Thyroid dysfunction during PD-1 inhibitor treatment in patients with cancer: Incidence and association with progression-free survival

YANFEI WU[1*], ZHI WANG[2*], HONGXIA BAI[3] and YAN GAO[4]

Departments of [1]Pathology and [2]Nuclear Radiation Injury Protection and Treatment, Navy Medical Center of People Liberation Army, Naval Medical University, Shanghai 200433; [3]Department of Pulmonary and Critical Care Medicine, Baotou Central Hospital, Baotou, Inner Mongolia Autonomous Region 014040; [4]Department of Nuclear Medicine, Baotou Tumor Hospital, Baotou, Inner Mongolia Autonomous Region 014030, P.R. China

Received January 7, 2022; Accepted March 22, 2022

DOI: 10.3892/ol.2022.13429

Abstract. The use of programmed cell death-1 (PD-1) inhibitors has recently been approved in China. As a consequence, the identification of relevant prognostic markers that can assess the efficacy of these compounds is required. Therefore, the present study aimed to explore the incidence of thyroid dysfunction and its ability to predict progression-free survival (PFS) in Chinese patients with cancer who received PD-1 inhibitor treatment. Data from 72 patients with cancer who received treatment with PD-1 inhibitors alone or in combination with chemotherapy or targeted drugs were analyzed. Moreover, the expression levels of free triiodothyronine, thyroxine, and thyrotropin during treatment were assessed to evaluate thyroid dysfunction. A total of 26 (36.1%) patients who had received PD-1 inhibitors developed thyroid dysfunction. Specifically, the incidence of thyroid dysfunction was 35.6% in patients with lung cancer, 25.0% in patients with malignant melanoma, and 46.7% in patients with other types of cancer. In addition, the median PFS was 7.0 (95% confidence interval, 4.9-9.1) months, whereas the 1- and 2-year PFS rates were 35.1 and 26.2%, respectively. Generally, patients with thyroid dysfunction exhibited longer PFS compared with those without thyroid dysfunction (P=0.001). Subgroup analyses were subsequently performed, which demonstrated that thyroid dysfunction was associated with longer PFS in patients with malignant melanoma (P=0.039) and other types of cancer (P=0.002), but not in those with lung cancer (P=0.083). These findings were noted in patients who received PD-1 inhibitor monotherapy (P=0.003), but not PD-1 inhibitor plus chemotherapy (P=0.172) or PD-1 inhibitor plus targeted therapy (P=0.582). Finally, thyroid dysfunction [P=0.001; hazard ratio (HR)=0.260] and PD-1 inhibitor monotherapy (P=0.015; HR=2.231) were identified as independent factors that could predict PFS. In conclusion, the present study demonstrated that thyroid dysfunction during PD-1 inhibitor treatment could be used as a potential marker for the prognosis of favorable PFS in patients with cancer.

Correspondence to: Dr Hongxia Bai, Department of Pulmonary and Critical Care Medicine, Baotou Central Hospital, 61 Huancheng Road, Donghe, Baotou, Inner Mongolia Autonomous Region 014040, P.R. China
E-mail: huanggang21558@163.com

Dr Yan Gao, Department of Nuclear Medicine, Baotou Tumor Hospital, 18 Tuanjie Street, Qingshan, Baotou, Inner Mongolia Autonomous Region 014030, P.R. China
E-mail: gongtang9614@163.com

*Contributed equally

Key words: thyroid dysfunction, PD-1 inhibitor, cancer patients, independent factors, progression-free survival

Introduction

Programmed cell death-1 (PD-1), also termed CD279, is a key co-inhibitory receptor expressed on T cells that functions as a T cell checkpoint and plays a vital role in inhibiting cancer cell proliferation (1-3). The binding of PD-1 to programmed death-ligand 1 (PD-L1) on activated T cells inhibits antitumor immunity and mediates immune escape (4-7). Moreover, treatment with PD-1 inhibitors suppresses the PD-1/PD-L1 interaction and restores the T cell-mediated antitumor immune responses, which promotes the killing of cancer cells (8). In recent years, PD-1 inhibitor therapy has been regarded as a promising strategy for various types of cancer, which is mainly administrated as a monotherapy, monotherapy plus chemotherapy, or monotherapy plus targeted therapy (5,9-11). Although the aforementioned therapeutic approaches open new horizons in tumor immunotherapy, the number of prognostic markers for the assessment of PD-1 inhibitor efficacy remains insufficient (12).

