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Report

Thyroid Transcription Factor-1 as a Potential Hematologic Toxicity Indicator for the Three-Drug Combination Regimen of Carboplatin, Pemetrexed, and Pembrolizumab in Patients with Advanced Recurrent Non-Squamous Non-Small Cell Lung Cancer

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Thyroid transcription factor-1 (TTF-1) expression in patients with non-squamous non-small cell lung cancer (NS-NSCLC) is reportedly useful in selecting treatment regimens and predicting life expectancy. However, only a few studies have reported the association between TTF-1 expression and the efficacy of the current first-line regimens containing immune checkpoint inhibitors. It is unclear whether TTF-1 can be a hematologic toxicity indicator in patients receiving these treatment regimens. Patients who received the three-drug combination regimen of carboplatin, pemetrexed, and pembrolizumab, i.e., KEYNOTE-189, between April 2019 and December 2021 at Tsuyama Chuo Hospital and who had known TTF-1 expression were retrospectively studied using electronic medical records. Among the seven patients included, four patients were TTF-1 positive, while three were TTF-1 negative. TTF-1-positive patients showed a trend toward improved progression-free survival and were more likely to experience thrombocytopenia than the TTF-1-negative patients. These results suggest that TTF-1 expression in patients with NS-NSCLC could play a role in determining both treatment efficiency and hematologic toxicity.

Key words thyroid transcription factor-1, immune checkpoint inhibitors, adverse events

INTRODUCTION

Drug therapy for non-squamous non-small cell lung cancer (NS-NSCLC) has transformed majorly with the advent of immune checkpoint inhibitors (ICIs). The addition of ICIs to the conventional standard regimen of pemetrexed plus platinum significantly prolongs the overall survival (OS) of patients.[1)] Therefore, the combination therapy comprising pemetrexed, platinum, and ICIs is the first-line treatment for patients without mutational translocations of driver genes such as KRAS, EGFR, ALK, RET, and ROS1.[2)]

Several studies have reported that thyroid transcription factors (TTFs) affect the efficacy of the three-drug combination regimen of carboplatin, pemetrexed, and pembrolizumab (KEYNOTE-189). Hosono *et al*. reported that TTF-1 directly induces gene expression of myosin binding protein H and suppresses cancer cell motility, invasion, and metastasis.[3)] Tanaka *et al*. reported that serglycin, specifically secreted by TTF-1-negative NS-NSCLC, induces the expression of cytokines and programmed death-ligand 1 (PD-L1) and enhances the migratory and invasive potential of cancer cells, resulting in NS-NSCLC progression and poor prognosis.[4)]

In 2020, Frost *et al*. reported the involvement of TTF-1 in conventional regimens without ICIs in patients treated with platinum and pemetrexed for NS-NSCLC. They showed that TTF-1-positive patients had significantly improved progression-free survival (PFS) and OS, whereas TTF-1-negative patients showed a reduced OS with platinum and pemetrexed.[5)] Additionally, Takeuchi *et al*. reported that the PFS and OS significantly improved in the TTF-1 positive patients after combination therapy with platinum, pemetrexed, and bevacizumab in the treatment of NS-NSCLC, whereas no significant improvement was observed in the TTF-1-negative patients.[6)] Furthermore, Ibusuki *et al*. reported for the first time in 2022 that the PFS significantly improved in TTF-1-positive patients even with regimens that included ICIs. However, the effect of TTF-1 expression on the side effects of KEYNOTE-189 remains unclear.[7)]

We investigated the effect of TTF-1 expression on the treatment efficiency and the occurrence of hematologic toxicities in patients with NS-NSCLC treated with KEYNOTE-189 to investigate the relevance of TTF-1 in determining the safety of KEYNOTE-189.

