wei MZ.Effect of sintilimab combined with synchronous radiochemotherapy on tumor markers and PD-1/PD-L1 in patients with advanced cervical cancer[J]. J Clin Pract Diagn Ther, 2022,36(7):740-743.

[20] Liu J, Liu XD, Zhu LQ. Literature analysis of adverse drug reactions induced by tislelizumab[J]. Drugs Clin, 2022, 37(9): 2122-2127. **[In Chinese]**

[21] Zheng R, Wang BS, Li ZH, et al. Combining chemotherapy and tislelizumab with preoperative split-course hypofraction radiotherapy for locally advanced rectal cancer: study protocol of a prospective, single-arm, phase II trial[J]. BMJ Open, 2023,13(3):e066976.

[22] Zhang ML,Zhu XB,Song AL,et al.PD-L1 inhibitors-induced hypophysitis in a patient with small cell lung cancer: a case report and literatures re- view[J]. J Diagn Concepts Pract, 2022,21(6):741-745.

Submission received: 2023-07-15/**Revised:**2023-08-20

·论　著·

替雷利珠单抗联合含铂双药方案治疗老年晚期肺腺癌的疗效

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摘要：目的　探讨替雷利珠单抗联合培美曲赛及卡铂化疗方案治疗晚期肺腺癌老年患者的疗效，及对血清胰岛素样生长因子 1（IGF-1）、胰岛素样生长因子结合蛋白 3（IGFBP-3）水平的影响。**方法**　选取 2021 年 7 月至 2022 年 12 月南京医科大学第四附属医院收治的 94 例驱动基因阴性的晚期肺腺癌老年患者为研究对象，采用随机数字表法分为化疗组（培美曲赛联合卡铂治疗，$n=48$）及替雷利珠单抗组（培美曲赛+卡铂+替雷利珠单抗，$n=46$），以 21 d 为 1 个周期，治疗 4 个周期。记录两组临床疗效及治疗前后的免疫功能[T 淋巴细胞亚群（$CD4^+$、$CD8^+$、$CD4^+/CD8^+$）]、血清指标（IGF-1、IGFBP-3）变化，评估不良反应发生情况。**结果**　替雷利珠单抗组临床疗效优于化疗组，客观有效率明显高于化疗组（58.70% *vs* 29.17%，$\chi^2=8.329$，$P<0.01$）。治疗 4 个周期后，两组 $CD4^+$、$CD4^+/CD8^+$及 IGFBP-3 水平均较治疗前显著升高（$P<0.05$），且治疗后替雷利珠单抗组高于化疗组（$P<0.05$）；两组 $CD8^+$及 IGF-1 均较治疗前显著降低（$P<0.05$），且治疗后替雷利珠单抗组低于化疗组（$P<0.05$）。两组不良反应以 1~2 级为主，发生率差异无统计学意义（$P>0.05$）。**结论**　替雷利珠单抗联合含铂双药一线治疗老年晚期肺腺癌可提升临床疗效，改善 $CD4^+/CD8^+$平衡，调节血清 IGF-1、IGFBP-3 水平，不良反应可控，治疗方案安全、可靠。

关键词：肺腺癌，晚期；替雷利珠单克隆抗体；卡铂；培美曲赛；免疫功能；胰岛素样生长因子 1；胰岛素样生长因子结合蛋白 3

中图分类号：R734.2　**文献标识码：**A　**文章编号：**1674-8182(2024)01-0029-05

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Abstract: Objective　To explore the efficacy of tislelizumab combined with pemetrexed and carboplatin chemotherapy in elderly patients with advanced lung adenocarcinoma and its effects on serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels. **Methods**　Ninety-four driver gene-negative elderly patients with advanced lung adenocarcinoma admitted to the Fourth Affiliated Hospital of Nanjing Medical University from July 2021 to December 2022 were selected as the study subjects. They were divided into chemotherapy group (pemetrexed combined with carboplatin, $n=48$) and tislelizumab group (pemetrexed+carboplatin+tislelizumab, $n=46$) by the random number table method, and both groups were treated for 4 cycles, with 21 days as a cycle. The clinical efficacy, immune function [T lymphocyte subsets ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$)] and serum indicators (IGF-1, IGFBP-3) before and after treatment were recorded in both groups, and the adverse reactions were assessed. **Results**　The clinical efficacy and objective response rate (58.70% *vs* 29.17%, $\chi^2=8.329$, $P<0.01$) in tislelizumab group were significantly higher than those in chemotherapy group. After 4 cycles of treatment, the $CD4^+$, $CD4^+/CD8^+$ and IGFBP-3