Immunological adverse events may occur during PD-1 inhibitor treatment, among which thyroid dysfunction is one of the most common (13,14). Thyroid dysfunction is easily ignored

due to its asymptomatic nature or milder symptoms compared with the severe symptoms of cancer itself (15). In addition, certain studies have shown that thyroid dysfunction during PD-1 inhibitor treatment correlates with prolonged survival in cancer. For example, it has been reported that patients who develop thyroid dysfunction during pembrolizumab treatment for non-small cell lung cancer (NSCLC) exhibit improved overall survival (OS) (16); patients with renal cell carcinoma, metastatic melanoma, and NSCLC who acquire overt thyroid dysfunction during nivolumab or pembrolizumab treatment also exhibit a satisfactory survival profile (17).

However, since the use of PD-1 inhibitors has been approved in China for only three years, relevant data are very limited or even unavailable. Therefore, the aim of the present study was to investigate the incidence of thyroid dysfunction and its relationship with progression-free survival (PFS) in Chinese patients with cancer in a clinical setting. In addition, key indices of thyroid function were assessed during PD-1 inhibitor treatment in these patients.

Materials and methods

Patients. A total of 72 patients who were treated in Baotou Tumor Hospital and Bayannur City Hospital between March 2018 and July 2020 were enrolled in the present study. The inclusion criteria used were the following: i) Use of PD-1 inhibitors for tumor treatment; ii) availability of the data from thyroid function assessment during treatment with PD-1 inhibitors; iii) availability of PFS data; and iv) pathological diagnosis of cancer. The patients were excluded from the present study according to the following criteria: i) Lack of available clinical characteristic data; ii) history of thyroid diseases or known thyroid dysfunction prior to treatment with PD-1 inhibitors. Written informed consent was obtained from all patients. The present study was approved by the Internal Review Boards of Baotou Center Hospital (approval no. 2018-4).

Data collection. The clinical characteristics of the patients were collected from their medical records. The collected clinical data were as follows: i) Demographic characteristics, which included age, sex, and history of smoking; ii) cancer type, which included lung cancer, malignant melanoma, and other types; iii) disease characteristics, including tumor-node-metastasis (TNM) stage and brain metastasis; iv) tumor markers; v) biochemical indexes; and vi) treatment, including PD-1 inhibitors (pembrolizumab, nivolumab, toripalimab, camrelizumab, and sintilimab) and combined treatment. In addition, PFS was estimated based on the follow-up data, and the final date of follow-up was November 10, 2020.

Thyroid dysfunction assessment. According to the clinical records, serum samples were collected prior to every second administration (every 4 or 6 weeks). The samples were used to perform serum thyroid function tests and assess the levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyrotropin (TSH). Thyroid dysfunction was evaluated at the first occurrence of thyroid function abnormality on the basis of the serum thyroid function tests. Thyroid dysfunction was defined as hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism in accordance with a previous study (18). Hyperthyroidism was defined as a decreased TSH level, and an elevated FT3 and/or FT4 level; subclinical hyperthyroidism was defined as suppressed TSH with normal FT3 and/or FT4 levels. Hypothyroidism was defined as an increased TSH level and a decreased FT3 and/or FT4 level; subclinical hypothyroidism was defined by a TSH level above the upper limit of the reference range with an FT3 and/or FT4 level within the reference range. The reference ranges for FT3, FT4 and TSH were 2.3-4.0 pg/ml, 12-24 pmol/l, and 0.27-4.2 μIU/ml, respectively.

Statistical analysis. SPSS 26.0 (IBM Corp.) and GraphPad Prism 7.02 (GraphPad Software Inc.) were used for data analysis and graph production. The comparisons of thyroid dysfunction and clinical characteristics were performed using an unpaired Student's t-test, and a χ^2 and Wilcoxon rank-sum tests. PFS was analyzed using Kaplan-Meier curves and compared with a log-rank test between the different groups of patients. PFS was defined as the time from the first day of administration of immunotherapeutic drugs to the date of the first documentation of disease progression, loss of follow-up, or patient death. The patients who were lost to follow-up were censored at the last visit date. The prognostic factors were determined by the multivariate Cox proportional-hazard regression model analysis. All tests were two-sided, and a $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics. A total of 72 patients with cancer who received PD-1 inhibitors were recruited. Their clinical characteristics are shown in Table I. In brief, the mean age of these patients was 59.6±12.7 years. Among them, 47 (65.3%) patients were males and 25 (34.7%) were females. With respect to cancer type, 45 (62.5%) patients had lung cancer, 12 (16.7%) presented with malignant melanoma, and 15 (20.8%) had other types of cancer. The mean levels of FT3, FT4 and TSH were 4.23±0.92 pg/ml, 16.51±3.47 pmol/l, and 4.36±4.75 μIU/ml, respectively. Moreover, the number of patients who received PD-1 inhibitor monotherapy, PD-1 inhibitors plus chemotherapy, or PD-1 inhibitors plus targeted therapy were 42 (58.3%), 18 (25.0%), and 12 (16.7%), respectively. The detailed administration schedule of the PD-1 inhibitors is shown in Table SI.

