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The relationship between PD-1 inhibitor treatment-related thyroid dysfunction and serum IL-21 levels of non-small cell lung cancer

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Abstract: Objective To analyze the relationship between immune-related thyroid dysfunction (irTD) induced by programmed death protein1 (PD-1) inhibitor therapy and the serum interleukin 21 (IL-21) level in non-small cell lung cancer (NSCLC), and to provide a reference for the treatment of irTD. **Methods** A total of 114 NSCLC patients treated with PD-1 inhibitors in Shaanxi Provincial Cancer Hospital from February 2019 to April 2023 were selected. The thyroid function of all 114 patients was normal before PD-1 inhibitor treatment, and a treatment cycle of every 3 weeks was adopted. Peripheral blood was collected dynamically to detect thyroid-related hormone levels, and general data including gender, age, type of PD-1 inhibitor, disease course, pre-medication treatment history (surgery, chemotherapy, radiotherapy), and thyroid ultrasound results were collected. Forty-three cases with thyroid dysfunction were classified as the irTD group, and 71 cases without thyroid dysfunction were classified as the non-irTD group. The serum IL-21 level of the two groups was detected by enzyme-linked immunosorbent assay. **Results** (1) After PD-1 inhibitor treatment, 23 cases (53.49%) in the irTD group developed subclinical hypothyroidism, 10 cases (23.26%) developed hypothyroidism, 8 cases (18.60%) developed hyperthyroidism, and 2 cases (4.65%) developed subclinical hyperthyroidism. The irTD group had females (26 cases, 60.47%), clinical stage IV (29 cases, 67.44%), and uneven internal echo of the thyroid gland (24 cases, 55.81%), which were significantly higher than those of the control group (P<0.05). (2) Binary logistic regression analysis showed that female (OR=8.775, 95%CI:3.031-25.405), clinical stage (OR=6.204, 95%CI:2.454-15.687), and uneven internal echo of the thyroid gland (OR=9.591, 95%CI:2.144-42.913) were the influencing factors of irTD in NSCLC patients treated with PD-1 inhibitors (P<0.05). (3) The serum IL-21 level of the irTD group (238.08±15.91) pg/mL was significantly higher than that of the non-irTD group (135.15±24.39) pg/mL (t=27.25, P<0.05). (4) The serum IL-21 level of the irTD group was positively correlated with thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) (r=0.362, r=0.333, P<0.05), but not with free triiodothyronine (FT3) , free thyroxine (FT4) and thyroid stimulating hormone (TSH) (r=0.250, r=0.216, r=- 0.154, P>0.05). **Conclusion** (1) PD-1 inhibitor treatment in NSCLC patients can increase the risk of thyroid-related disorders. Female, clinical stage IV, and uneven internal echo of the thyroid gland are high-risk factors. (2) The serum IL-21 level is related to the thyroid autoantibodies levels of patients with irTD after immunotherapy in lung cancer. The serum IL-21 may be involved in the occurrence and development of irTD in lung cancer patients.

Keywords: Non-small cell lung cancer; Programmed death protein1 inhibitor; Thyroid dysfunction; Interleukin-21
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Lung cancer is the malignant tumor with the highest incidence and mortality rates globally, among which non-small cell lung cancer (NSCLC) accounts for approximately 85% [1]. In recent years, with the development of immunotherapy, immune checkpoint inhibitors (ICIs) have become one of the main treatment regimens for NSCLC. However, while exerting anti-tumor effects, they can also cause immune-related adverse effects (irAE). Immune-related thyroid dysfunction (irTD) is one of the most common endocrine adverse events, and the incidence of irTD varies widely depending on the treatment regimen, drug type, study population, and diagnostic criteria, ranging from 5% to 50% [2-4]. Interleukin (IL)-21 exerts its effects by binding to the IL-21 receptor and the common type I cytokine receptor gamma chain (γc). Previous studies have shown that IL-21 is involved in regulating the body's innate and adaptive immune responses, is closely associated with the occurrence and development of allergic reactions, inflammation, and autoimmune diseases, and also plays a role in various malignant tumors such as lung cancer, breast cancer, and gastric cancer [5]. This study analyzed the serum IL-21 levels and their relationship with irTD in 114 NSCLC patients treated with programmed death protein 1 (PD-1) inhibitors at Shaanxi Provincial Cancer Hospital, providing a basis for further in-depth exploration of the clinical application value of IL-21.

1 Data and Methods

1.1 General Data

A retrospective study was conducted on 114 NSCLC patients treated with PD-1 inhibitors at Shaanxi Provincial Cancer Hospital from February 2019 to April 2023 (Ethics Approval Number: 2022-094). Among them, there were 72

males and 42 females, aged 37–75 years.

Inclusion criteria:(1) Age > 18 years; (2) Pathologically confirmed diagnosis of NSCLC (adenocarcinoma, squamous cell carcinoma); (3) Eastern Cooperative Oncology Group (ECOG) performance status score 0–2; (4) Expected survival time > 3 months; (5) Received > 3 cycles of PD-1 immunotherapy; (6) Normal baseline thyroid function;(7) No relevant contraindications to treatment.