DOI: 10.13429/j.cnki.cjcr.2024.01.007

基金项目：江苏省卫健委医学科研项目（ZD2021012）

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出版日期：2024-01-20

QR code for English version

levels in both groups were significantly increased compared with those before treatment (P<0.05), and the indicators in tislelizumab group were higher than those in chemotherapy group (P<0.05); $CD8^+$ and IGF-1 levels were significantly decreased in both groups compared with those before treatment (P<0.05), and the indicators in tislelizumab group were lower than those in chemotherapy group (P<0.05). Adverse reactions were mainly grade 1-2 in both groups, and there was no significant difference in the incidence of adverse reactions between two groups (P>0.05). **Conclusion** The first-line therapy of tislelizumab combined with platinum-containing dual-drug for elderly advanced lung adenocarcinoma can improve the clinical efficacy, improve the balance of $CD4^+/CD8^+$, regulate the expression of serum IGF-1 and IGFBP-3 levels. The adverse reactions are controllable, and the treatment regimen is safe and reliable.

Keywords: Lung adenocarcinoma, advanced; Tislelizumab; Carboplatin; Pemetrexed; Immune function; Insulin-like growth factor 1; Insulin-like growth factor binding protein 3

Fund program: Medical Research Project of Jiangsu Provincial Health Commission(ZD2021012)

肺腺癌为肺癌最常见的组织学类型,老年人为其主要发病群体,由于缺乏典型症状,大部分患者确诊时已处于中晚期,失去最佳手术治疗时机,5 年生存率较低[1]。含铂双药治疗是晚期非小细胞肺癌的一线化疗方案,培美曲塞对腺癌敏感,培美曲塞+卡铂也是临床治疗晚期肺腺癌的常用方案,但含铂双药化疗效果有限,难以显著提升患者生存期[2]。研究发现,程序性死亡受体 1(programmed cell death protein 1, PD-1)抑制剂对肿瘤细胞介导的效应 T 细胞反应性降低有抑制作用,从而减少免疫逃逸,信迪利单抗、替雷利珠单抗等 PD-1 抑制剂也逐渐应用于晚期肺癌的治疗,以提升肿瘤控制率,延长生存期[3]。替雷利珠单抗较其他 PD-1 抑制剂有特异性结合表位,修饰 Fc 段结构,可避免巨噬细胞的吞噬效应,降低 T 细胞损伤,发挥更佳的免疫治疗效果[4]。替雷利珠单抗上市时间短,在 2021 年 6 月获得我国药监局批准用于晚期驱动基因阴性的非鳞状非小细胞肺癌的一线治疗[5],但其应用效果及安全性的报道仍少见。本研究采用随机对照试验分析替雷利珠单抗+培美曲塞+卡铂一线治疗晚期肺腺癌老年患者的疗效及安全性,为替雷利珠单抗的临床应用提供数据支持。

1　资料与方法

1.1　一般资料　选取 2021 年 7 月至 2022 年 12 月南京医科大学第四附属医院收治的 94 例驱动基因阴性的晚期肺腺癌老年患者为研究对象。纳入标准:(1) 年龄为 60~70 岁;(2) 经病理学检查确诊为肺腺癌,结合影像学等明确为ⅢB~Ⅳ期;(3) 表皮生长因子(epidermal growth factor receptor, EGFR)敏感突变阴性及间变性淋巴瘤激酶(anaplastic lymphoma kinase, ALK)融合突变阴性;(4) 既往未接受针对晚期肺腺癌的系统性抗肿瘤治疗;(5) 预期生存时间>3 个月;(6) 对治疗可能造成的不良反应及注意事项充分了解,并签署纸质知情同意书。排除标准:(1) 拟行择期手术治疗;(2) 既往脏器或血液系统移植治疗史;(3) 有症状的中枢神经系统转移或有帕金森、癫痫等神经精神疾病史;(4) 需长期使用全身性糖皮质激素治疗;(5) 合并免疫缺陷性疾病;(6) 合并严重肝肾功能障碍、凝血功能障碍。所有患者知情同意,且通过医院医学伦理委员会审核(审批号:IIT-IRB-2023-003)。将 94 例患者采用随机数字表法分为化疗组(n=48)及替雷利珠单抗组(n=46),两组基线资料比较,差异无统计学意义(P>0.05)。见表 1。