Thyroid dysfunction incidence. In total, 26 (36.1%) patients developed thyroid dysfunction, which were all hypothyroidism. The incidence of thyroid dysfunction was 35.6% in patients with lung cancer, 25.0% in patients with malignant melanoma, and 46.7% in patients with other types of cancer (Fig. 1). Moreover, 23 patients received L-thyroxine for the treatment of hypothyroidism.

Association between clinical characteristics and the incidence of thyroid dysfunction. Subsequently, the association between clinical characteristics and thyroid dysfunction was examined in patients who received PD-1 inhibitor therapy. The results indicated that the levels of cancer antigen 125 were downregulated in patients with thyroid dysfunction ($P=0.037$).

Table I. Clinical characteristics of the patients.

A, Demographic characteristics

Parameter	Value
Mean age ± SD, years	59.6±12.7
Sex, n (%)	
Male	47 (65.3)
Female	25 (34.7)
Ethnic group, n (%)	
Han	72 (100.0)
Others	0 (0.0)
History of smoking, n (%)	24 (33.3)

B, Cancer type

Parameter	Value
Lung cancer, n (%)	45 (62.5)
ADC	20 (27.8)
SCC	17 (23.6)
SCLC	8 (11.1)
Malignant melanoma, n (%)	12 (16.7)
Others[a], n (%)	15 (20.8)

C, Disease characteristics

Parameter	Value
TNM stage, n (%)	
I/II/III	15 (20.8)
IV	57 (79.2)
Brain metastases, n (%)	
Yes	19 (26.4)
No	53 (73.6)

D, Tumor markers

Parameter	Value
Median CEA (IQR), ng/ml	3.6 (2.0-6.8)
Median CA125 (IQR), U/ml	17.4 (11.0-58.1)
Median SCCA (IQR), ng/ml	1.8 (1.2-18.4)
Median NSE (IQR), ng/ml	24.1 (10.8-62.5)
Median LDH (IQR), U/l	189.5 (163.5-236.0)

E, Thyroid function indexes

Parameter	Value
Mean FT3 ± SD, pg/ml	4.23±0.92
Mean FT4 ± SD, pmol/l	16.51±3.47
Mean TSH ± SD, μIU/ml	4.36±4.75

Table I. Continued.

F, Treatment

Parameter	Value
PD-1 inhibitor monotherapy, n (%)	42 (58.3)
PD-1 inhibitor plus chemotherapy, n (%)	18 (25.0)
PD-1 inhibitor plus targeted therapy, n (%)	12 (16.7)

[a]Bladder cancer, gallbladder cancer, malignant pleural mesothelioma, liver cancer, esophageal cancer, gastric cancer, malignant mesenchymoma, rectum cancer and angiosarcoma. ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; TNM, Tumor-Node-Metastasis; CEA, carcinoembryonic antigen; IQR, interquartile range; CA125, cancer antigen 125; SCCA, squamous cell carcinoma antigen; NSE, neuron-specific enolase; LDH, lactic dehydrogenase; PD-1, programmed cell death-1; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotropin.

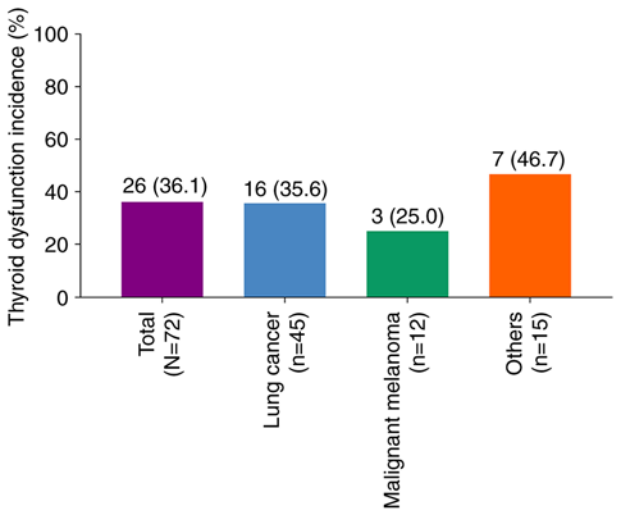

Figure 1. Thyroid dysfunction incidence. The incidence of thyroid dysfunction in all patients, and individually in patients with lung cancer, malignant melanoma and other cancer types.

However, none of the other examined characteristics differed between patients who developed thyroid dysfunction and those who did not (all P>0.05; Table II).

Association of thyroid dysfunction with PFS. The median PFS of all patients who received PD-1 inhibitors was 7.0 [95% confidence interval (CI), 4.9-9.1] months. In addition, the 1- and 2-year PFS rates of these patients were 35.1 and 26.2%, respectively (Fig. 2A). Moreover, the median PFS (95% CI) values of patients with lung cancer, malignant melanoma, and other types of cancer were 7.0 (4.5-9.5) months, 9.0 (3.4-14.6) months, and 3.0 (1.4-4.6) months, respectively. There were no significant differences in the PFS of patients with different cancer types (P>0.05; Fig. 2B).

