Development of thyroid dysfunction is associated with clinical response to PD-1 blockade treatment in patients with advanced non-small cell lung cancer

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ABSTRACT

Purpose: Drugs that blockade interaction between programmed cell-death protein 1 (PD-1) and its ligand (PD-L1) are promising. Immune-related adverse events (irAEs) might be associated with favorable clinical outcomes, and thyroid dysfunction is one of the most common irAE. We evaluated the association of thyroid dysfunction during PD-1 blockade with the treatment efficacy in patients with non-small cell lung cancer (NSCLC).

Experimental Design: A total 58 patients with stage IV NSCLC treated with PD-1 blockade were enrolled. Patients were categorized into thyroid dysfunction and euthyroid groups. Overall survival (OS) and progression-free survival (PFS) of the two groups were compared. Patients, tumor, and medication factors were adjusted using Cox proportional hazard modeling. Objective response rate (RR) and durable control rate were assessed according to the severity of thyroid dysfunction.

Results: OS [median 118.0 (73.0-267.0) vs. 71.0 (28.0-160.0) days, log-rank P = 0.025] and PFS [118.0 (73.0-267.0) vs. 61.0 (28.0-130.0) days, log-rank P = 0.014] were longer in the thyroid dysfunction group. After adjustment, thyroid dysfunction was an independent predictive factor for favorable outcome [adjusted HR = 0.11 (95% CI) 0.01-0.92 for overall death; 0.38 (0.17-0.85) for disease progression]. The severity of thyroid dysfunction was associated with durable control rate (P for trend = 0.008).

Conclusions: Thyroid dysfunction during PD-1 blockade is associated with treatment response and can provide supplementary information for immune monitoring in patients with advanced NSCLC.

Introduction

Immune checkpoint inhibitors are currently in the spotlight as promising therapeutics for advanced non-small cell lung cancer (NSCLC). Among these drugs, nivolumab and pembrolizumab, which are classified as blockade for programmed cell-death protein 1 (PD-1) and its ligand (PD-L1) are recently approved as standard drugs for subsequent treatment of NSCLC patients by FDA.

Compared to molecular targeted agents, the response rate to PD-1 blockade is low (15-30%), but also maintained for a long period of time. Programmed cell-death protein ligand 1 (PD-L1) has been known as a biomarker which is associated with favorable clinical response, but the measurement is not widely available.

It is noteworthy that thyroiditis, which is one of the most common immune-related adverse event (irAE), is associated with the mechanism of the antitumor effect of immunotherapy, and can be easily monitored with a thyroid function test (TFT) in a clinical setting. In patients treated with several other drugs, side effects related to drug mechanisms such as skin rash after epidermal growth factor receptor tyrosine kinase inhibitor use (EGFR-TKIs) or vitiligo and thyroiditis after IL-2 treatment are associated with a good prognosis. Interestingly, Dr. Osorio et al. recently reported that thyroid dysfunction after pembrolizumab in NSCLC patients was associated with longer OS in an unadjusted analysis. However, to our knowledge, the association between thyroid dysfunction and clinical response in NSCLC patients treated with PD-1 blockade has not been thoroughly evaluated in an independent cohort, and it is unclear whether this phenomenon is characteristic of the entire PD-1 drug class. The aim of this study was to evaluate the association between thyroid dysfunction during PD-1 blockade treatment and the efficacy of PD-1 blockade in patients with NSCLC.
Baseline characteristics of the 58 patients (41 patients in open-label clinical trial and 17 patients outside clinical trial) with stage IV NSCLC are listed in Table 1. The median age was 63.1 years (IQR 49.0-68.0) and 43 patients (74.1%) were male. The median follow-up period after treatment with PD-1 blockade was 89.0 days (IQR 42.0-170.0). There was no significant difference in age, sex, current or former smoking status, pathological subtype, cancer staging at drug start, and type of medications between the euthyroid group and thyroid dysfunction group.

Clinical features of thyroid dysfunction during PD-1 blockade treatment

Thyroid dysfunction was persistently observed in 19 of 58 patients (32.7%). Similar to previous studies,14,15 the median time to first development of thyroid dysfunction was 40.0 days (IQR 28.0-61.0). In 10 (52.6%) of these cases, thyroid dysfunction initially presented as subclinical or overt hypothyroidism, and most of them persisted in hypothyroidism status except one patient who converted to subclinical thyrotoxicosis due to over-use of levothyroxine. In contrast to this pattern, the remaining 9 patients (47.3%) developed subclinical or overt thyrotoxicosis first. Six of them rapidly progressed to hypothyroidism whereas the other 3 patients with relatively short follow up duration remained subclinical thyrotoxicosis throughout the treatment period.