1.2　方法　化疗组给予含铂双药方案治疗:培美曲塞

表 1　两组基线资料比较　[例(%)]

Tab. 1　Comparison of baseline data between the two groups　[case(%)]

项目	替雷利珠单抗组(n=46)	化疗组(n=48)	χ^2 值	P 值
性别				
男	31(67.39)	34(70.83)	0.131	0.718
女	15(32.61)	14(29.17)		
年龄				
<65 岁	26(56.52)	30(62.50)	0.349	0.555
65~70 岁	20(43.48)	18(37.50)		
吸烟史				
有	29(63.04)	26(54.17)	0.763	0.383
无	17(36.96)	22(45.83)		
活动状态评分[a]				
0~1 分	39(84.78)	41(85.42)	0.008	0.931
2 分	7(15.22)	7(14.58)		
临床分期				
ⅢB 期	10(21.74)	13(27.08)		
ⅢC 期	5(10.87)	7(14.58)	0.835	0.659
Ⅳ期	31(67.39)	28(58.33)		
脑转移				
有	9(19.57)	7(14.58)	0.413	0.521
无	37(80.43)	41(85.42)		
肝转移				
有	5(10.87)	4(8.33)	0.005	0.946
无	41(89.13)	44(91.67)		

注:[a] 为美国东部肿瘤协作组 ECOG。

(国药准字 H20133215, 0.1 g,南京先声东元制药)使用剂量为 500 mg/m^2,d1,静脉滴注;卡铂(国药准字 H10950273,50 mg,云南植物药业)使用剂量 AUC5,d1,静脉滴注,按血药浓度—时间曲线下面积(area under the cure, AUC)和肌酐清除率来计算卡铂的剂量,AUC [mg/(mL · min)]取值 5;以 21 d 为 1 个周期,治疗 4 个周期。化疗期间按时监测血常规、肝肾功能。替雷利珠单抗组在化疗组基础上联合替雷利珠单抗治疗:替雷利珠单抗注射液(国药准字 S20190045,100 mg,广州百济神州生物制药)使用剂量为 200 mg,d1,静脉滴注,21 d 为 1 个周期,治疗 4 个周期。

1.3　观察指标　(1) 临床疗效:治疗 4 个周期后,使用实体瘤疗效评定标准 1.1(RECIST1.1)[6],分为完全缓解、部分缓解、稳定及进展,并计算客观有效率(objective response rate, ORR)及疾病控制率(disease control rate, DCR),其中 ORR 为完全缓解+部分缓解例数占比,DCR 为完全缓解+部分缓解+稳定例数占比。(2) 免疫功能指标:在治疗前及治疗 4 个周期后采集空腹外周肘静脉血 3~4 mL,使用全自动流式细胞仪(美国 BD 公司,型号:FACSCalibur)检测外周血 T 淋巴细胞亚群 CD4$^+$、CD8$^+$,并计算 CD4$^+$/CD8$^+$。(3) 血清指标:将采集的外周肘静脉血以 3 500 r/min 离心 10 min(半径 8 cm)得到血清标本,采用酶联免疫分析法(试剂盒购自上海碧云天生物技术)检测胰岛素样生长因子 1(insulin-like growth factor 1, IGF-1)、胰岛素样生长因子结合蛋白 3(insulin-like growth factor binding protein 3, IGFBP-3)水平。(4) 不良反应:参考美国卫生及公共服务部常见不良反应事件评价标准 4.0 版[7]评估不良反应发生等级。

1.4　统计学方法　使用 SPSS 24.0 软件处理数据。符合正态分布的计量数据以 $\bar{x}\pm s$ 表示,两组间采用独立样本 t 检验,组内治疗前后采用配对样本 t 检验;计数资料以例(%)表示,采用 χ^2 检验;等级资料采用 Mann-Whitney U 检验。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　两组临床疗效比较　替雷利珠单抗组临床疗效明显优于化疗组(P<0.01),且 ORR 较化疗组显著升高(P<0.01)。见表 2。