The patients with thyroid dysfunction had a longer PFS (median, 18.0 months; 95% CI, not reached) compared with those without thyroid dysfunction (median, 5.0 months; 95% CI:

Table II. Clinical characteristics by thyroid dysfunction status groups.

Items	Thyroid dysfunction		P-value
	No (n=46)	Yes (n=26)	
Mean age ± SD, years	57.5±14.4	63.3±8.1	0.062
Sex, n (%)			0.309
Male	32 (69.6)	15 (57.7)	
Female	14 (30.4)	11 (42.3)	
History of smoking, n (%)			0.386
Yes	17 (37.0)	7 (26.9)	
No	29 (63.0)	19 (73.1)	
Disease type, n (%)			0.503
Lung cancer	29 (63.0)	16 (61.5)	
Malignant melanoma	9 (19.6)	3 (11.5)	
Others	8 (17.4)	7 (26.9)	
Lung cancer, n (%)			0.992
ADC	13 (44.8)	7 (43.8)	
SCC	11 (37.9)	6 (37.5)	
SCLC	5 (17.2)	3 (18.8)	
TNM stage, n (%)			0.119
I/II/III	7 (15.2)	8 (30.8)	
IV	39 (84.8)	18 (69.2)	
Brain metastases, n (%)			0.699
Yes	13 (28.3)	6 (23.1)	
No	33 (71.7)	20 (76.9)	
Median CEA (IQR), ng/ml	3.6 (2.1-6.8)	3.5 (2.0-5.7)	0.548
Median CA125 (IQR), U/ml	27.0 (13.8-90.3)	12.0 (6.7-17.1)	0.037
Median SCCA (IQR), ng/ml	1.6 (1.0-43.5)	1.8 (1.4-18.4)	0.498
Median NSE (IQR), ng/ml	24.9 (8.7-57.9)	14.4 (11.1-66.4)	0.935
Median LDH (IQR), U/l	192.0 (136.8-236.8)	185.5 (168.5-204.3)	0.836
Treatment, n (%)			0.835
PD-1 inhibitor monotherapy	28 (60.9)	14 (53.8)	
PD-1 inhibitor plus chemotherapy	11 (23.9)	7 (26.9)	
PD-1 inhibitor plus targeted therapy	7 (15.2)	5 (19.2)	

ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; TNM, tumor-node-metastasis; CEA, carcinoembryonic antigen; IQR, interquartile range; CA125, cancer antigen 125; SCCA, squamous cell carcinoma antigen; NSE, neuron-specific enolase; LDH, lactic dehydrogenase; PD-1, programmed cell death-1.

3.2-6.8 months) (P=0.001; Fig. 2C). Furthermore, subgroup analysis demonstrated that thyroid dysfunction was associated with longer PFS in patients with malignant melanoma (P=0.039) and other cancer types (P=0.002), but not in patients with lung cancer (P=0.083; Fig. 3A-C). Moreover, thyroid dysfunction was associated with improved PFS in patients who received monotherapy with PD-1 inhibitors (P=0.003; Fig. 3D). However, no association was found between thyroid dysfunction and PFS in patients who received PD-1 inhibitors plus chemotherapy (P=0.172; Fig. 3E) or those who received PD-1 inhibitors plus targeted therapy (P=0.582; Fig. 3F).

Factors affecting PFS. Univariate Cox regression analysis indicated that thyroid dysfunction was the only factor associated with a longer PFS [yes vs. no; P=0.003; hazard ratio (HR)=0.350]. In addition, multivariate Cox regression analysis indicated that thyroid dysfunction (yes vs. no; P=0.001; HR=0.260) served as an independent factor for satisfactory PFS, while monotherapy with PD-1 inhibitors compared with PD-1 inhibitor plus chemotherapy or targeted therapy (P=0.015; HR=2.231) served as an independent factor for unsatisfactory PFS (Table III).