Exclusion criteria: (1) Abnormal baseline thyroid function; (2) Death before the 4th immunotherapy treatment;(3) Concomitant immunodeficiency or autoimmune disease with infection; (4) Participation in other clinical trials; (5) Patients managed by guardians or custodial institutions.

1.2 Research Methods

Data collected included patient gender, age, disease course, type of PD-1 inhibitor, treatment cycles, history of surgery, chemotherapy, and radiotherapy before medication, and thyroid ultrasound results. Baseline laboratory data (before the first PD-1 inhibitor infusion) were collected, including total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroglobulin antibody (TGAb), and thyroid peroxidase antibody (TPOAb). All enrolled patients had normal thyroid function before the initiation of PD-1 inhibitor treatment. With a 3-week treatment cycle, peripheral blood was dynamically collected to detect the levels of the aforementioned thyroid-related hormones. Serum TT3, TT4, FT3, FT4, and TSH levels were measured in the clinical laboratory using an automated chemiluminescence immunoassay analyzer (Siemens ADVIA Centaur XP, USA) with its reagents and calibrators. TGAb and TPOAb were measured using Roche kits (Roche Diagnostics Cobas e601, Germany) according to the instructions for use. Peripheral blood samples were obtained from patients at the end of the immunotherapy cycle via venipuncture. Serum IL-21 levels were detected using an enzyme-linked immunosorbent assay kit (purchased from Aceman Biotechnology, KTE3004).

1.3 Diagnostic Criteria

(1) Positive thyroid antibodies: At least one positive result for TGAb or TPOAb; (2) Clinical hyperthyroidism: Decreased serum TSH, elevated FT4 and FT3; (3) Subclinical hyperthyroidism: Decreased serum TSH, normal FT4 and FT3; (4) Clinical hypothyroidism: Elevated serum TSH, decreased FT4 and FT3; (5) Subclinical hypothyroidism: Elevated serum TSH, normal FT4 and FT3.

1.4 Statistical Methods

SPSS 20.0 software was used for data analysis. Measurement data were expressed as $\bar{x} \pm s$ deviation, and comparisons between groups were performed using the independent samples *t*-test. Count data were expressed as cases (%), and comparisons between groups were performed using the χ^2 test. Correlation analysis was performed using Pearson correlation analysis. $P<0.05$ was considered statistically significant.

2 Results

2.1 Baseline Characteristics

This study initially collected information on 242 NSCLC patients treated with PD-1 inhibitors. After excluding 98 patients with incomplete information, 14 patients with hypothyroidism or receiving replacement therapy before treatment initiation, and 16 patients with thyroid dysfunction due to other causes, a total of 114 patients were finally included (**Figure 1**). The PD-1 inhibitors received by the patients included: nivolumab, sintilimab, pembrolizumab, tislelizumab, toripalimab, and camrelizumab.

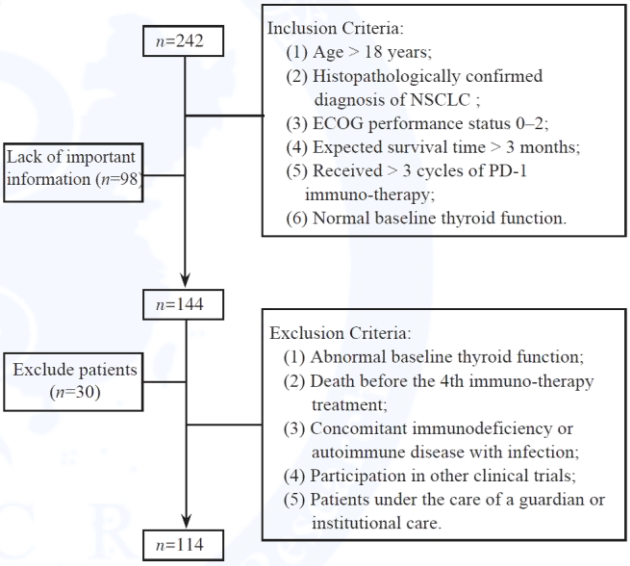

Fig.1 Flow chart of patient screening

2.2 Incidence of irTD in NSCLC Patients Treated with PD-1 Inhibitors

Among the 114 patients, 43 who developed irTD were assigned to the irTD group, and 71 who did not develop irTD were assigned to the non-irTD group. In the irTD group, after treatment, 23 cases (53.49%) developed subclinical hypothyroidism, 10 cases (23.26%) developed hypothyroidism, 8 cases (18.60%) developed hyperthyroidism, and 2 cases (4.65%) developed subclinical hyperthyroidism.

2.3 Relationship Between irTD from PD-1 Inhibitor Treatment and Clinical Characteristics of NSCLC

In the irTD group, there were 26 females (60.47%),

29 patients (67.44%) with clinical stage IV disease, and 12 patients (27.91%) with heterogeneous thyroid internal echoes on pre-treatment ultrasound. These proportions were all higher than those in the non-irTD group, with statistically significant differences (P<0.05) (**Table 1**).