According to serum thyroid stimulating hormone (TSH) and free T4 (FT4) levels, overt thyroid dysfunction developed in 10 patients (55.5%); 4 patients had overt hypothyroidism and 4 patients had overt thyrotoxicosis. The other 2 patients progressed to overt hypothyroidism after suffering from overt thyrotoxicosis. The remaining 9 patients in the thyroid dysfunction group developed only subclinical thyroid dysfunction during follow-up.

Response to PD-1 blockade treatment according to the development of thyroid dysfunction

During the median 89 days of follow-up, 13 patients (22.4%) died, including 1 patient (5.2%) in the thyroid dysfunction group and 12 patients (30.7%) in the euthyroid group. OS was significantly longer in the thyroid dysfunction group than in the euthyroid group (P = 0.025; Fig. 1A). In multivariate analysis, development of thyroid dysfunction was an independent prognostic factor for OS (adjusted HR = 0.11, 95% CI 0.01-0.92, P = 0.041, Table 2). Age, sex, smoking status, pathological subtype, cancer staging at drug start, and type of medications were not associated with OS.

The median PFS of the thyroid dysfunction and euthyroid groups was 118.0 (IQR 73.0-267.0) and 61.0 days (IQR 28.0-130.0), respectively. There was a significant difference in PFS between the two groups (P = 0.014; Fig. 1B). Similar to OS, development of thyroid dysfunction was the only independent prognostic factor (adjusted HR = 0.38, 95% CI 0.17-0.85, P = 0.018, Table 2) while age, sex, smoking status, pathological subtype, cancer staging at drug start, and type of medications were not.

In addition, the thyroid dysfunction group had significantly higher durable control rate (15.8% vs. 0.0%, P = 0.011) and objective RR (31.6% vs. 10.3%, P = 0.044) compared to the euthyroid group (Fig. 2A and B).

Table 1. Baseline clinical characteristics of patients with stage IV NSCLC who underwent PD-1 blockade treatment.

| Characteristics                  | All patients (N = 58) | Euthyroid group (N = 39) | Thyroid dysfunction group (N = 19) | p-value |
|----------------------------------|-----------------------|--------------------------|-----------------------------------|---------|
| Age, median(IQR)                 | 63.1 (49.0-68.0)      | 63.0 (49.0-68.0)         | 63.3 (52.9-68.0)                  | 0.602   |
| Male sex, n (%)                  | 43 (74.1)             | 29 (74.4)                | 14 (72.7)                         | 0.956   |
| Smoking status                   |                       |                          |                                   | 0.894   |
| Current or ex-smoker             | 39 (67.2)             | 26 (66.7)                | 13 (68.4)                         |         |
| Never smoker                     | 19 (32.8)             | 13 (33.3)                | 6 (31.6)                          |         |
| Pathological subtype             |                       |                          |                                   | 0.150   |
| SqCC                             | 20 (34.5)             | 11 (28.2)                | 9 (47.4)                          |         |
| Non-SqCC                         | 38 (65.5)             | 28 (71.8)                | 10 (52.6)                         |         |
| Cancer staging at drug start     |                       |                          |                                   | 0.624   |
| Stage IV, M1a                    | 24 (41.4)             | 17 (43.6)                | 7 (36.8)                          |         |
| Stage IV, M1b                    | 34 (58.6)             | 22 (56.4)                | 12 (63.2)                         | 0.375   |
| PD-1 blockade                    |                       |                          |                                   |         |
| Nivolumab                        | 52 (89.7)             | 34 (87.2)                | 18 (94.7)                         |         |
| Pembrolizumab                    | 6 (10.3)              | 5 (12.8)                 | 1 (5.3)                           |         |

SqCC, squamous cell carcinoma; PD-1, Programmed cell-death protein 1 and its ligand.
Response to PD-1 blockade treatment according to the severity of thyroid dysfunction

By CTCAE 4.0 criteria, all patients in the thyroid dysfunction group were classified into grade 1 or 2 irAEs. After re-classification of thyroid dysfunction based on both serum TSH and FT4 levels, 10 patients were placed in the overt thyroid dysfunction group (both serum TSH and FT4 levels beyond the normal reference range) and 9 in the subclinical thyroid dysfunction group (only serum TSH levels beyond the normal reference range).