Discussion

The conclusions of the present study can be summarized as follows: i) The incidence of thyroid dysfunction was 36.1%; ii) thyroid dysfunction was associated with longer PFS in patients with

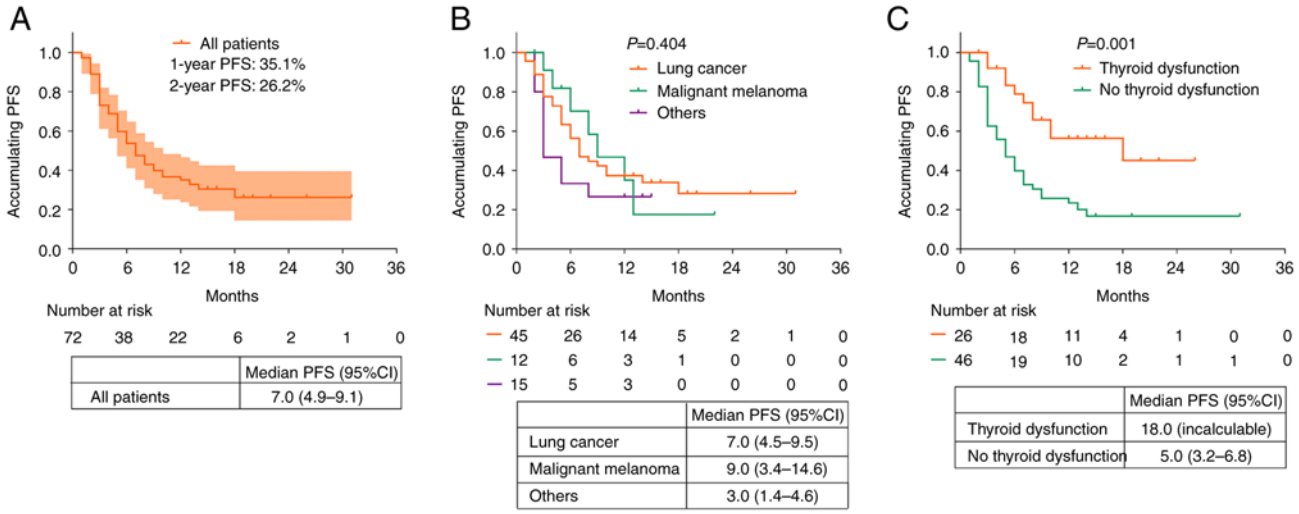

Figure 2. PFS in patients with cancer who received PD-1 inhibitor treatment. PFS of all patients who received PD-1 inhibitors. (A) Comparison of PFS in patients with lung cancer, malignant melanoma, and other cancer types. (B) Comparison of PFS between patients with and without thyroid dysfunction. (C) PFS, progression-free survival; PD-1, programmed cell death-1; CI, confidence interval.

