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LETTER TO THE EDITOR

HTLV-1 seropositive patients with lung cancer treated with PD-1 inhibitors

Adult T cell leukemia-lymphoma (ATL) is a peripheral T cell malignancy caused by human T cell leukemia virus type 1 (HTLV-1).[1] Frequent structural variations that disrupt the 3′ untranslated region of the programmed cell death ligand-1 (PD-L1) gene have been found to result in overexpression of PD-L1 in ATL patients.[2] The programmed cell death–1 (PD-1)-PD-L1 axis has therefore attracted attention as a potential therapeutic target for ATL. However, in a phase 2 trial of the PD-1 inhibitor nivolumab in ATL patients with an increased mutational load and overexpression of PD-L1, the first 3 patients unexpectedly developed rapid progression of disease after a single dose of nivolumab.[3] Analysis of primary cells obtained from these patients revealed a tumor-suppressive role for PD-1 in ATL.[4] Conversely, in a Japanese phase 2 trial, 8 patients with ATL received at least 1 dose of nivolumab without such rapid acceleration of disease.[5]

HTLV-1 is a human retrovirus that causes HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) and other inflammatory diseases in addition to ATL.[6] Although the precise mechanisms of progression from the asymptomatic state to HTLV-1–associated disease in HTLV-1 carriers are unknown, risk factors for ATL development in such individuals are thought to include a high HTLV-1 proviral load in peripheral blood, older age, a family history of ATL, and the presence of symptoms.[7]

PD-1 inhibitors have shown unprecedented clinical activity and have changed the standard of care for many types of cancer.[8] Although HTLV-1 is not routinely tested for, ~5% of cancer patients have been found to be HTLV-1 carriers in HTLV-1 endemic areas.[9] However, the risk for development of HTLV-1–associated disease in asymptomatic carriers treated with PD-1 inhibitors for cancer is not known. Given the concern that PD-1 inhibitors may influence the response of the immune system to the virus and thereby promote the development of HTLV-1–associated disease in HTLV-1-positive cancer patients, we performed a retrospective study of medical records for individuals with non–small-cell lung cancer (NSCLC) who had undergone monotherapy with the PD-1 inhibitors nivolumab or pembrolizumab at Kyushu University Hospital between January 2016 and December 2019. Patients who had undergone a serum HTLV-1 antibody test were eligible for the study. HTLV-1 antibodies were detected with a gelatin particle agglutination test followed by western blot analysis. Asymptomatic carriers of HTLV-1 were defined as individuals without any clinical evidence of ATL, HAM/TSP, HTLV-1–associated uveitis, or HTLV-1–associated dermatitis. This study was approved by the institutional review board of Kyushu University Hospital (approval number, 2020-54). The characteristics of the study patients are shown in Table 1. Sixty-seven NSCLC patients were tested for antibodies to HTLV-1, and 3 (4.5%) of these individuals were found to be asymptomatic carriers of the virus. The high prevalence of HTLV-1 infection in this cohort may be attributed to the endemic area. All 3 of these patients were >60 y old and had no family history or symptoms of HTLV-1–associated disease. White blood cell counts were normal and lymphocyte counts were less than 4000 without abnormal lymphocytes. Lactate dehydrogenase and serum calcium were also normal in these patients. Although all of the patients had not been tested for HTLV-1 proviral load, these were diagnosed with HTLV-1 carriers. A 68-y-old man with adenocarcinoma received nivolumab for 1 mo, after which the drug was discontinued because of disease progression. The patient did not develop HTLV-1–associated disease before he died of lung cancer 12 mo after receiving nivolumab. A 62-y-old man with squamous cell carcinoma received nivolumab for 4 mo, after which the drug was again discontinued as a result of disease progression. This patient also did not manifest HTLV-1–associated disease before his death 7 mo after first receiving nivolumab. Finally, a 75-y-old man with adenocarcinoma was treated with pembrolizumab for >16 mo without evidence of HTLV-1–associated disease and without progression of lung cancer. The median follow-up period for these 3 patients was 12 mo (range, 7-16 mo), and none of them developed ATL or any other disease related to HTLV-1 infection during the follow-up period.

As far as we are aware, our study is the first to describe asymptomatic HTLV-1 carriers who were treated with PD-1 inhibitors for cancer and did not show rapid progression of ATL or other HTLV-1–associated disease. Limitations of the present study include the small number of patients and relatively short observation period. The patients also had not been tested for HTLV-1 proviral load, given that the test is not approved by health insurance in Japan. Our findings nevertheless suggest that the use of PD-1 inhibitors should not be restricted in such patients for the treatment of cancer with a poor prognosis, such as advanced NSCLC. Further prospective evaluation of risk factors for the development of ATL, such as HTLV-1 proviral load, in asymptomatic HTLV-1 carriers treated with PD-1 inhibitors for cancer is warranted.

TABLE 1 Characteristics of patients with HTLV-1 and NSCLC treated with PD-1 inhibitors

Case	Age	Sex	ECOG PS	Histology	Driver mutation	PD-L1 TPS	Line/drugs	BOR[a]	Duration of PD-1 therapy	Follow-up period
1	68	M	1	Adeno	None detected	85%	2/Pembro	PR	16 mo, ongoing	16 mo
2	62	M	1	Sq	None detected	N/A	3/Nivo	SD	4 mo, discontinued due to PD	7 mo
3	75	M	0	Adeno	None detected	N/A	5/Nivo	PD	1 mo, discontinued due to PD	12 mo

Abbreviations: Adeno, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; M, male; N/A, not available; Nivo, nivolumab; PD, progression disease; PD-L1, programmed death ligand-1; Pembro, pembrolizumab; PR, partial response; SD, stable disease; Sq, squamous cell carcinoma; TPS, tumor proportion score.

[a]Best overall response (BOR) as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

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Yasuto Yoneshima[1]
Koji Kato[2]
Haruna Minami[3]
Munehiko Ikeda[3]
Hiroyuki Watanabe[3]
Goichi Yoshimoto[2]
Toshihiro Miyamoto[2]
Koichi Akashi[2]
Yoichi Nakanishi[1]
Isamu Okamoto[1]

[1]*Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[2]*Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[3]*Department of Pharmacy, Kyushu University Hospital, Fukuoka, Japan*

Correspondence
Isamu Okamoto, Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
Email: okamotoi@kokyu.med.kyushu-u.ac.jp

Yoneshima and Kato contributed equally to this study.

ORCID

Isamu Okamoto https://orcid.org/0000-0002-7587-6096

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