2.2　两组免疫功能指标比较　治疗 4 个周期后,两组外周血 CD4$^+$、CD4$^+$/CD8$^+$水平均较治疗前均升高,且治疗后替雷利珠单抗组高于化疗组(P<0.05);两组外周血 CD8$^+$水平较治疗前均降低,且治疗后替雷利珠单抗组低于化疗组(P<0.05)。见表 3。

2.3　两组血清指标比较　治疗 4 个周期后,两组血清 IGF-1 水平较治疗前均降低,且治疗后替雷利珠单抗组 IGF-1 水平低于化疗组($P<0.05$);两组血清 IGFBP-3水平较治疗前均升高,且治疗后替雷利珠单抗组 IGFBP-3 水平高于化疗组(P<0.05)。见表 4。

表 2　两组临床疗效比较

Tab. 2　Comparison of clinical efficacy between the two groups

组别	例数	疗效(例)				ORR	DCR
		完全缓解	部分缓解	稳定	进展	[例(%)]	[例(%)]
替雷利珠单抗组	46	2	25	11	8	27(58.70)	38(82.61)
化疗组	48	0	14	19	15	14(29.17)	33(68.75)
Z/χ^2 值			2.787			8.329	2.441
P 值			0.005			0.004	0.118

表 3　两组免疫功能指标比较　($\bar{x}\pm s$)

Tab. 3　Comparison of immune function indicators between the two groups　($\bar{x}\pm s$)

组别	例数	CD4$^+$(%)		CD8$^+$(%)		CD4$^+$/CD8$^+$	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
替雷利珠单抗组	46	30.79±5.04	39.36±4.13[a]	30.05±3.82	23.46±2.97[a]	1.09±0.21	1.82±0.35[a]
化疗组	48	31.85±4.38	35.27±4.22[a]	29.13±3.15	25.73±3.04[a]	1.15±0.24	1.59±0.31[a]
t 值		1.097	4.747	1.554	3.660	1.288	3.376
P 值		0.275	<0.001	0.124	<0.001	0.201	0.001

注:与同组治疗前比较,[a]P<0.05。

表 4　两组血清指标比较　(ng/mL, $\bar{x}\pm s$)

Tab. 4　Comparison of serum indicators between the two groups　(ng/mL, $\bar{x}\pm s$)

组别	例数	IGF-1		IGFBP-3	
		治疗前	治疗后	治疗前	治疗后
替雷利珠单抗组	46	290.42±45.12	227.96±34.35[a]	3 349.41±328.49	4 315.85±387.22[a]
化疗组	48	283.79±37.45	249.28±32.48[a]	3 297.05±297.25	4 117.08±368.45[a]
t 值		0.777	3.093	0.811	3.550
P 值		0.439	0.003	0.420	0.012

注:与同组治疗前比较,[a]P<0.05。

2.4　两组不良反应比较　两组未发生不良反应致死事件,不良反应以 1~2 级为主,两组不良反应发生率比较差异均无统计学意义(P>0.05)。见表 5。

表 5　两组不良反应比较　[例(%)]

Tab. 5　Comparison of adverse reactions between the two groups　[case(%)]

不良反应	替雷利珠单抗组(n=46)	化疗组(n=48)	χ^2 值	P 值
白细胞减少	19(41.30)	18(37.50)	0.142	0.706
贫血	25(54.35)	21(43.75)	1.056	0.304
中性粒细胞减少	11(23.91)	9(18.75)	0.374	0.541
血小板减少	11(23.91)	9(18.75)	0.374	0.541
恶心呕吐	19(41.30)	15(31.25)	1.029	0.311
食欲下降	5(10.87)	4(8.33)	0.005	0.946
腹泻	10(21.74)	9(18.75)	0.130	0.718
乏力	4(8.70)	4(8.33)	0.094	0.759
皮疹	6(13.04)	1(2.08)	2.658	0.103
肝功能异常	6(13.04)	7(14.58)	0.047	0.829
肾功能异常	4(8.69)	3(6.25)	0.003	0.953
甲状腺功能减退	6(13.04)	3(6.25)	0.590	0.442