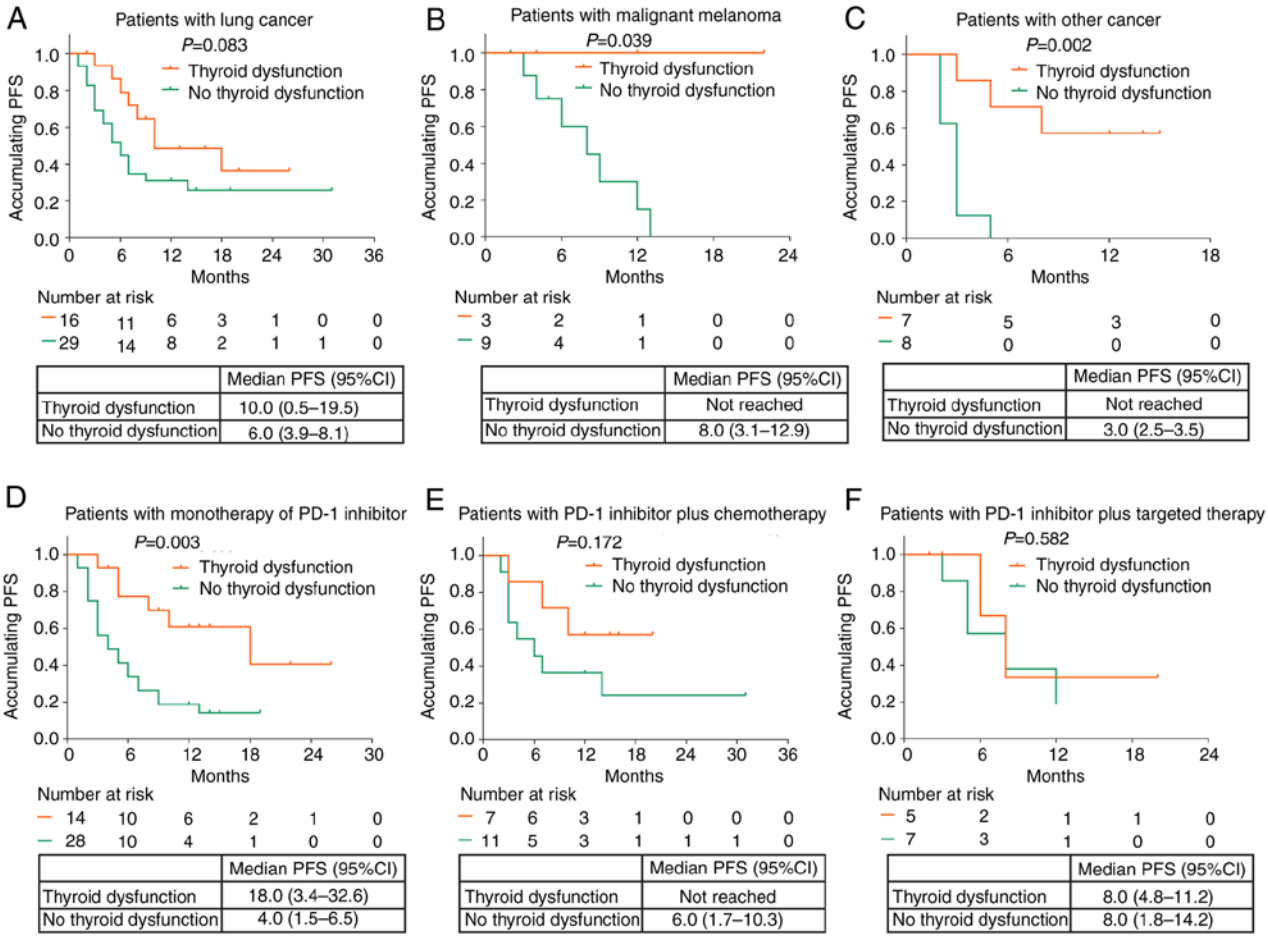

Figure 3. Subgroup analysis of PFS. Association of thyroid dysfunction with PFS in patients with (A) lung cancer, (B) malignant melanoma, and (C) other cancer types. Association of thyroid dysfunction with accumulating PFS in patients who received (D) monotherapy with PD-1 inhibitors, (E) PD-1 inhibitors plus chemotherapy, and (F) PD-1 inhibitors plus targeted therapy. PFS, progression-free survival; PD-1, programmed cell death protein 1; CI, confidence interval.

malignant melanoma and other cancer types, as well as in patients who received PD-1 inhibitor monotherapy; moreover, thyroid dysfunction served as an independent factor for satisfactory PFS.

With respect to thyroid dysfunction incidence in cancer patients who received PD-1 inhibitors, a previous study demonstrated that among patients who received PD-1 inhibitors,

Table III. Cox proportional-hazards regression analysis of factors affecting PFS.

	Univariate Cox regression		Multivariate Cox regression	
Parameter	P-value	HR (95% CI)	P-value	HR (95% CI)
Thyroid dysfunction (yes vs. no)	0.003	0.350 (0.177-0.691)	0.001	0.260 (0.115-0.585)
Age (vs. ≥70 years)				
≥70 years	Reference		Reference	
60-69 years	0.088	2.506 (0.873-7.195)	0.098	2.740 (0.831-9.038)
50-59 years	0.088	2.404 (0.878-6.585)	0.069	3.110 (0.916-10.566)
<50 years	0.966	0.978 (0.348-2.747)	0.754	1.203 (0.377-3.836)
Sex (male vs. female)	0.510	1.223 (0.672-2.225)	0.209	1.627 (0.762-3.472)
History of smoking (yes vs. no)	0.306	0.724 (0.391-1.343)	0.077	0.539 (0.272-1.069)
Cancer type (vs. others)				
Others	Reference		Reference	
Lung cancer	0.238	0.656 (0.326-1.321)	0.110	0.501 (0.215-1.168)
Malignant melanoma	0.302	0.606 (0.234-1.568)	0.053	0.344 (0.117-1.013)
TNM stage (IV vs. I/II/III)	0.185	1.675 (0.781-3.595)	0.460	1.402 (0.572-3.434)
Brain metastases (yes vs. no)	0.345	1.352 (0.722-2.531)	0.391	1.395 (0.652-2.986)
PD-1 inhibitor monotherapy (yes vs. no)	0.361	1.315 (0.730-2.369)	0.015	2.231 (1.172-4.247)

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; TNM, Tumor-Node-Metastasis; PD-1, programmed cell death-1.

9 (7.5%) had melanoma and 5 (7.1%) lung cancer, whereas only 2 (6.5%) patients with renal cell carcinoma developed thyroid dysfunction (16). In another previous study involving 150 patients with cancer who received PD-1 inhibitor treatment, 25 out of 150 (16.7%) patients experienced thyroid dysfunction during treatment (19). In the present study, it was shown that 26 (36.1%) patients developed thyroid dysfunction after PD-1 inhibitor treatment. The incidence of thyroid dysfunction was 35.6% in patients with lung cancer, 25.0% in patients with malignant melanoma and 46.7% in patients with other cancer types. Compared with previous studies, the incidence of thyroid dysfunction was relatively high. Possible explanations could include the following: i) The definitions of thyroid dysfunction differed between our study and previous ones (16,19); ii) the patient demographics differed between the studies; or iii) come patients in the present study received PD-1 inhibitors combined with chemotherapy or targeted therapy, which may have aggravated thyroid injury. However, the current study showed that there was no association between baseline characteristics of cancer patients and thyroid dysfunction. A possible explanation might be that thyroid dysfunction is closely related to PD-1 inhibitor treatment, but not the characteristics of cancer patients. However, another study suggests that the incidence of thyroid dysfunction is higher in patients with head and neck cancer treated with chemotherapy (20); thus the correlation of characteristics with thyroid dysfunction needs to be further verified.