MATERIALS AND METHODS

Eligible Patients This study included seven patients who received at least four courses of KEYNOTE-189 at Tsuyama

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Table 1. Patient Characteristics

		Total n = 7	TTF-1 negative n = 3	TTF-1 positive n = 4	*p*-value
Age (years)		68 ± 9.4	67 ± 9.2	68 ± 10.9	0.9032
Sex					0.4857
	Male	3	2	1	
	Female	4	1	3	
Body surface area (m^2)		1.54 ± 0.200	1.51 ± 0.273	1.57 ± 0.169	0.7821
Dose (mg)					
	Carboplatin	365.7 ± 48.99	328.3 ± 53.98	393.8 ± 20.29	0.0717
	Pemetrexed	735.9 ± 68.29	723.7 ± 86.32	745.0 ± 64.03	0.7205
Dose (%)					
	Carboplatin	96 ± 4.8	98 ± 2.1	95 ± 5.9	0.8309
	Pemetrexed	95 ± 4.5	95 ± 6.4	95 ± 3.4	0.3407

Data are expressed as numbers or means ± standard deviations.
p-value; TTF-1 negative vs TTF-1 positive
TTF-1, thyroid transcription factor-1

Chuo Hospital between April 2019 and December 2021 and had known TTF-1 expression.

Survey Methods and Items This retrospective study used electronic medical records. We collected the data on the age, sex, TTF-1 expression, body surface area, carboplatin and pemetrexed dose rate (%), dosage of the drugs (mg), PFS, progressive disease, and date of blood sampling. PFS data was collected for a maximum of two years post-initiation of combination therapy involving Carboplatin, Pemetrexed, and Pembrolizumab. In accordance with the final analysis of the KEYNOTE-189 trial,[1] and considering a median overall survival of 22.0 months, we acquired data for up to two years. The duration of survival (in days) from treatment initiation to either death or progression of the disease was documented.

Ethical Considerations This study was approved by the Ethics Committee of Tsuyama Chuo Hospital (Reception No. 536).

Statistical Analysis We employed a t-test for comparing continuous variables and Fisher's exact test for comparing categorical variables, with a significance level of 5%. Survival curves were constructed using the Kaplan-Meier method, and the statistical significance of the differences in survival curves between the TTF-1 positive and TTF-1 negative groups was assessed using the log-rank test. JMP®Pro17 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

RESULTS

Among the seven patients included, four patients were TTF-1 positive, while three were TTF-1 negative. The mean age of the patients in this study was 68 ± 9.4 years, while that of the TTF-1-positive and TTF-1-negative patients was 68 ± 10.9 years and 67 ± 9.2 years, respectively. One of the four TTF-1-positive patients and two of the three TTF-1-negative patients were male. The mean body surface area of the TTF-1-positive and TTF-1-negative patients was 1.57 ± 0.169 m^2 and 1.51 ± 0.273 m^2, respectively. The administration dosage and dose rate of carboplatin and pemetrexed did not exhibit statistically significant differences between TTF-1 positive and TTF-1 negative patients (Table 1).

The PFS (median, 95% confidence interval) of the TTF-1-positive and TTF-1-negative patients was 696 (184-730) days and 217 (155-427) days, respectively. A trend of prolonged PFS was observed in the TTF-1-positive patients, though it was not statistically significant (p = 0.0931, log rank test) (Fig. 1).

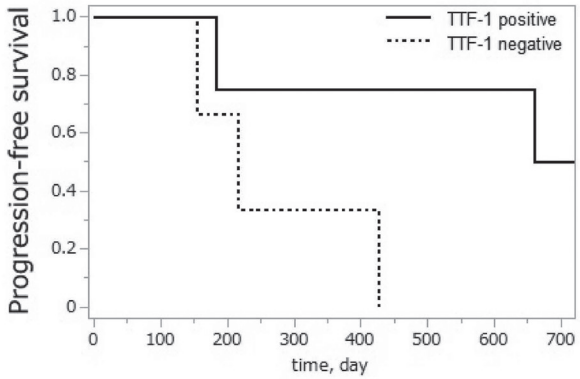

Fig. 1. Progression-Free Survival in Patients with and without Thyroid Transcription Factor-1 Expression

TTF-1, thyroid transcription factor-1.

We evaluated the blood test data for up to four courses at the completion of the three-drug combination therapy with Carboplatin, Pemetrexed, and Pembrolizumab. This was conducted as all patients completed four courses, enabling us to compare blood toxicities under the same dosing conditions. We compared platelet and neutrophil counts at the point of minimum white blood cell count following each course of treatment. As a result, the blood cell counts were significantly lower in the TTF-1-positive patients receiving ≤ four courses of KEYNOTE-189 than in the TTF-1-negative patients: white blood cells (WBC), 4.0 ± 1.89 $\times 10^3$ /μL vs. 5.8 ± 2.32 $\times 10^3$ /μL (p = 0.0029); platelets (PLT), 167.0 ± 80.84 $\times 10^3$ /μL vs. 304.1 ± 150.56 $\times 10^3$ /μL (p < 0.0001); neutrophil percentage (Neutr), 54.5 ± 13.24% vs. 67.5 ± 13.06% (p = 0.0009), and neutrophil count (Neutr count), 2585.1 ± 1859.02 /μL vs. 4493.5 ± 1933.53 /μL (p = 0.0007) (Fig. 2).

