

Incidence of Active Tuberculosis in Lung Cancer Patients Receiving Immune Checkpoint Inhibitors

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Although it ameliorates lung cancer, immunotherapy with immune checkpoint inhibitors (ICIs) presents complications of infectious diseases, including tuberculosis. Incidence of tuberculosis during immunotherapy remains unclear. We found that 1.7% of patients developed active tuberculosis during immunotherapy at our institution. In patients with a positive interferon-gamma release assay status before ICI therapy, physicians should pay close attention to developing tuberculosis.

Keywords. anti-PD-1 antibody; epidemiology; immune checkpoint inhibitor; lung cancer; tuberculosis.

Recent advances in immunotherapy with immune checkpoint inhibitors (ICIs) have benefited lung cancer patients [1]. Despite the dramatic effects of ICIs, immune-related adverse events typically occur during treatment, during which time infectious diseases are a major concern [2]. Development of mycobacterial infections during immunotherapy with ICIs are also an emerging concern [3–7]. Tuberculosis (TB) has specifically been the focus of several case reports [3–6]. Because it has a great impact on public health, TB has increasingly become a matter of concern. Two meta-analyses showed a high incidence of TB in patients with lung cancer [8, 9]. These studies targeted patients who received cytotoxic chemotherapy and did not include patients who received ICIs. Until now, we have not had a complete picture of TB incidence in patients receiving immunotherapy with ICIs. In this study, we aimed to evaluate the incidence and characteristics of active TB in patients with lung cancer who received ICIs in a single-center lung cancer cohort.

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PATIENTS AND METHODS

This retrospective study was conducted at the National Hospital Organization Kyoto Medical Center (600-bed), located in the southern part of Kyoto city, Japan. We reviewed lung cancer patients receiving a minimum of 1 cycle of ICIs between December 1, 2016 and December 31, 2019. We included patients who developed or had reactivation of TB while receiving ICIs treatment and calculated its incidence. We also evaluated the following: history of lung cancer treatment, type and source of TB infection, number of cycles of ICI monotherapy, and interferon-gamma release assay (IGRA) status before treatment. We looked at patients who received nivolumab, pembrolizumab, atezolizumab, and durvalumab as the ICIs because only these 4 ICIs were approved for the treatment of lung cancer in Japan during the study period. The T-SPOT TB test was the only IGRA test used at our institution.

Ethical Approval

This study was approved by the Institutional Ethical Review Board (approval number 19-076).

RESULTS

We reviewed 297 lung cancer patients receiving ICIs monotherapy, 5 (1.7%) of whom developed active TB during treatment. Three patients (60%) showed pulmonary TB and 2 (40%) showed extrapulmonary TB (cervical and hilar tuberculous lymphadenitis, tuberculous knee arthritis). No patients in our cohort were infected by human immunodeficiency virus. Table 1 presents the characteristics of these 5 cases. The mean age of patients with active TB was 74.6 ± 5.6 years. All patients had advanced, non-small cell lung cancer. Anti-PD-1 antibody was used in 4 patients (80%) and anti-PD-L1 antibody; durvalumab was used in a patient (20%) to treat lung cancer. The median time to a diagnosis of TB was 80 days (range, 22–398) after first administration of ICIs, and the median number of ICI cycles was 4 (range, 2–24). Positive IGRA test results were observed in 3 patients (60%) at lung cancer diagnosis, which took place before ICI treatment. Two patients had undergone radiotherapy before ICI treatment. All patients had a history of cytotoxic chemotherapy before ICI treatment. After the diagnosis of active TB, all patients received standard anti-TB treatment.

DISCUSSION

We found that active TB occurred in 1.7% of patients receiving ICIs. Previously, only 1 study has evaluated the incidence of TB in lung cancer patients. In those receiving cytotoxic chemotherapy, 1.2% (3 cases in 257) developed TB [10]. Our results

Table 1. Characteristics of Patients Who Developed Active Tuberculosis

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age at TB diagnosis, years	79	74	79	64	77
Sex	Female	Male	Male	Male	Female
Histopathology	Adenocarcinoma	Squamous cell	NOS	Squamous cell	NOS
Staging at diagnosis	4B	3B	4B	3B	3A
Driver oncogene alteration	Exon 21 L858R	NE	Wild type	NE	Wild type
PD-L1 expression	NE	NE	NE	80%	NE
Type of ICI	Nivolumab	Pembrolizumab	Nivolumab	Pembrolizumab	Durvalumab
TB infected organ	Knee joint	Lung	Lung	Lung	Cervical and hilar lymph nodes
Source of sample	Knee joint fluid	Sputum	Sputum	Sputum	Lymph nodes
Days to diagnosis ^a	80	135	29	22	398
Cycles of ICI	5	4	4	3	24
IGRA test before ICI	Positive	Positive	Negative	Positive	Negative
Prior radiotherapy	-	66 Gy (2Gy*33Fr)	-	-	60 Gy (2Gy*30Fr)
Prior chemotherapy					
1st line	Erlotinib	nabPTX	Carboplatin + nabPTX	Carboplatin + nabPTX	Carboplatin + nabPTX
2nd line	Pemetrexed	-	-	-	-