With regards to the association between thyroid dysfunction and the survival outcome in patients with cancer who received PD-1 inhibitors, a previous study revealed that patients with cancer who were treated with pembrolizumab and developed thyroid dysfunction exhibited a higher median OS than those without thyroid dysfunction (40 months vs. 14 months) (21). Another study indicated that patients with NSCLC and thyroid dysfunction who received PD-1 inhibitors exhibited significantly higher OS and PFS than those without thyroid dysfunction (22). In addition, patients with NSCLC, renal cell carcinoma and metastatic melanoma who received PD-1 inhibitors and acquired overt thyroid dysfunction exhibited improved OS and PFS than those without thyroid dysfunction (17). In the present study, general, thyroid dysfunction was associated with a longer PFS in Chinese patients receiving PD-1 inhibitors, which was similar to previous studies focusing of Caucasian cancer patients receiving PD-1 inhibitors (23,24). Thus, it could be deduced that the prognostic value of thyroid dysfunction was not affected by ethnicity, although further studies should verify this hypothesis. Moreover, our study also found that thyroid dysfunction was an independent factor for a higher PFS in Chinese patients who received PD-1 inhibitors. This could be explained by the fact that patients with thyroid dysfunction presented with a higher susceptibility to autoimmunity. This may affect antitumor treatment through an autoimmune-mediated pathway and improve the therapeutic effects, contributing to a higher PFS (17). In addition, based on subgroup analysis, it was found that the prognostic value of thyroid dysfunction was high in patients with melanoma and other cancer types and in patients who received PD-1 inhibitor monotherapy. Possible explanations include the fact that the majority of enrolled patients with NSCLC received combined therapy, which attenuated the predictive value of thyroid dysfunction with regard to the therapeutic effect of the PD-1 inhibitors.

Despite the aforementioned findings, certain limitations are apparent in the present study. Firstly, the sample size was small, which may lead to limited representativeness of the results. However, the use of PD-1 inhibitors has been recently

approved in China and this sample size was relatively large under this circumstance. Secondly, the mechanism of thyroid dysfunction during PD-1 inhibitor treatment was not investigated. Therefore, further *in vivo* and *in vitro* experiments are required. Thirdly, the association of thyroid dysfunction with prognosis in cancer patients without the treatment of PD-1 inhibitors could be investigated in the future.

In conclusion, the present study revealed that thyroid dysfunction occurred in 36.1% of patients with cancer who underwent PD-1 inhibitor treatment and was associated with prolonged PFS, notably in those who received PD-1 inhibitor monotherapy. These findings suggest that thyroid dysfunction may serve as a potential prognostic marker to guide patient management. Further studies with larger sample sizes should be conducted to verify these findings.

Acknowledgements

Not applicable.

Funding

The present study was supported by The Wu Jieping Medical Foundation (grant no. 320.6750.2020-19-37).

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HB and YG contributed to the conception and design of the study. YW contributed to performing the experiments. ZW contributed to data acquisition and analysis. YW and ZW contributed to the preparation of the manuscript. HB and YG confirm the authenticity of all the raw data. All authors contributed to the review of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Internal Review Boards of Baotou Center Hospital (approval no. 2018-4). Written informed consent was obtained from all patients