Serum IL-21 levels were significantly higher in the irTD group compared with the non-irTD group (P<0.05). Based on univariate analysis, whether irTD occurred was used as the dependent variable (no irTD = 0, irTD occurred = 1), and variables with P<0.1 in the univariate analysis were used as independent variables, including: gender, TNM stage, and pre-immunotherapy thyroid ultrasound results. Binary logistic regression analysis indicated that female gender (*OR*=8.775, 95%*CI*: 3.031-25.405), TNM stage (*OR*=6.204, 95%*CI*: 2.454-15.687), and heterogeneous thyroid internal echoes (*OR*=9.591, 95%*CI*: 2.144-42.913) were influencing factors for the occurrence of irTD in NSCLC patients during PD-1 inhibitor treatment (P<0.05). (**Table 2**)

2.4 Correlation Between IL-21 Levels and Thyroid Function Levels in irTD Patients

Pearson correlation analysis showed that in patients with irTD, serum IL-21 level were positively correlated with TPOAb (r=0.362, P<0.05) and TGAb (r=0.333, P<0.05). There was no significant correlation with FT3 (r=0.250, P>0.05) and FT4 (r=0.216, P>0.05) or with TSH (r=-0.154, P>0.05) (**Table 3**).

Tab.1 Relationship between clinical features and irTD treated with PD-1 inhibitor [case (%)]

Clinical characteristics	irTD group (n=43)	Non-irTD group (n=71)	t/χ^2 value	P value
Age			0.31	0.577
≥60 years	25(58.14)	45 (63.38)		
<60 years	18 (41.86)	26(36.62)		
Gender			16.56	<0.001
Male	17 (39.53)	55 (77.46)		
Female	26 (60.47)	16 (22.54)		
PD-1 inhibitor			0.86	0.973
Pembrolizumab	9 (20.93)	13 (18.31)		
Nivolumab	8 (18.60)	12 (16.90)		
Sintilimab	7 (16.28)	14 (19.72)		
Tislelizumab	6 (13.95)	13 (18.31)		
Camrelizumab	6 (13.95)	10 (14.08)		
Toripalimab	7 (16.28)	9 (12.68)		
TNM stage			15.67	<0.001
I	0	0		
II	2 (4.65)	9 (12.68)		
III	12 (27.91)	41 (57.75)		
IV	29 (67.44)	21 (29.58)		
Disease duration			2.37	0.124
≥1 year	31 (72.09)	41 (57.75)		
<1 year	12 (27.91)	30 (42.25)		
Surgery	5 (11.63)	10 (14.08)	0.14	0.707
Yes				
No	38 (88.37)	61 (85.92)		
Radiotherapy			1.2	0.274
Yes	13 (30.23)	15 (21.13)		
No	30 (69.77)	56 (78.87)		
Chemotherapy			0.99	0.321
Yes	35 (81.40)	52 (73.24)		
No	8 (18.60)	19 (26.76)		
Thyroid color Doppler ultrasound[a]			6.28	0.012
Normal	31 (72.09)	64 (90.14)		
Abnormal	12 (27.91)	7 (9.86)		
IL-21 level ($\overline{x}$ ±s)	238.08 ± 15.91	135.15 ± 24.39	27.25	<0.001

Note: [a], before the immunotherapy.

Tab.2 The results of binary logistic regression analysis

Indicators	β	SE	Wald χ^2	P value	OR value	OR (95% CI)
Female	2.172	0.542	16.034	<0.001	8.775	3.031 - 25.405
TNM stage	1.825	0.473	14.871	<0.001	6.204	2.454 - 15.687
Abnormal thyroid color Doppler ultrasound	2.261	0.764	8.746	0.003	9.591	2.144 - 42.913

Tab.3 Correlation between IL-21 level and thyroid function in 43 patients with irTD

Indicators	r value	P value
TSH	-0.154	0.323
FT3	0.25	0.105
FT4	0.216	0.165
T3	0.169	0.279
T4	0.152	0.331
TPOAb	0.362	0.017
TGAb	0.333	0.029

3 Discussion

Currently, ICIs have become one of the main treatment methods for NSCLC. Among them, PD-1 inhibitors exert anti-tumor effects by blocking immune checkpoints to enhance tumor-specific immune responses. Currently, pembrolizumab, nivolumab, sintilimab, tislelizumab, camrelizumab, toripalimab are all widely used in the clinical treatment of NSCLC [6-7]. However, while immunotherapy activates T cells to exert anti-tumor effects, it can also activate autoimmune reactive cells, leading to irAE in patients' organs, affecting patient survival and causing a significant economic burden. Among these, thyroid dysfunction is one of the most common endocrine adverse events [3, 8].

In this study of 114 patients, the incidence of thyroid dysfunction was 37.72%. Among the 43 cases in the irTD group, 23 (53.49%) developed subclinical hypothyroidism, 10 (23.26%) developed hypothyroidism, 8 (18.60%) developed hyperthyroidism, and 2 (4.65%) developed subclinical hyperthyroidism. These results are similar to those of many previous cohort studies on thyroid irAE, although some differences exist [9-10]. In this study, subclinical hypothyroidism accounted for 53.48% (23/43) of irTD cases, making it the predominant subtype, followed by hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism in decreasing order. This trend in subtype distribution is consistent with domestic and international studies [4], but the specific proportions differ. This may be related to the relatively small sample size and the high proportion of enrolled patients with advanced-stage tumors, long disease duration, and abnormal thyroid ultrasound findings. Secondly, the baseline positivity rate of thyroid autoantibodies (such as TPOAb, TGAb) in Asian populations (especially the Chinese population) is

