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Short communication

Development of tuberculosis in cancer patients receiving immune checkpoint inhibitors

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ABSTRACT

Background: Limited data exist on the development of tuberculosis (TB) in cancer patients receiving immune checkpoint inhibitors (ICIs).
Method: s: We evaluated the development of TB in 1144 solid-cancer patients who started ICIs (pembrolizumab, nivolumab, or atezolizumab) between July 2014 and December 2018.
Results: A total of 1144 cancer patients were treated with ICIs. The median age of the patients at the start of ICI treatment was 62 years (interquartile range [IQR]; 53–69 years). Lung cancer (n = 796, 69.6%) was the most common cancer followed by melanoma (n = 115, 10.1%), and lymphoma (n = 85, 7.4%). Pembrolizumab (n = 612, 53.5%) was the most common treatment, followed by nivolumab (n = 474, 41.4%) and atezolizumab (n = 58, 5.1%). The median treatment duration with ICIs was 42 days (IQR; 18–154 days), and the median follow-up duration after initiating ICIs was 187 days (IQR; 70–342 days). Overall, three patients developed TB, two of whom received nivolumab and one who received pembrolizumab.
Conclusions: Our data showed that TB can develop in cancer patients receiving ICIs. However, due to the small number of study population, it is insufficient to draw accurate conclusions about the role of ICIs in the development of TB. Moreover, it is unclear whether the incidence of TB would be comparable with the incidence of TB in elderly cancer patients. Further studies are needed to evaluate whether diagnosis and treatment of latent TB infections before starting ICIs could be helpful in preventing the development of TB in these patients.

1. Brief communication (word count: 1119/1000)

Immune checkpoint inhibitors (ICIs) have antitumor activity against several types of malignances [1]. ICIs reinforce the host immune system in attacking tumor cells, and they revitalize antitumor immune responses by disrupting co-inhibitory T-cell signaling, such as pembrolizumab and nivolumab's effects on programmed death-1 (PD-1) and atezolizumab's effects on programmed death-ligand 1 [2]. Thus, some immune-related adverse events, such as thyroiditis, pneumonitis, and organizing pneumonia have been reported with ICIs [3–5]. Interestingly, the occurrence of tuberculosis (TB) after ICI use has been steadily increasing [6–13]; however, no previous reports have studied the development of TB associated with the use of ICIs in a large cohort. Therefore, we investigated the occurrence of TB after starting ICIs among a large cancer-patient cohort.

We retrospectively screened 1248 cancer patients who started ICIs (pembrolizumab, nivolumab, or atezolizumab) for palliative chemotherapy between July 2014 and December 2018, using the immunotherapy registry of Samsung Medical Center (a 1979-bed referral hospital in Seoul, South Korea). Patients who received concurrent

Abbreviations: CI, confidence interval; DRESS, drug reaction with eosinophilia and systemic symptoms; ICI, immune checkpoint inhibitors; IQR, interquartile range; LTBI, latent tuberculosis infection; PD-1, programmed death-1; TB, tuberculosis; TNF, tumor necrosis factor.

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cytotoxic agents along with ICIs (n = 30) or other types of ICIs (n = 74) involved in clinical trials were excluded. The final study population included 1144 patients. Patients received ICIs intravenously at 2 mg/kg or 200 mg every 3 weeks for pembrolizumab, 3 mg/kg every 2 weeks for nivolumab, or 1200 mg every 3 weeks for atezolizumab until malignancy progression, intolerable toxicity, or the patient's refusal to continue. Our Institutional Review Board approved this study (2019-03-154-001) and waived the requirement for informed consent.

Clinical characteristics of study patients, use of ICIs, and confirmed diagnosis, treatment modality and outcomes of pulmonary TB were collected retrospectively. The incidence of TB was calculated as the number of new cases occurring in the population in a given period of time divided by the total number of people in the same population during the same period of time and expressed in terms of 100,000 person-years.

In total, 1144 patients who received ICIs were analyzed (Table 1). The median age of patients at the start of ICIs was 62 years (interquartile range [IQR] 53–69 years), and 69% were male. Lung cancer (n = 796, 69.6%) was the most common malignancy, followed by melanoma (n = 115, 10.1%) and lymphoma (n = 85, 7.4%). Pembrolizumab (n = 612, 53.5%) was the most common treatment, followed by nivolumab (n = 474, 41.4%) and atezolizumab (n = 58, 5.1%). The median treatment duration with ICIs was 42 days (IQR 18–154 days), and the median follow-up period after starting ICIs was 187 days (IQR 70–342 days). No patients received immunosuppressive medication including TNF inhibitors and mycophenolate. There were 7.4% (85/1144) of patients, who were diagnosed with lymphoma and received high dose steroids. However, none of these patients were diagnosed with TB during the study.