3　讨　论

PD-1 为 T 淋巴细胞表面的免疫抑制跨膜蛋白,可与肿瘤细胞表达的配体结合,导致 PD-1 胞内结构域酪氨酸磷酸化,诱导 T 淋巴细胞受体信号分子去磷酸化,抑制其下游信号通路,T 淋巴细胞增殖活化及细胞因子生成受限,使肿瘤细胞“逃过”机体免疫杀伤作用[8-9]。替雷利珠单抗等 PD-1 抑制剂则能阻断上述通路,减少肿瘤细胞免疫逃逸,且替雷利珠单抗具有天冬氨酸 Asp77 和精氨酸 Arg86 残基等特异性结合表位,具有较强的靶向亲和力,还改造 Fc 段的结构,减少吞噬效应介导的 T 细胞损伤,抗肿瘤效果好[10]。

$CD4^+/CD8^+$平衡是评估恶性肿瘤免疫治疗效果的重要指标,其中 $CD4^+$T 淋巴细胞不仅促进免疫应答,还能促 B 淋巴细胞产生特异性抗体,增强体液免疫的肿瘤细胞杀伤作用[11];$CD8^+$T 淋巴细胞则对 $CD4^+$T 淋巴细胞具有负反馈抑制效应[12];若 $CD4^+/CD8^+$比值变大,即平衡向左移动,提示机体细胞免疫及体液免疫增强,肿瘤细胞的免疫逃逸得到抑制[13]。本研究中,两组治疗 4 个周期结束时,外周血 $CD4^+/CD8^+$比值均较治疗前均升高,而替雷利珠单抗组治疗后高于化疗组,提示替雷利珠单抗联合含铂双药一线治疗,能有效调节免疫功能,使晚期肺腺癌免疫逃逸减少,对增强抗肿瘤作用有利。本研究还显示,替雷利珠单抗组 ORR 较化疗组显著升高,证实替雷利珠单抗的免疫治疗效果显著,可增强抗肿瘤效果。Zhou 等[14]的 3 期开放标签随机对照试验也显示,替雷利珠单抗对进展期非小细胞肺癌免疫治疗效果显著,可使患者长期获益,延长生存期。然而,由于替雷利珠单抗在我国获批用于晚期肺腺癌一线治疗的时间较短,本研究入组样本量也较少,故未对两组生存期作分析,后续应作长期随访观察,评估替雷利珠单抗对晚期肺腺癌老年患者生存期的影响。

据文献报道,IGF-1 为一种有丝分裂原,是细胞从 G1 期向 S 期转变的必备因子,IGF-1 的上调提示细胞生长作用增强;超过 90%的 IGF-1 在外周血循环中与 IGFBP-3 特异性结合[15-16]。有研究认为,监测患者血清 IGF-1、IGFBP-3 水平的变化,对评估肿瘤细胞生长有利[17]。本研究中,两组治疗后血清 IGF-1 水平较治疗前降低,IGFBP-3 水平较治疗前升高,替雷利珠单抗组变化幅度大于化疗组,提示替雷利珠单抗能下调血清 IGF-1 水平,抑制肿瘤细胞生长及增殖,联合治疗可增强抗肿瘤效果。免疫治疗与化疗的安全性一致是临床关注的焦点,血液系统毒性、胃肠道反应等为含铂化疗方案的常见不良反应[18-19];PD-1 抑制剂,包括替雷利珠单抗不良反应有甲状腺功能减退、皮疹等[20-22]。本研究中,虽然替雷利珠单抗组甲状腺功能减退、皮疹发生率略高于化疗组,但两组间差异无统计学意义。考虑该结果与替雷利珠单抗不良反应不多有关,也与本研究样本量较小,检验效能偏低有关,可能造成研究结果存在偏倚。但两组不良反应均以 1~2 级为主,未发生严重致死事件,提示替雷利珠单抗联合培美曲塞、卡铂方案安全性良好。

综上所述,替雷利珠单抗联合含铂双药一线治疗老年晚期肺腺癌的抗肿瘤效果较好,可改善 $CD4^+/CD8^+$平衡,调节血清 IGF-1、IGFBP-3 水平的表达,不良反应可控,治疗方案安全可靠。

利益冲突　无

参考文献

[1]　陈广英,马俊勋,胡毅.DNA 修复基因及其 TP53 共突变在肺腺癌免疫治疗疗效预测中的价值[J].肿瘤防治研究,2021,48(7):704-708.
Chen GY, Ma JX, Hu Y. Value of DNA repair gene and TP53 co-mutation in predicting effect of immunotherapy on lung adenocarcinoma[J]. Cancer Res Prev Treat, 2021, 48(7): 704-708.