higher than in European and American populations. Positive autoantibodies are a risk factor for irTD (especially subclinical hypothyroidism). After immunotherapy breaks immune tolerance, the pre-existing autoimmune tendency of the thyroid is more likely to manifest as subclinical hypothyroidism rather than directly progressing to clinical hypothyroidism or hyperthyroidism. Additionally, some international studies included patients who received longer courses of immunotherapy (e.g., ≥6 cycles), whereas the average treatment course for patients in this study was relatively short (>3 cycles), which may have resulted in more patients remaining in the subclinical hypothyroidism stage. This study identified female gender, clinical stage, and heterogeneous thyroid internal echoes as influencing factors for the occurrence of irTD in NSCLC patients during PD-1 inhibitor treatment. This suggests that during the clinical application of PD-1 inhibitors, regular monitoring of patients' thyroid function and thyroid ultrasound, as well as attention to patient symptoms, is still necessary. Especially for females, patients with advanced stage, those with a history of prior chemotherapy, and those with long disease duration, the dosage should be carefully managed to avoid the occurrence of severe irTD.

Because normal thyroid tissue expresses PD-1, after treatment with PD-1 inhibitors, cytotoxic T cells can attack normal thyroid cells, destroying thyroid follicles and leading to thyroid dysfunction. However, the mechanism by which PD-1 inhibitors cause adverse thyroid reactions is not yet fully understood. Previous studies have found that some cells and cytokines may also play a role in the occurrence of irTD [11-12]. Kurimoto *et al.* [13] found elevated IL-2 and decreased granulocyte-colony stimulating factor (G-CSF) in the peripheral blood of patients who developed irTD. Since helper T cells are positively correlated with G-CSF, it is speculated that the decrease in G-CSF may be related to decreased activity of helper T cells [14]. IL-21 is a member of the cytokine family [15] and is an autocrine cytokine mainly produced by follicular helper T cells and helper T cells 17. It has been confirmed to play important roles in the immune system, such as promoting the proliferation and development of follicular helper T cells and helper T cells 17, balancing helper T cell subsets, inducing B cell generation and differentiation into plasma cells, and enhancing immunoglobulin production. These effects are mainly achieved by activating the JAK/STAT, MAPK, and PI3K pathways. Some IL-21 target genes, such as B lymphocyte-induced maturation protein-1, suppressor of cytokine signaling, C-X-C motif chemokine receptor, and B cell lymphoma 6 protein, play important roles in immune responses. Therefore, IL-21 is associated with autoimmune diseases. Previous studies have found that IL-21 levels are elevated in the peripheral blood and tissues of patients with autoimmune thyroid diseases [16-17]. However, currently no relevant research reports on the relationship between IL-21 levels and irTD, either domestically or internationally. The results of this study found that serum IL-21 levels in the irTD group were significantly higher than those in the non-irTD group. Patients' serum IL-21 levels were positively correlated with TPOAb and TGAb but showed no significant correlation with FT3, FT4, or TSH. This suggests that IL-21 may be involved in the occurrence and development of irTD, and early changes in IL-21 may predict the development of irTD. The underlying mechanisms and pathways require further investigation.

In summary, the results of this study indicate that IL-21 is an independent risk factor for irTD complicating lung cancer, and its level is closely related to TPOAb and TGAb levels, suggesting that clinical monitoring of IL-21 levels is of great significance for assessing the occurrence and development of irTD. However, this study still has some limitations. First, the sample size of included subjects is limited, and studies with larger sample sizes are needed to further validate the results. Second, the expression of IL-21 in the thyroid tissue of irTD patients and its mechanism related to the occurrence and development of irTD still require further investigation.

Conflict of Interest None

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·肺癌专题·论著·

PD-1 抑制剂治疗相关甲状腺功能障碍与非小细胞肺癌血清 IL-21 水平的关系

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摘要：目的　分析程序性死亡受体 1（PD-1）抑制剂治疗导致的免疫相关甲状腺功能障碍（irTD）与非小细胞肺癌（NSCLC）患者血清白细胞介素 21（IL-21）水平的关系，为 irTD 的治疗提供参考。**方法**　选择 2019 年 2 月至 2023 年 4 月陕西省肿瘤医院收治的经 PD-1 抑制剂治疗的 NSCLC 患者 114 例，应用 PD-1 抑制剂前 114 例患者甲状腺功能均正常，每 3 周为一个治疗周期，动态采集外周血，检测甲状腺相关激素水平，同时收集包括性别、年龄、PD-1 抑制剂类型、病程、用药前治疗史（手术、化疗、放疗）、甲状腺彩超结果等一般资料。发生甲状腺功能障碍的 43 例为 irTD 组，未发生甲状腺功能障碍的 71 例为非 irTD 组。采用酶联免疫吸附实验检测两组患者血清 IL-21 水平。**结果**　（1）irTD 组治疗后发生亚临床甲状腺功能减退（甲减）23 例（53.49%）、甲减 10 例（23.26%）、甲状腺功能亢进（甲亢）8 例（18.60%）、亚临床甲亢 2 例（4.65%）。irTD 组女性 26 例（60.47%）、临床分期为 IV 期 29 例（67.44%）、甲状腺内部回声不均匀 12 例（27.91%），较对照组更高，差异有统计学意义（P<0.05）。（2）二元 logistic 回归分析显示，女性（OR=8.775，95%CI：3.031~25.405）、临床分期高（OR=6.204，95%CI：2.454~15.687）、甲状腺内部回声不均匀（OR=9.591，95%CI：2.144 ~42.913）为 NSCLC 患者在 PD-1 抑制剂治疗中发生 irTD 的危险因素（P<0.05）。（3）irTD 组血清 IL-21 水平显著高于非 irTD 组［（238.08±15.91）pg/mL *vs* （135.15±24.39）pg/mL，t=27.25，P<0.05）］。（4）irTD 组血清 IL-21 水平与甲状腺过氧化物酶抗体（TPOAb）、甲状腺球蛋白抗体（TGAb）呈正相关（r=0.362，r=0.333，P<0.05），与游离三碘甲状腺原氨酸（FT3）、游离甲状腺素（FT4）以及促甲状腺激素（TSH）无明显相关性（r=0.250，r=0.216，r=−0.154，P>0.05）。**结论**　（1）NSCLC 患者 PD-1 抑制剂治疗可导致甲状腺相关疾病风险升高，女性、临床分期 IV 期，甲状腺内部回声不均匀为高风险因素。（2）血清 IL-21 水平与肺癌 irTD 患者的甲状腺自身抗体水平相关，血清 IL-21 可能参与了 NSCLC 患者 irTD 的发生发展。