Kaplan Meier curves for OS (P = 0.075) and PFS (P = 0.049) revealed differences among the three groups. A significant trend between the severity of thyroid dysfunction and OS (P for trend = 0.026) or PFS (P for trend = 0.016) was observed (Table 3). There was also a significant trend between the severity of thyroid dysfunction and durable control rate (P for trend = 0.008, Fig 2D) whereas objective RR (P for trend = 0.074, Fig 2C) and severity of thyroid dysfunction did not reach the statistical significance.

| Variable | HR (95% CI)       | p-value |
|----------|------------------|---------|
| OS       | Thyroid dysfunction | 0.11 (0.01-0.92) | 0.041* |
| PFS      | Thyroid dysfunction | 0.38 (0.17-0.85) | 0.018* |

*Multivariate Cox regression analysis with backward elimination procedure. Model: thyroid dysfunction, age, sex, current or former smoking status, pathological subtypes, staging at the starting point, and type of medications. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

**Discussion**

In this study, thyroid dysfunction during PD-1 blockade treatment was associated with longer OS and PFS, with adjustment of other factors. Objective response and durable control, which were related to unique response patterns to PD-1 blockade, were more common in the thyroid dysfunction group. This was the first study to demonstrate that thyroid dysfunction was an independent factor related to treatment response of PD-1 blockade in advanced NSCLC patients in a severity-dependent manner.

PD-1 blockade acts as a novel immunotherapy for metastatic malignancies by inhibiting the mechanism by which cancer cells avoid host T-cells. However, in the process of activating host T cells against malignant antigens, inhibition of checkpoint blockade may also lead to an attack toward other tissues. Consequently, PD-1 blockade can result in irAEs, a unique spectrum of adverse effects related to autoimmune tissue destruction, and thyroid-related irAEs are common. In the present study, thyroid dysfunction related to PD-1 blockade treatment occurred in 19 (32.7%) patients, with a median time to onset of 40 days from the start of drugs. This could be an overestimation of the real incidence of thyroid-related irAEs in PD-1 treatment considering that pembrolizumab therapy has been associated with a 12–14% incidence of thyroid-related irAEs in previous studies. But recent studies report an incidence of over 20% (95% confidence interval 10% to 35%) for thyroid dysfunction after PD-1 blockade treatment, and ethnic difference might have contributed to the higher prevalence rate in this study. The clinical course of thyroid dysfunction was similar to previous studies; most patients with...
thyroid dysfunction progressed to hypothyroidism with or without a previous transient hyperthyroidism period. Our findings are consistent with a mechanism of acute inflammation followed by destruction of the thyroid gland.

It is important to note that this side effect of PD-1 blockade is closely related to the anti-tumor mechanism. For many other drugs, side effects associated with drug mechanisms are a herald of good prognosis. A meta-analysis of skin rash and outcomes of NSCLC with EGFR-TKIs treatment found a significant association between skin rash and favorable outcomes. In IL-2 treatment of metastatic melanoma, many studies have shown that immunologic side effects such as vitiligo and thyroiditis correlate with good clinical response to IL-2 therapy. Furthermore, a meta-analysis of immune checkpoint inhibitor therapy in melanoma found that vitiligo (skin irAE) was significantly associated with both longer PFS and OS, although thyroiditis was not in another study. In contrast to melanoma, however, less is known about irAEs as a prognostic factor in NSCLC. A recent study of thyroid dysfunction after pembrolizumab in NSCLC patients suggested the possibility that OS is related to thyroid dysfunction, without adjustment. In the present study, thyroid dysfunction during PD-1 blockade treatment was an independent protective factor for overall death and disease progression after adjusting for patient, tumor, and drug factors. In particular, this association could be suggested as a class characteristic for PD-1 blockade in real clinical settings, because the two drugs in this study are representative of PD-1 blockade agents approved by FDA.