Abbreviations: Fr, fraction; ICI, immune checkpoint inhibitor; IGRA, interferon gamma release assay; nabPTX, nanoparticle albumin-bound paclitaxel; NE, not evaluated; NOS, not otherwise specified; PD-L1, programmed cell death-(ligand) 1; TB, tuberculosis.

^aTime from initial ICI treatment to TB diagnosis.

showed a slightly higher incidence than the previous study. Because the previous study was conducted in the 1980s and the types of chemotherapy and management methods evaluated were outdated, the observed incidence cannot be simply compared with that of the present study. However, the exact incidence of TB among patients with lung cancer receiving cytotoxic chemotherapy is difficult to define given the heterogeneity of the patient population.

In our study, 3 important considerations arose. First, 3 of 5 patients (60%) showed a positive IGRA test before receiving ICIs. Screening with IGRA before administration of ICIs may be important for identifying patients who require special attention. Second, it is noteworthy that 2 of 5 patients (40%) had extrapulmonary TB. Because patients with lung cancer are usually examined for tumors by chest computed tomography (CT) at regular intervals, it might be more likely to suspect pulmonary TB in this population than in other situations, but this method might underestimate extrapulmonary TB. Third, the time to diagnosis of TB had a very wide range (range, 22–398 days). This means that physicians should remain alert to the possible development of TB at all stages of immunotherapy.

Although several case reports have been published, the mechanisms of the development of TB during immunotherapy with ICIs remain unknown. In many such cases, reactivation of latent infection is suspected [4, 5]. In this connection, some authors point out a similarity to the phenomenon of immune reconstitution inflammatory syndrome [3]. Some previous reports speculated that ICIs treatment may enhance CD4 T cell-mediated immunity, which cause excessive inflammation and tissue destruction of the TB-infected environment and, it seems, reactivation of TB [11–13]. Moreover, Langan et al [14] have

summarized all published cases of TB infection during immunotherapy with ICIs and pointed out that non-small cell lung cancer patients receiving ICIs are at increased risk because TB activation could arise from activation of particular immune-cell subsets. In the 2 cases with negative IGRA before ICI, there was a stronger suspicion of new TB infection than reactivation of latent TB infection or old TB granuloma. The mechanisms of development of active TB may differ between reactivation and new infection. The cause of new TB infection might require a greater emphasis on host physical condition and treatment history of cytotoxic chemotherapy than ICI treatment itself. Furthermore, the possibility of false-negative results of IGRA was also important. Unfortunately, we did not re-evaluate IGRA in these 2 patients. Serial IGRA tests at regular intervals may be necessary.

It is also important to consider statistical aspects. Japan falls in the middle of countries when ranked by TB burden, with an incidence of 12.3 per 100 000 of population in 2018, according to the Japanese Ministry of Health, Labour and Welfare [15]. The city of Kyoto was also a high TB burden city, where the annual TB incidence rate per 100 000 population was 15.5 in 2018 [15]. Immunotherapy with ICIs is also widespread in Japan. Thus, physicians in countries both where ICIs are frequently used, and there is a middle and more burden of TB or where accepting great number of immigrants who come from countries at high risk of TB should be alerted to the development of active TB during immunotherapy with ICIs.

This study had several limitations. First, it was conducted in a single tertiary medical center, and, therefore, it may be biased for residential areas and a particular severity of disease. Second, because all patients received chemotherapy before ICI treatment, the possible effects of cytotoxic chemotherapeutic agents

on the development of TB cannot be ignored. Third, although we excluded typical TB abnormalities by the CT and positron emission tomography (PET)-CT imaging before ICIs treatment, there is the potential for missing TB lesions mimicking lung cancer or cancer-like nodules. Nonetheless, this study is important in raising an alarm concerning the possibility of enhanced risk for TB during immunotherapy with ICIs.

CONCLUSIONS

The incidence of active TB in lung cancer patients receiving ICIs was 1.7%. Patients with positive IGRA test before ICI treatment should be closely monitored for development of TB during immunotherapy.

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Author contributions. K. F. designed this study. K. F., Y. Y., O. K., M. O., M. H., K. N., S. S., and T. M. treated lung cancer patients in this cohort. K. F., O. K., M. O., K. N., and T. M. treated tuberculosis in this cohort. K. N., S. S., and T. M. supervised this study. K. F. drafted and revised the manuscript.

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