关键词：非小细胞肺癌；程序性死亡受体 1 抑制剂；甲状腺功能障碍；白细胞介素 21

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The relationship between PD-1 inhibitor treatment-related thyroid dysfunction and serum IL-21 levels of non-small cell lung cancer

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Abstract: Objective　To analyze the relationship between immune-related thyroid dysfunction (irTD) induced by programmed death protein 1 (PD-1) inhibitor therapy and the serum interleukin 21 (IL-21) level in non-small cell lung cancer (NSCLC), and to provide a reference for the treatment of irTD. **Methods**　A total of 114 NSCLC patients treated with PD-1 inhibitors in Shaanxi Provincial Cancer Hospital from February 2019 to April 2023 were selected. The thyroid function of all 114 patients was normal before PD-1 inhibitor treatment, and a treatment cycle of every 3 weeks was adopted. Peripheral blood was collected dynamically to detect thyroid-related hormone levels, and general data

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including gender, age, type of PD-1 inhibitor, disease course, pre-medication treatment history (surgery, chemotherapy, radiotherapy), and thyroid ultrasound results were collected. Forty-three cases with thyroid dysfunction were classified as the irTD group, and 71 cases without thyroid dysfunction were classified as the non-irTD group. The serum IL-21 level of the two groups was detected by enzyme-linked immunosorbent assay. **Results** (1) After PD-1 inhibitor treatment, 23 cases (53.49%) in the irTD group developed subclinical hypothyroidism, 10 cases (23.26%) developed hypothyroidism, 8 cases (18.60%) developed hyperthyroidism, and 2 cases (4.65%) developed subclinical hyperthyroidism. The irTD group had 60.47% females (26 cases), 67.44% clinical stage Ⅳ (29 cases), and 27.91% uneven internal echo of the thyroid gland (12 cases), which were significantly higher than those of the control group (P<0.05). (2) Binary logistic regression analysis showed that female (OR=8.775, 95%CI: 3.031-25.405), high clinical stage (OR=6.204, 95%CI: 2.454-15.687), and uneven internal echo of the thyroid gland (OR=9.591, 95%CI: 2.144-42.913) were the risk factors of irTD in NSCLC patients treated with PD-1 inhibitors (P<0.05). (3) The serum IL-21 level of the irTD group was significantly higher than that of the non-irTD group [(238.08±15.91) pg/mL *vs* (135.15±24.39) pg/mL, t=27.25, P<0.05)]. (4) The serum IL-21 level of the irTD group was positively correlated with thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) (r=0.362, r=0.333, P<0.05), but not with free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) (r=0.250, r=0.216, r=-0.154, P>0.05). **Conclusion** (1) PD-1 inhibitor treatment in NSCLC patients can increase the risk of thyroid-related disorders. Female, clinical stage Ⅳ, and uneven internal echo of the thyroid gland are high-risk factors. (2) The serum IL-21 level is related to the thyroid autoantibodies levels of patients with irTD after immunotherapy in lung cancer. The serum IL-21 may be involved in the occurrence and development of irTD in lung cancer patients.

Keywords: Non-small cell lung cancer; Programmed death protein 1 inhibitor; Thyroid dysfunction; Interleukin-21

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肺癌是全球发病率及死亡率最高的恶性肿瘤，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)约占85%[1]。近年来，随着免疫治疗的发展，免疫检查点抑制剂(immune checkpoint inhibitors，ICIs)成为NSCLC的主要治疗方案之一。但其在发挥抗肿瘤作用时也会造成免疫相关不良反应(immune-related adverse effect，irAE)，免疫相关甲状腺功能障碍(immune-related thyroid dysfunction，irTD)是其中最常见的内分泌不良事件之一，irTD的发生率因治疗方案、药物类型、研究人群与诊断标准不同差异较大，为5%~50%[2-4]。白细胞介素(interleukin，IL)21可通过与IL-21受体和常见的Ⅰ型细胞因子受体γ链(γc)结合发挥作用。既往研究表明，IL-21参与调节机体的先天性和获得性免疫反应，与过敏反应、炎症以及自身免疫性疾病的发生发展密切相关，同时在肺癌、乳腺癌、胃癌等多种恶性肿瘤中发挥作用[5]。本研究对陕西省肿瘤医院收治的经程序性死亡受体1(programmed death protein 1，PD-1)抑制剂治疗的NSCLC患者114例血清IL-21水平及与irTD的关系进行分析，为进一步深入探讨IL-21的临床应用价值提供基础。