During the study period, three patients with advanced lung cancer developed pulmonary TB at 22.0, 14.0, and 7.0 months after starting ICIs (Table 2); two had received nivolumab and one received pembrolizumab. The overall incidence rate of TB was 394.4 cases (95% confidence interval [CI] 100.3–1073.4) per 100,000 person-years. No patients developed nontuberculous mycobacterial infections.

To our knowledge, this is the first report on TB development associated with ICI use in a large cancer-patient cohort. The incidence rate of TB was 394.4 cases per 100,000 person-years, much higher than that seen in the overall South Korean population in 2018 (51.5 cases per 100,000 person-years) [14,15] but similar to two previous studies that included cancer patients (361.3 per 100,000 person-years, excluding lung cancer and 307 per 100,000 person-year, including lung cancer) [16,17]. However, the observation period of our study patients was much shorter than in the previous studies (median follow-up period of 6.1 vs. 19.2 vs. 29.0 months), likely because our patients had more advanced disease. Therefore, our data may underestimate the overall incidence rate.

Table 1
Characteristics of study patients receiving immune checkpoint inhibitors.

Characteristics	Total (n = 1144)
Sex, male	786 (69.0)
Age, years	62 (53–69)
Type of cancer	
Lung cancer	796 (69.6)
Melanoma	115 (10.1)
Lymphoma	85 (7.4)
Gastric cancer	73 (6.4)
Head and neck cancer	35 (3.1)
Thymic cancer	32 (2.7)
Mesothelioma	5 (0.4)
Sarcoma	3 (0.3)
Overall duration of immunotherapy, days	42 (18–154)
Median cycles of chemotherapy	
Pembrolizumab (n = 612, 53.5%)	4 (2–9)
Nivolumab (n = 474, 41.4%)	3 (2–8)
Atezolizumab (n = 58, 5.1%)	3 (1–5)
Median follow up duration after starting ICIs, days	187 (70–342)

The data are presented as either n (%) or median (interquartile range). ICIs, immune checkpoint inhibitors.

Immunomodulatory drugs, including immunosuppressants, steroids, and anti-tumor necrosis factor (TNF), are well-known risk factors for developing TB. Recent studies from South Korea have reported that the incidence of TB among patients receiving anti-TNF alpha therapy was >1000 cases per 100,000 person-years [18,19]. However, adequate therapy for latent TB infections can significantly reduce the risk of TB occurrence in such patients [19], which highlights the importance of screening for latent TB infections in cancer patients receiving immunotherapy. Additionally, due to side effects that can occur when treating latent TB infections and cancer simultaneously, active screening for and treatment of latent TB infections before immunotherapy is a treatment strategy worth considering.

Previously, ICIs were suggested to upregulate the immune response not only to cancer but also to microorganisms such as HIV and chronic hepatitis B infections [20]. Conversely, some studies have shown the activation of TB after initiation of ICIs [8,21]. In PD-1-knockout mice, *Mycobacterium tuberculosis*-specific CD4 T-cell responses are increased, and high levels of inflammatory cytokines are expressed in the lungs [21]. Similarly, PD-1 staining is less strong in TB granulomas after the use of ICIs, and activated T cells recruit permissive monocytes or neutrophils to the TB granuloma, which may lead to cavitation of lung tissue [8]. The mechanism for these paradoxical reactions is unclear, but it appears to develop due to a disruption of immune system homeostasis. Further studies are needed to explore the pathophysiology behind the development of TB after immune checkpoint inhibition.

In this study, two of the patients later diagnosed with TB had previously received high-dose steroid therapy either due to severe immune-related adverse events related to ICIs (three months before developing TB) or to prevent toxicity due to cytotoxic chemotherapy (two months before developing TB). Therefore, we could not rule out whether the development of TB was caused by the high-dose steroid medications. Nevertheless, attention should be paid to the development of TB after ICIs, since serious adverse events after the administration of ICIs can require steroid therapy, which might reactivate TB.