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Jiang Y, Chen M, Nie H and Yuan Y: PD-1 and PD-L1 in cancer immunotherapy: Clinical implications and future considerations. Hum Vaccin Immunother 15: 1111-1122, 2019.
2. Ai L, Xu A and Xu J: Roles of PD-1/PD-L1 pathway: Signaling, cancer, and beyond. Adv Exp Med Biol 1248: 33-59, 2020.
3. Han Y, Liu D and Li L: PD-1/PD-L1 pathway: Current researches in cancer. Am J Cancer Res 10: 727-742, 2020.
4. Kythreotou A, Siddique A, Mauri FA, Bower M and Pinato DJ: Pd-L1. J Clin Pathol 71: 189-194, 2018.
5. Ni JM and Ni AP: Landscape of PD-1/PD-L1 regulation and targeted immunotherapy. Chin Med Sci J 33: 174-182, 2018.
6. Gou Q, Dong C, Xu H, Khan B, Jin J, Liu Q, Shi J and Hou Y: PD-L1 degradation pathway and immunotherapy for cancer. Cell Death Dis 11: 955, 2020.
7. Sun C, Mezzadra R and Schumacher TN: Regulation and function of the PD-L1 checkpoint. Immunity 48: 434-452, 2018.
8. Xie W, Medeiros LJ, Li S, Yin CC, Khoury JD and Xu J: PD-1/PD-L1 pathway and its blockade in patients with classic hodgkin lymphoma and non-hodgkin large-cell lymphomas. Curr Hematol Malig Rep 15: 372-381, 2020.
9. Wu X, Gu Z, Chen Y, Chen B, Chen W, Weng L and Liu X: Application of PD-1 blockade in cancer immunotherapy. Comput Struct Biotechnol J 17: 661-674, 2019.
10. Feng M, Xiong G, Cao Z, Yang G, Zheng S, Song X, You L, Zheng L, Zhang T and Zhao Y: PD-1/PD-L1 and immunotherapy for pancreatic cancer. Cancer Lett 407: 57-65, 2017.
11. Hayashi H and Nakagawa K: Combination therapy with PD-1 or PD-L1 inhibitors for cancer. Int J Clin Oncol 25: 818-830, 2020.
12. Salmaninejad A, Valilou SF, Shabgah AG, Aslani S, Alimardani M, Pasdar A and Sahebkar A: PD-1/PD-L1 pathway: Basic biology and role in cancer immunotherapy. J Cell Physiol 234: 16824-16837, 2019.
13. D'Andrea G, Lassalle S, Guevara N, Mograbi B and Hofman P: From biomarkers to therapeutic targets: The promise of PD-L1 in thyroid autoimmunity and cancer. Theranostics 11: 1310-1325, 2021.
14. Manolis AA, Manolis TA, Melita H and Manolis AS: Subclinical thyroid dysfunction and cardiovascular consequences: An alarming wake-up call? Trends Cardiovasc Med 30: 57-69, 2020.
15. Chalan P, Di Dalmazi G, Pani F, De Remigis A, Corsello A and Caturegli P: Thyroid dysfunctions secondary to cancer immunotherapy. J Endocrinol Invest 41: 625-638, 2018.
16. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, Rodriguez C, Cambridge L, Rizvi H, Wolchok JD, *et al*: Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 28: 583-589, 2017.
17. Basak EA, van der Meer JWM, Hurkmans DP, Schreurs MWJ, Oomen-de Hoop E, van der Veldt AAM, Bins S, Joosse A, Koolen SLW, Debets R, *et al*: Overt thyroid dysfunction and anti-thyroid antibodies predict response to anti-PD-1 immunotherapy in cancer patients. Thyroid 30: 966-973, 2020.
18. Wolffenbuttel BHR, Wouters HJCM, Slagter SN, van Waateringe RP, Muller Kobold AC, van Vliet-Ostaptchouk JV, Links TP and van der Klauw MM: Thyroid function and metabolic syndrome in the population-based LifeLines cohort study. BMC Endocr Disord 17: 65, 2017.
19. Sakakida T, Ishikawa T, Uchino J, Chihara Y, Komori S, Asai J, Narukawa T, Arai A, Kobayashi T, Tsunezuka H, *et al*: Clinical features of immune-related thyroid dysfunction and its association with outcomes in patients with advanced malignancies treated by PD-1 blockade. Oncol Lett 18: 2140-2147, 2019.
20. Endo K, Masatani T, Tsuji A, Kondo S, Wakisaka N, Murono S and Yoshizaki T: Thyroid dysfunction after intra-arterial chemotherapy for hypopharyngeal and laryngeal cancer. Auris Nasus Larynx 42: 231-234, 2015.
21. Breimer LH, Nousios P, Olsson L and Brunnström H: Immune checkpoint inhibitors of the PD-1/PD-L1-axis in non-small cell lung cancer: Promise, controversies and ambiguities in the novel treatment paradigm. Scand J Clin Lab Invest 80: 360-369, 2020.
22. Zhou Y, Xia R, Xiao H, Pu D, Long Y, Ding Z, Liu J and Ma X: Thyroid function abnormality induced by PD-1 inhibitors have a positive impact on survival in patients with non-small cell lung cancer. Int Immunopharmacol 91: 107296, 2021.
23. Chmielewska I, Dudzińska M, Szczyrek M, Świrska J, Wojas-Krawczyk K and Zwolak A: Do endocrine adverse events predict longer progression-free survival among patients with non-small-cell lung cancer receiving nivolumab? PLoS One 16: e0257484, 2021.
24. Frelau A, Jali E, Campillo-Gimenez B, Pracht M, Porneuf M, Dinulescu M, Edeline J, Boussemart L and Lesimple T: Prognostic impact of thyroid dysfunctions on progression-free survival in patients with metastatic melanoma treated with anti-PD-1 antibodies. Melanoma Res 31: 208-217, 2021.