1 资料与方法

1.1 *一般资料* 回顾性研究2019年2月至2023年4月陕西省肿瘤医院收治的经PD-1抑制剂治疗的NSCLC患者114例(伦理审查批号：2022-094)。其中男性72例，女性42例，年龄37~75(50.12±11.24)岁。纳入标准：(1)年龄>18岁；(2)经病理学检查确诊为NSCLC(腺癌、鳞癌)；(3)美国东部肿瘤协作组(Eastern Cooperative Oncology Group，ECOG)评分0~2分；(4)预计生存时间>3个月；(5)经PD-1免疫治疗>3周期；(6)基线甲状腺功能正常；(7)无相关治疗禁忌证。排除标准：(1)基线甲状腺功能异常者；(2)第4次免疫治疗前死亡；(3)伴有免疫缺陷或自身免疫性疾病伴感染；(4)参加了其他临床试验；(5)由监护人或托管机构管理的患者。

1.2 *研究方法* 收集患者性别、年龄、病程、PD-1抑制剂类型及剂量、用药周期、用药前手术史、化疗史、放疗史、甲状腺彩超结果等相关数据。收集基线(PD-1单抗第1次输注前)实验室数据，包括血总三碘甲状腺原氨酸(total triiodothyronine，TT3)、总甲状腺素(total thyroxine，TT4)、游离三碘甲状腺原氨酸(free triiodothyronine，FT3)、游离甲状腺素(free thyroxine，FT4)、促甲状腺激素(thyroid stimulating hormone，TSH)、甲状腺球蛋白抗体(thyroglobulin antibody，TGAb)、甲状腺过氧化物酶抗体(thyroid peroxidase antibody，TPOAb)等指标。应用PD-1抑制剂前纳入患者的甲状腺功能均正常，每3周为1个治疗周期，动态采集外周血，检测上述甲状腺相关激素水

平。检验科实验室采用自动化化学发光免疫分析仪（西门子 ADVIA Centaur XP，美国）及其配套试剂和校准品测量血清 TT3、TT4、FT3、FT4 和 TSH 水平。TGAb、TPOAb 按照使用说明书采用罗氏试剂盒（罗氏诊断 Cobas e601，德国）测定。通过静脉穿刺获得患者免疫治疗周期末外周血样本，通过酶联免疫吸附实验试剂盒（购于亚科因生物技术有限公司，货号：KTE3004）检测患者血清 IL-21 水平。

1.3　判定标准　（1）甲状腺抗体阳性：TGAb、TPOAb 至少一个阳性；（2）临床甲状腺功能亢进（甲亢）：血清 TSH 降低，FT4、FT3 升高；（3）亚临床甲亢：血清 TSH 降低，FT4、FT3 正常；（4）临床甲状腺功能减退（甲减）：血清 TSH 升高，FT4、FT3 降低；（5）亚临床甲减：血清 TSH 升高，FT4、FT3 正常。

1.4　统计学方法　采用 SPSS 20.0 软件分析数据。计量资料以 $\bar{x}\pm s$ 表示，组间比较采用独立样本 t 检验；计数资料以例（%）表示，组间比较行 χ^2 检验。相关性采用 Pearson 相关系数分析。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　基线特征　本研究共收集 242 例接受 PD-1 抑制剂治疗的 NSCLC 患者信息，排除了信息不完整的患者 98 例，治疗开始前存在甲状腺功能减退或替代治疗的患者 14 例，及其他原因致甲状腺功能障碍的患者 16 例，最终共纳入患者 114 例（图 1）。患者接受的 PD-1 抑制剂类型包括：纳武利尤单抗、信迪利单抗、帕博利珠单抗、替雷利珠单抗、特瑞普利单抗、卡瑞利珠单抗。

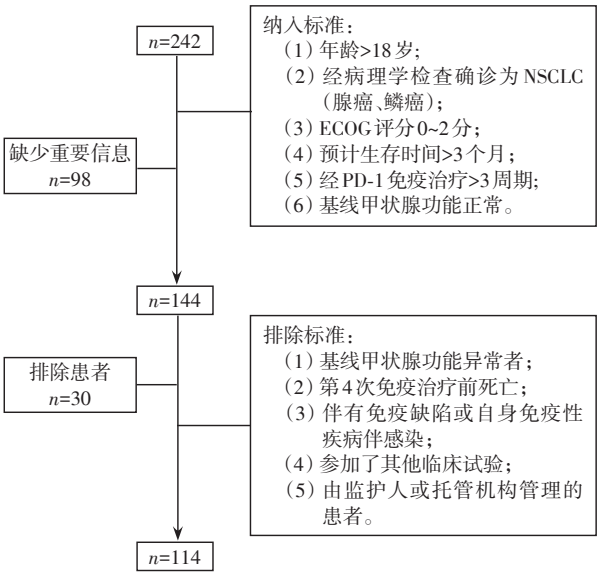

图 1　患者筛选流程图

Fig.1　Flow chart of patient screening

2.2　NSCLC PD-1 抑制剂治疗 irTD 发生率　114 例患者中发生 irTD 的 43 例为 irTD 组，未发生 irTD 的 71 例为非 irTD 组。irTD 组治疗后发生亚临床甲减 23 例（53.49%）、甲减 10 例（23.26%）、甲亢 8 例（18.60%）、亚临床甲亢 2 例（4.65%）。