[2]　关业兰,胡红林,金莹,等.帕博利珠单抗联合培美曲塞和卡铂对比培美曲塞和卡铂一线治疗晚期、非鳞状非小细胞肺癌:Ⅱ期、随机、开放研究 KEYNOTE-021G 队列研究及长期随访数据解读[J].肿瘤学杂志,2022,28(9):786-796.
Guan YL, Hu HL, Jin Y, et al. Pembrolizumab in combination with pemetrexed and carboplatin versus pemetrexed plus carboplatin for

the first-line treatment of advanced, non-squamous NSCLC: interpretation of data from the phase Ⅱ, randomized, open study KEYNOTE-021G cohort study and long-term follow up[J]. J Chin Oncol, 2022, 28(9): 786-796.

[3] 徐璐,黄栎有,王延花,等.PD-1 抑制剂联合脑部放疗治疗驱动基因阴性非小细胞肺癌脑转移的疗效及安全性分析[J].实用医学杂志,2022,38(24):3100-3105.
Xu L, Huang LY, Wang YH, et al. Efficacy and safety of PD-1 inhibitor combined with brain radiotherapy for brain metastases in patients with pan-negative non-small cell lung cancer[J]. J Pract Med, 2022, 38(24): 3100-3105.

[4] 陈美元,沈宏亮,佟昕,等.替雷利珠单抗治疗局部晚期或转移性尿路上皮癌的疗效和安全性分析[J].癌症进展,2022,20(20):2095-2097,2101.
Chen MY, Shen HL, Tong X, et al. Efficacy and safety of tislelizumab in the treatment of locally advanced or metastatic urothelial carcinoma[J]. Oncol Prog, 2022, 20(20): 2095-2097, 2101.

[5] 刘一,刘青,黄琳,等.程序性死亡受体 1 抑制剂——替雷利珠单抗[J].临床药物治疗杂志,2022,20(1):37-42.
Liu Y, Liu Q, Huang L, et al. A programmed death receptor-1 inhibitor—Tislelizumab[J]. Clin Med J, 2022, 20(1): 37-42.

[6] Sun JM, Ahn MJ, Park MJ, et al. Accuracy of RECIST 1.1 for non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors[J]. Lung Cancer, 2010, 69(1): 105-109.

[7] Liu YJ, Zhu GP, Guan XY. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma[J]. Oral Oncol, 2012, 48(6): 554-559.

[8] Zucali PA, Lin CC, Carthon BC, et al. Targeting CD38 and PD-1 with isatuximab plus cemiplimab in patients with advanced solid malignancies: results from a phase Ⅰ/Ⅱ open-label, multicenter study[J]. J Immunother Cancer, 2022, 10(1): e003697.

[9] 郑杨,帕提古力·阿尔西丁.CTLA-4 和 PD-1/PD-L1 免疫检查点抑制剂在广泛期小细胞肺癌中的研究进展[J].中国临床研究,2023,36(6):805-809.
Zheng Y, Patiguli Aerxiding. CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors in extensive stage small cell lung cancer[J]. Chin J Clin Res, 2023, 36(6): 805-809.

[10] Zhu LK, Li ZJ, Wang ZB, et al. A rare case of bladder cancer that metastasized to brain, heart, and lung lymph nodes benefited from immunotherapy[J]. World J Surg Oncol, 2022, 20(1): 1-8.

[11] Hoek KL, Greer MJ, McClanahan KG, et al. Granzyme B prevents aberrant IL-17 production and intestinal pathogenicity in $CD4^+$ T cells[J]. Mucosal Immunol, 2021, 14(5): 1088-1099.

[12] Ba W, Yang HH, Wang WJ, et al. $CD8^+$ mycosis fungoides with ichthyosiform clinical presentation and angiocentric feature[J]. J Cutan Pathol, 2022, 49(5): 487-490.