Thyroid dysfunction reflects not only conventional clinical outcomes like OS and PFS, but also the unique pattern of response to PD-1 blockade. The response patterns of PD-1 blockade are quite different from conventional chemotherapy or molecular target therapy; the response rate is low (15-30%), but demonstrates a durable control in responders, known as the long “tail” of survival of curves or “exceptional responders”. Because of this unique feature, the milestone PFS rate at specific late time point (that is, durable control) better reflects the benefit of PD-1 blockade. Although debate exists, cancer cell expression of PD-L1 as measured by immunohistochemistry (IHC) or T-cell infiltration has been suggested as a biomarker predicting response before treatment begins. In our data of real clinical practice, there were only 7 patients that had accessible record of PD-L1 IHC measurement. Among 4 patients whose tumor cells did not express PD-L1 [IHC negative (Tumor proportion score < 50%)], one patient with thyroid dysfunction had relatively long PFS (141 days) though negative PD-L1 IHC, which was longer than those of 3 patients without thyroid dysfunction (46, 11, and 139 days). Of the 3 patients with positive PD-L1 IHC, one patient without thyroid dysfunction showed relatively short PFS (89 days) compared to 2 patients with thyroid dysfunction (287 and 115 days).

In the present study, thyroid dysfunction during PD-1 blockade treatment was associated with objective response and durable control in a severity-dependent manner. Unlike the euthyroid group in which no one showed a durable control, 20% of the overt thyroid dysfunction group had a good response. These findings suggest that patients with overt thyroid dysfunction after use of PD-1 blockade might be “exceptional responders” with high probability. In a study of prognostic factors in the response to CTLA-4 blockade in melanoma, the duration of response was longer in patients who experienced high-grade irAEs, which supports our data. In the case of other irAEs, assessing the severity by CTC-AE has the disadvantage of poor reproducibility depending on the physician in charge, because there are no objective criteria for symptoms, treatment, or admission decisions. However, the severity of thyroid dysfunction could be assessed objectively based on TSH and free T4 levels.

We carried out the same analysis with alternative definition of thyroid dysfunction (elevated TSH ≥10.00 mU/L with or without low FT4, which is ‘overt hypothyroidism’ in recent report) as a part of sensitivity analysis. By alternative definition, 12 patients (20.6%) were categorized into thyroid dysfunction group. Thyroid dysfunction was still associated with fewer disease progression [Log-rank P = 0.054, adjusted HR 0.37 (0.14-0.98), P = 0.046] and higher durable control rate (16.7% vs. 2.2%, P = 0.044). Median OS was longer in thyroid dysfunction group although the difference did not reach statistical significance [Log-rank P = 0.152, adjusted HR 0.22 (0.03-1.76), P = 0.158]. These consistent results between existing and alternative definitions of thyroid dysfunction support the validity of our main findings. However, thyroid dysfunction by alternative definition has no association with objective RR (25.0% vs. 15.2%, P = 0.424) (Supplementary Table 1). Coupled with evidence that clinical significance of minor fluctuation in thyroid function is unclear, discordant results about objective RR suggested that this topic need to be substantiated by additional research.

The strength of the present study was the first demonstration of thyroid dysfunction as an independent prognostic factor of PD-1 blockade class efficacy in NSCLC. Although the significant association between thyroid dysfunction and clinical outcomes in this multicenter study was impressive, the results should be validated with further large prospective patient cohorts. However, the fact that treatment efficacy was associated with thyroid dysfunction in a severity-dependent manner suggests that transient destruction of thyroid tissue might be closely connected with the release of harnessed antitumor immunity by the immune checkpoint blockades. Because of the small number of enrolled patients, we could not perform a stratified analysis according to individual medications, which might discern different impacts of thyroid dysfunction on

Table 3. Trend analysis of overall survival and progression-free survival according to the severity of thyroid dysfunction.

| Variables | Overt thyroid dysfunction group | Subclinical thyroid dysfunction group | Euthyroid group | p-trend |
|-----------|-------------------------------|-------------------------------------|----------------|--------|
| OS, median (IQR), days | 128.0 (108.2-342.0) | 73.0 (33.5-211.0) | 71.0 (28.0-160.0) | 0.026* |
| PFS, median (IQR), days | 128.0 (108.2-342.0) | 73.0 (24.5-211.0) | 61.0 (28.0-130.0) | 0.016* |

*Jonckheere-Terpstra test.

OS, overall survival; PFS, progression-free survival.
treatment response. We expect that TFT may not be a substitute for IHC measurement of PD-L1 because thyroid dysfunction could not be identified before starting treatment. Given the convenience of TFT which can be easily assessed without tissue specimen unlike the PD-L1 IHC, thyroid dysfunction could be a good complementary measure that foretells PD-1 blockade efficacy. In addition, there is a possibility of higher response rate in patients with other irAE than no irAE although it is not covered in this study. However, it should be considered that the majority of them needs immunosuppression clinically which might blunt an immune response.