2.3　PD-1 抑制剂治疗 irTD 与 NSCLC 临床特征的关系　irTD 组女性 26 例（60.47%）、临床分期为Ⅳ期 29 例（67.44%）、甲状腺内部回声不均匀 12 例（27.91%），均高于非 irTD 组，差异有统计学意义（$P<0.05$）。irTD 组患者血清 IL-21 水平显著高于非 irTD 组（$P<0.05$）。见表 1。以单因素分析为基础，将是否发生 irTD 作为因变量（未发生 irTD=0，发生 irTD=1），将

表 1　患者临床特征与 PD-1 抑制剂治疗 irTD 的关系　［例（%）］

Tab.1　Relationship between clinical features and irTD treated with PD-1 inhibitors　［case (%)］

临床特征	总例数（n=114）	irTD 组（n=43）	非 irTD 组（n=71）	χ^2/t 值	P 值
年龄					
≥60 岁	70(61.40)	25(58.14)	45(63.38)	0.31	0.577
<60 岁	44(38.60)	18(41.86)	26(36.62)		
性别					
男性	72(63.16)	17(39.53)	55(77.46)	16.56	<0.001
女性	42(36.84)	26(60.47)	16(22.54)		
PD-1 抑制剂类型					
帕博利珠单抗	22(19.30)	9(20.93)	13(18.31)		
纳武利尤单抗	20(17.54)	8(18.60)	12(16.90)		
信迪利单抗	21(18.42)	7(16.28)	14(19.72)	0.86	0.973
替雷利珠单抗	19(16.67)	6(13.95)	13(18.31)		
卡瑞利珠单抗	16(14.04)	6(13.95)	10(14.08)		
特瑞普利单抗	16(14.04)	7(16.28)	9(12.68)		
TNM 分期					
Ⅰ	0	0	0		
Ⅱ	11(9.65)	2(4.65)	9(12.68)	15.67	<0.001
Ⅲ	53(46.49)	12(27.91)	41(57.75)		
Ⅳ	50(43.86)	29(67.44)	21(29.58)		
病程					
≥1 年	72(63.16)	31(72.09)	41(57.75)	2.37	0.124
<1 年	42(36.84)	12(27.91)	30(42.25)		
手术					
是	15(13.16)	5(11.63)	10(14.08)	0.14	0.707
否	99(86.84)	38(88.37)	61(85.92)		
放疗					
是	28(24.56)	13(30.23)	15(21.13)	1.20	0.274
否	86(75.44)	30(69.77)	56(78.87)		
化疗					
是	87(76.32)	35(81.40)	52(73.24)	0.99	0.321
否	27(23.68)	8(18.60)	19(26.76)		
甲状腺彩超结果[a]					
正常	95(83.33)	31(72.09)	64(90.14)	6.28	0.012
异常	19(16.67)	12(27.91)	7(9.86)		
IL-21(pg/mL)[b]	173.97±54.53	238.08±15.91	135.15±24.39	27.25	<0.001

注：[a]为免疫治疗前；[b]为数据以 $\bar{x}\pm s$ 表示。

单因素分析中P<0.1的变量作为自变量，包括性别、TNM分期、免疫治疗前甲状腺彩超结果，多因素logistic回归分析结果显示，女性（OR=8.775，95%CI：3.031~25.405）、TNM分期高（OR=6.204，95%CI：2.454~15.687）、甲状腺内部回声不均匀（OR=9.591，95%CI：2.144~42.913）为NSCLC患者在PD-1抑制剂治疗中发生irTD的危险因素（P<0.05）。见表2。

2.4 IL-21水平与irTD患者甲状腺功能水平相关性 经Pearson相关性分析，irTD组血清IL-21水平与TPOAb、TGAb呈正相关（r=0.362，r=0.333，P<0.05），与FT3、FT4（r=0.250，r=0.216，P>0.05）及TSH无明显相关性（r=−0.154，P>0.05）。见表3。

表2 多因素logistic回归分析结果

Tab.2 The results of multivariate logistic regression analysis

项目	β	SE	Wald χ^2	P值	OR	95%CI
女性	2.172	0.542	16.034	<0.001	8.775	3.031~25.405
TNM分期	1.825	0.473	14.871	<0.001	6.204	2.454~15.687
免疫治疗前甲状腺彩超异常	2.261	0.764	8.746	0.003	9.591	2.144~42.913

