Immune Checkpoint Inhibitor drugs and Tuberculosis

Introduction

In this issue I will describe about "tuberculosis" as an adverse effect of ICI anticancer drugs.

Report on tuberculosis as an adverse effect of ICI

Currently two epoch-making anticancer drugs, OPDIVO® (nivolumab) and KETRUDA® (pembrolizumab), are commercially available in Japan. These anti-cancer drugs are called as Immune Checkpoint Inhibitor (ICI) in terms of action mechanism. Their efficacy of anti-cancer are against malignant melanoma, non-small cell carcinoma, renal cell carcinoma, Hodgkin lymphoma, etc. Recently "tuberculosis" has been newly reported as an adverse effect of these drugs. The Ministry of Health Labor and Welfare issued a notice on June 4, 2019, regarding revision of "Precautions for use" and instructed pharmaceutical companies (1). Correspondingly, the manufacturers revised the package inserts of these products (2, 3). According to the publication of the Pharmaceuticals and Medical Devices Agency (PMDA) on drugs adverse effects, tuberculosis has been reported in 10 cases in Opdivo and 4 case in Keytruda (4). As a search result of PMDA database, there are 11 adverse effects of tuberculosis in Opdivo (5). In terms of age, a total 11 of cases of tuberculosis as Opdivo's adverse effect consisted of 1 in the 50s, 4 in the 60s, and 6 in the 70s, which showed its occurrence tendency seems to be shifted to the elderly.

Action mechanism of ICI anticancer drugs (6)

The ICI anticancer drugs are humanized monoclonal antibodies against PD-1 (PD-1 = programmed cell death-1), and bind to PD-1 on activated T cells, thereby causing PD on cancer cells. PD-L1 (PD-L1 = Programmed cell death-ligand 1) and PD-L2 (PD-L2 = programmed cell death-ligand 2) inhibits the suppression of activated T cells by cancer cells. As a result, when the suppressed T cell recognizes the cancer antigen again, it is reactivated and the cancer cell can be eliminated (6). In addition, CTLA-4 molecule is expressed on activated T cells and regulatory T cells (Regulatory T cells: Treg) and inhibits these cells' activation via binding to B7 (CD80/CD86) on antigen-presenting cells. Anti-CTLA-4 antibody, another ICI anticancer drug, inhibits the binding of CTLA-4 and B7 (CD80/CD86), allowing the binding of CD28 and B7 (CD80/CD86), which are costimulatory molecules on T cells, reactivate the T cells (6). In other words, cancer cells escape from the immune surveillance mechanism using these molecules responsible for maintaining a state of tolerance to self. By inhibiting biding these molecules with corresponding receptors, cancer cells are lead to be eliminated.

Mechanism of development of active TB during treatment of ICI anticancer drug

In general, the development of tuberculosis from latent tuberculosis (LTBI) caused by a therapeutic drug is due to reduced host immune function caused by the therapeutic drug. An example would be tuberculosis in LTBI patients with rheumatoid arthritis as a result of treatment with an anti-rheumatic biologic or an immunosuppressant such as a steroid (7, 8).

Development of active tuberculosis during the treatment of rheumatic patients with a biologic that is one of the anti-rheumatic agents has led to the development of latent tuberculosis infection (LTBI) due to the reduced immune function of the subject's host during the treatment (9).

However, ICI anticancer drugs enhance the immune function against tumors, but also stimulate autoimmunity to normal tissues, resulting in a variety of adverse events that are different from those of conventional cytotoxic anticancer drugs and molecular targeted drugs. This adverse event is called an immune-related adverse event (irAE), which has been reported on various organs such as the skin, lungs, gastrointestinal tract, liver, and endocrine organs go into autoimmune disease-like disorders, and some of which are severe and fatal (9).

Treatment with ICI and irAE was one of the important topics for the physicians of respiratory fields. And TB as an adverse effect of ICDs was presented and discussed by several Japanese doctors at a symposium of the annual meeting of the Japanese Society of Tuberculosis 2019.

For example, Immune Reconstitution Inflammatory Syndrome (IRIS) occurred due to ICI treatment, the possibility of manifestation of IRIS in pulmonary tuberculosis was also suggested. In addition, a phenomenon called hyperprogression due to ICI treatment is also known in cancer cells, and a report suggesting a mechanism by tumor cell-related macrophages and inhibitory T lymphocytes (Tregs) by inhibiting PD-1 was presented (10). However, in any case, the pathogenesis of tuberculosis caused by ICI treatment is still unclear.

ICI treatment and Detection of LTBI by IGRA

There are no reports evaluate whether IGRA can accurately detect LTBI in subjects undergoing ICI treatment. However, T cells are inevitably involved in tuberculosis infection and it might be possible to detect tuberculosis infection by IGRA.

The combination of these innovative anti-cancer drugs with other existing anti-cancer drugs is currently being clinically evaluated (11). When the life expectancy of cancer patients is extended (12), which has never been imagined, new side effects will occur and it will be necessary to deal with them. Tuberculosis is also considered one of them. It may be important to determine whether the subject is infected with tuberculosis before ICI treatment, including measures for nosocomial infections.

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