In conclusion, our data showed that TB can develop in cancer patients receiving ICIs. However, the retrospective nature of this study conducted in a single referral hospital limits the generalizability of these findings. In particular, due to the small number of study population, it is insufficient to draw accurate conclusions about the role of ICIs in the development of TB. More data on the incidence rate of TB in different settings are required. Moreover, it is unclear whether the incidence of pulmonary TB would be comparable with the incidence of pulmonary TB in elderly cancer patients, therefore national study with appropriate sample size is needed to establish whether ICIs might be responsible to development of TB on patients with cancer. Further studies are also needed to evaluate whether diagnosis and treatment of latent TB infections before starting ICIs could be helpful in preventing the development of TB in these patients.

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Authors' contributions

Conception and design: Y. Im, W-J. Koh, B.W. Jhun; Acquisition of data: J. Lee, S.J. Kim, S–H. Lee; Analysis and interpretation of data: Y. Im, W-J. Koh, B.W. Jhun, S–H. Lee; Writing, review and critical revision of the manuscript: All authors.

Table 2
Characteristics of patients diagnosed with pulmonary tuberculosis after treatment with ICIs.

Characteristics	Case 1	Case 2	Case 3
Age/Sex	63/male	79/male	59/female
Type of cancer	adenocarcinoma, lung	squamous cell carcinoma, lung	adenocarcinoma, lung
Previous rounds of chemotherapy[a]	3	1	6
Type of ICI	nivolumab	pembrolizumab	nivolumab
Time interval between initiation of ICI and diagnosis of TB, months	22	14	7
Time interval between last dose of ICI and diagnosis of TB, months	1	6	6
Duration of ICIs before diagnosis of TB, months	21 (41 cycles)	8 (14 cycles)	1 (3 cycles)
Lymphocyte counts, before the start of ICIs and at the time of TB diagnosis,/mcgL	1880 → 2089	1448 → 30	1778 → 412
Evaluation of cancer response after initiating ICI[b]	partial response	stable disease	progressive disease; changed to cytotoxic chemotherapy
Other immune-related adverse events	Yes (drug-induced thyroiditis at 20 months after initiating ICI)	Yes (drug-induced thyroiditis at 7 months, and biopsy-proven membranous glomerulonephritis at 11 months after initiating ICI)	No
Use of steroids before diagnosis of TB	No	Yes (oral prednisolone 30 mg once daily for a month at 11 months after initiating ICI due to membranous glomerulonephritis)	Yes (a cumulative dosage of 128 mg dexamethasone at 2 months after initiating ICI to prevent toxicity from cytotoxic chemotherapy)
Diagnosis of TB	positive culture for *Mycobacterium tuberculosis* in bronchoalveolar lavage fluid	detection of *Mycobacterium tuberculosis* complex using Xpert MTB/RIF assay of sputum	positive culture for *Mycobacterium tuberculosis* in sputum
Radiological findings at the time of diagnosis of lung cancer	a 51-mm-sized mass in the left upper lobe with ipsilateral mediastinal lymphadenopathy	a 31-mm-sized mass in the right middle lobe with segmental atelectasis	a 36-mm-sized mass in the right middle lobe without mediastinal lymphadenopathy
Radiological findings at the time of diagnosis of pulmonary TB	pneumonic consolidation in the right upper lobe without cavity; no change of primary tumor in left upper lobe	air-fluid level and wall thickening of bullae in left upper lobe; no change of primary tumor in the right middle lobe	nodular infiltration with hematolymphangitic metastasis and pleural seeding; increased size of metastatic lymphadenopathy in the mediastinum and left supraclavicular area
Treatment of pulmonary TB	INH, RIF, EMB, and PZA[c]	INH, RIF, EMB, and PZA	INH, RIF, EMB, and PZA
Prognosis	DRESS syndrome developed after initiating anti-TB medication; patient is still undergoing nivolumab treatment	died 14 months after initiating ICI due to peritonitis	died 11 months after initiating ICI due to progression of cancer

ICIs, immune checkpoint inhibitors; TB, tuberculosis; DRESS, drug reaction with eosinophilia and systemic symptoms.
[a] Number of previous rounds of cytotoxic chemotherapy prior to use of ICI.
[b] Based on RECIST criteria (Response evaluation criteria in solid tumors).
[c] INH, isoniazid; RIF, rifampin; EMB, ethambutol; PZA, pyrazinamide.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Se-Hoon Lee received grants and personal fees from Merck Sharp & Dohme Corp (MSD), and personal fees from Novartis, AstraZeneca, Bristol-Myers Squibb (BMS), and Roche, not associated with the submitted work. Dr. Won-Jung Koh has served on Advisory Boards for Insmed Inc. and Johnson and Johnson, not associated with the submitted work. The authors have no additional conflicts of interest to declare.

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