表3 irTD组患者IL-21水平与甲状腺功能的相关性

Tab.3 Correlation between IL-21 level and thyroid function in patients with irTD

项目	IL-21
TSH	r=−0.154，P=0.323
FT3	r=0.250，P=0.105
FT4	r=0.216，P=0.165
TT3	r=0.169，P=0.279
TT4	r=0.152，P=0.331
TPOAb	r=0.362，P=0.017
TGAb	r=0.333，P=0.029

3 讨 论

目前ICIs已成为NSCLC主要治疗方法之一，其中PD-1抑制剂可通过阻断免疫检查点增强肿瘤特异性免疫反应而发挥抗肿瘤作用，目前包括帕博利珠单抗、信迪利单抗、纳武利尤单抗、替雷利珠单抗、特瑞普利单抗及卡瑞利珠单抗均广泛用于NSCLC临床治疗[6-7]。但免疫治疗在激活T细胞发挥抗肿瘤效应的同时也会激活自身免疫反应细胞，从而导致患者的脏器出现irAE，影响患者生存并造成较重经济负担，其中甲状腺功能障碍是最为常见的内分泌不良事件之一[3,8]。

在本研究114例患者中，甲状腺功能障碍的发生率为37.72%（43/114），43例病例组中发生亚临床甲减23例（53.49%）、甲减10例（23.26%）、甲亢8例（18.60%）、亚临床甲亢2例（4.65%），与此前多项甲状腺irAE队列研究结果相似，但存在一定差异[9-10]。本研究亚临床甲减占irTD病例的53.48%（23/43），为最主要亚型，甲减、甲亢、亚临床甲亢占比依次降低，与国内外研究的亚型分布趋势一致[4]，但具体比例存在差异，可能与样本量较小及纳入患者中晚期肿瘤、长病程及甲状腺彩超异常者占比高有关。其次，亚洲人群（尤其中国人群）基线甲状腺自身抗体（如TPOAb、TGAb）阳性率高于欧美人群，而自身抗体阳性是irTD（尤其亚临床甲减）的危险因素，免疫治疗打破免疫耐受后，已存在的甲状腺自身免疫倾向更易表现为亚临床甲减，而非直接进展为临床甲减或甲亢，且部分国外研究纳入的患者免疫治疗疗程更长（如≥6周期），而本研究纳入患者平均疗程较短（>3周期），可能导致更多患者停留在亚临床甲减阶段。本研究中显示女性、临床分期高、甲状腺内部回声不均匀为NSCLC患者在PD-1抑制剂治疗中发生irTD的危险因素。提示在临床应用PD-1抑制剂时，仍需对患者甲状腺功能及甲状腺超声进行定期监测并关注患者症状，尤其对于女性、分期晚、既往有化疗史以及长病程的患者，应把控给药剂量以避免严重irTD的发生。

由于正常甲状腺组织表达PD-1，因此在接受PD-1抑制剂治疗后，细胞毒性T细胞可攻击正常的甲状腺细胞，破坏甲状腺滤泡从而导致甲状腺功能障碍。但PD-1抑制剂引起甲状腺不良反应的机制尚未完全明确。既往研究发现一些细胞及细胞因子在irTD的发生过程中也可能发挥作用[11-12]。Kurimoto等[13]在发生irTD患者的外周血中，发现IL-2升高而粒细胞集落刺激因子（granulocyte-colony stimulating factor，G-CSF）降低。由于辅助性T细胞与G-CSF呈正相关，猜测G-CSF的降低可能与辅助性T细胞的活性降低有关[14]。IL-21是细胞因子家族中的一员[15]，是一种主要由滤泡辅助性T细胞和辅助性T细胞17产生的自分泌细胞因子，已被证实对免疫系统具有重要作用，例如促进滤泡辅助性T细胞和辅助性T细胞17的增殖和发育、平衡辅助性T细胞亚群、诱导B细胞生成并分化为浆细胞，以及增强免疫球蛋白的产生。这些作用主要通过激活JAK/STAT、MAPK和PI3K通路来实现。一些IL-21目标基因，如B淋巴细胞诱导成熟蛋白-1、细胞因子信号抑制因子、C-X-C基序趋化因子受体和B细胞淋巴瘤6蛋白，对免疫反应起着重要作用。因此，IL-21与自身免疫性疾病有关。既往研究发现自身免疫性甲状腺疾病患者外周血和组

织中，IL-21 水平会升高[16-17]。但关于 IL-21 水平与 irTD 的关系，目前国内外仍无相关研究报道。本研究结果发现 irTD 组患者血清 IL-21 水平显著高于非 irTD 水平。患者血清 IL-21 水平与 TPOAb、TGAb 呈正相关，与 FT3、FT4 及 TSH 无显著相关性，提示 IL-21 可能参与 irTD 的发生发展，IL-21 的早期变化可能预示着 irTD 的发展，其背后机制及通路亟待进一步研究。

综上，本研究结果表明 IL-21 是肺癌合并 irTD 的独立危险因素，且其水平与 TPOAb、TGAb 水平密切相关，提示临床监测 IL-21 水平对评估 irTD 发生、发展具有重要意义。但本研究仍存在一些不足之处，首先，研究对象纳入样本数量有限，需要更大样本量的研究来进一步验证结果，其次，IL-21 在 irTD 患者甲状腺组织中的表达情况及其与 irTD 发生发展的机制仍有待进一步研究。

利益冲突　无

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