In conclusion, thyroid dysfunction, especially overt thyroid dysfunction, in early course of PD-1 blockade use was associated with treatment response in patients with advanced NSCLC. For patient safety and more exact immune monitoring, clinicians should keep in mind that regular testing of thyroid hormones before and during the course of PD-1 immunotherapy, especially during first 1–3 months after beginning of treatment, is important.

Materials and method

Study subjects

Patients who underwent serial thyroid function tests during treatment for metastatic NSCLC (stage IV) with nivolumab or pembrolizumab from January 2014 to December 2016 were included in this study. Patients with thyroid dysfunction before starting PD-1 blockade therapy (n = 3), transient change of TFT defined as spontaneous normalization without levothyroxine treatment (n = 2) were excluded. We also excluded the patients who underwent TFT not routinely (N = 9). A total of 58 patients from two tertiary referral institutions in Korea were enrolled [35 patients from Samsung Medical Center (SMC) and 23 from Asan Medical Center (AMC)]. The enrolled patients were composed of 41 patients within open-label clinical trials, and 17 patients outside of the trial after Korean FDA approval of the drug. Our study protocol was approved by the Institutional Review Boards of SMC (2016-12-112) and AMC (2016-1254).

Study protocol and definitions

All enrolled patients received PD-1 blockade according to a schedule of 3 mg/kg every 2 weeks for nivolumab and 2 mg/kg every 3 weeks for pembrolizumab. TFTs, including TSH and FT4 levels, were carried out every 4–8 weeks using a commercialized immunoradiometric assay kit prepared by Immunotech (Normal range: 0.30–6.00 mIU/L for male, 0.30–6.50 mIU/L for female) and commercialized radioimmunoassay (RIA) kits prepared by Immunotech (Cedex, France) (Normal range: 10.16–23.94 pmol/L for male, 8.23–22.13 pmol/L for female), respectively. Evaluation of clinical response was based on investigator-determined irRC (immune-related response criteria),26 and radiologic study was conducted every 2–4 cycles of PD-1 blockade treatment.

According to development of thyroid dysfunction, we categorized patients into two groups: the thyroid dysfunction group (patients with one or more abnormal TFT results during PD-1 blockade treatment) and the euthyroid group (patients without any abnormal TFT results during PD-1 blockade treatment). The primary end point of this study was overall survival (OS) and progression-free survival (PFS). PFS was defined as the time (in days) from the date of starting treatment to the date of documented disease progression or death due to any cause. OS was defined as time from start of treatment to death due to any cause. To evaluate unique response patterns for PD-1 blockade, the response rate (RR; percentage of patients with a clinical response of irPR or irCR) and durable control rate (percentage of patients who maintained a progression-free status for more than 1 years) were assessed as secondary endpoints.

To evaluate whether the severity of thyroid dysfunction impacts clinical response, we additionally classified patients according to the severity of thyroid dysfunction. Because assessing severity using NCI-CTCAE 4.0 criteria has poor reproducibility due to the absence of objective criteria for symptoms, treatment, or admission decisions, we classified patients based on serum levels of TSH and FT4 into the overt thyroid dysfunction group (both serum TSH and FT4 levels beyond the normal reference range), subclinical thyroid dysfunction group (only serum TSH levels beyond the normal reference range), and euthyroid group. Overt and subclinical thyroid dysfunction groups were further categorized into thyrotoxicosis (low serum TSH level) and hypothyroidism (high serum TSH level) groups according to direction of serum TSH level change. Other prognostic variables influencing clinical responses such as age, sex, current or former smoking status, subtype of tumor, stage at the starting point, and type of medications were also evaluated. Smoking status was classified into 2 groups: current or ex-smoker, and never smoker. We defined a never-smoker as someone who has smoked <1 cigarettes per lifetime.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) according to their distribution. Categorical variables are presented as number with percentages. Student’s t-test or Mann-Whitney U test was used to compare continuous variables between the thyroid dysfunction and euthyroid groups. The Chi-square test (or Fisher’s exact test) was used to compare categorical variables. Kaplan-Meier cumulative-event curves with log-rank test were used to compare OS and PFS between the two groups. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS according to thyroid dysfunction, age, gender, smoking history, subtype of tumor, stage at the starting point, and type of medications. The Jonckheere-Terpstra test was used for trend analysis for OS and PFS according to severity of thyroid dysfunction. All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY). P-values less than 0.05 were considered statistically significant. All p-values were two-sided.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.
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