DISCUSSION

In this study, while there was no statistical significance, TTF-1 positive patients tended to have longer PFS than TTF-1 negative patients. In 2022, Ibusuki *et al*. first reported the association between ICI-containing regimens and TTF-1, showing a significantly improved PFS in TTF-1-positive patients, even with ICI-containing regimens.[7] The results of that study corroborate our findings. Therefore, KEYNOTE-189 is recommended for TTF-1-positive patients.

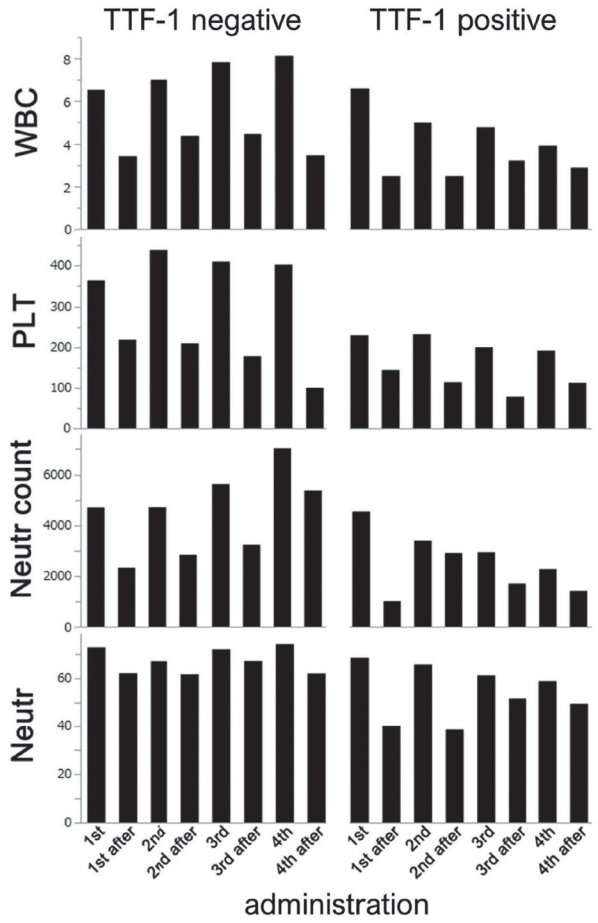

Fig. 2. Changes in Blood Cell Counts at the Time of Administration in Patients with and without Thyroid Transcription Factor-1 Expression

Data are expressed as means of each groups. TTF-1, thyroid transcription factor-1; WBC, white blood cells; PLT, platelets; Neutr count, neutrophil count; Neutr, neutrophil percentage

However, the aforementioned study did not address TTF-1 and PD-L1 expression or the side effects of KEYNOTE-189, and the safety of this regimen remains unknown. The findings of this study suggest that the expression of TTF-1 contributes to the development of adverse effects. The WBC, PLT, Neutr, and Neutr count were significantly lower in the TTF-1-positive patients than in the TTF-1-negative patients, suggesting that the former may be more prone to myelosuppression than the latter. This finding also suggests that platinum and pemetrexed-induced myelosuppression is more likely to occur in TTF-1-positive patients than in TTF-1-negative patients. With ICIs, PFS is prolonged by the presence of immune-related adverse events.[8] In the future, clarifying the effects of TTF-1 and PD-L1 on adverse events is warranted.

A limitation of this study is that the number of cases was insufficient because it was a single-institution study and a relatively new treatment regimen; hence, more cases should be studied in the future. As revealed in this study, considering the possibility that TTF-1 expression may affect the therapeutic efficiency and hematologic toxicity of KEYNOTE-189, it is recommended that active TTF-1 immunostaining be used as not only an adjunctive method when the histological type of lung cancer is unclear but also a strategy for selecting regimens with higher therapeutic efficacy. Proactive detection of TTF-1 may be necessary to select therapeutic regimens that are more effective.

Conflict of interest The authors declare no conflict of interest.

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