[13] 朱燕,朱永祺,张晓娟,等.肿瘤相关成纤维细胞与 $CD4^+$、$CD8^+$T 淋巴细胞在乳腺癌发生发展及淋巴结转移中的相关性研究[J].南京医科大学学报(自然科学版),2021,41(4):575-579.
Zhu Y, Zhu YQ, Zhang XJ, et al. Correlation of cancer-associated fibroblasts, $CD4^+$ and $CD8^+$ T lymphocytes with development and lymph node metastasis of breast carcinoma[J]. J Nanjing Med Univ Nat Sci, 2021, 41(4): 575-579.

[14] Zhou CC, Huang DZ, Fan Y, et al. Tislelizumab versus docetaxel in patients with previously treated advanced NSCLC (RATIONALE-303): a phase 3, open-label, randomized controlled trial[J]. J Thorac Oncol, 2023, 18(1): 93-105.

[15] Haldrup D, Wei CS, Holland-Fischer P, et al. Effects of lifestyle intervention on IGF-1, IGFBP-3, and insulin resistance in children with obesity with or without metabolic-associated fatty liver disease[J]. Eur J Pediatr, 2023, 182(2): 855-865.

[16] Kim M, Kim EY, Kim EY, et al. Investigating whether serum IGF-1 and IGFBP-3 levels reflect the height outcome in prepubertal children upon rhGH therapy: LG growth study database[J]. PLoS One, 2021, 16(11): e0259287.

[17] 欧阳长理,李智勇,李洪春.IGF-1、IGFBP-3 在非小细胞肺癌血清和组织中的表达及临床意义[J].临床肿瘤学杂志,2022,27(6):522-526.
Ouyang CL, Li ZY, Li HC. Expression and clinical significance of IGF-1 and IGFBP-3 in serum and tissues of non-small cell lung cancer[J]. Chin Clin Oncol, 2022, 27(6): 522-526.

[18] 李玮,杨永丽,胡佳佳,等.参芪扶正注射液联合含铂双药化疗治疗晚期非小细胞肺癌的疗效评价[J].中国医院药学杂志,2022,42(3):299-303.
Li W, Yang YL, Hu JJ, et al. Efficacy of Shenqi Fuzheng injection combined with platinum-based dual-drug chemotherapy for advanced non-small-cell lung cancer[J]. Chin J Hosp Pharm, 2022, 42(3): 299-303.

[19] 冯成军,张日光,韦蒙专.信迪利单抗联合同步放化疗对晚期宫颈癌患者肿瘤标志物及程序性死亡受体-1/程序性死亡配体 1 的影响[J].中华实用诊断与治疗杂志,2022,36(7):740-743.
Feng CJ, Zhang RG, Wei MZ. Effect of sintilimab combined with synchronous radiochemotherapy on tumor markers and PD-1/PD-L1 in patients with advanced cervical cancer[J]. J Clin Pract Diagn Ther, 2022,36(7):740-743.

[20] 刘俊,刘晓丹,朱立勤.替雷利珠单抗致不良反应的文献分析[J].现代药物与临床,2022,37(9):2122-2127.
Liu J, Liu XD, Zhu LQ. Literature analysis of adverse drug reactions induced by tislelizumab[J]. Drugs Clin, 2022, 37(9): 2122-2127.

[21] Zheng R, Wang BS, Li ZH, et al. Combining chemotherapy and tislelizumab with preoperative split-course hypofraction radiotherapy for locally advanced rectal cancer: study protocol of a prospective, single-arm, phase II trial[J]. BMJ Open, 2023,13(3):e066976.

[22] 张美玲,朱潇邦,宋爱玲,等.小细胞肺癌患者采用 PD-L1 抑制剂治疗致垂体炎 1 例报道并文献复习[J].诊断学理论与实践,2022,21(6):741-745.
Zhang ML, Zhu XB, Song AL, et al. PD-L1 inhibitors-induced hypophysitis in a patient with small cell lung cancer: a case report and literatures re-view[J]. J Diagn Concepts Pract, 2022, 21(6): 741-745.

收稿日期:2023-07-15　**修回日期**:2023-08-20　**编辑**:王宇