

Development and comparison between three type of checkpoint inhibitor drug

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Abstract. In the recent years, many monoclonal antibody drugs related to the immunotherapy is taken by many cancer patients. This passage will give the information about the three common checkpoint inhibitor drugs. Information of each of drug will be divide into three parts including mechanism and structure, efficiency and strength, drawback and side-effect. Then limitation and new improvement of checkpoint inhibitor drugs of all three drugs will be introduced in the last part.

Keywords: Checkpoint inhibitor, Cancer, Immune.

1. Introduction

Immunotherapy is a treatment approach that treats illnesses by artificially enhancing or inhibiting the body's immune function depending on whether it is in a low or high immunological state. Numerous immunotherapy techniques exist, and they can be used to treat a wide range of illnesses. The goal of tumor immunotherapy is to stimulate the immune system, which is dependent on autoimmunity to eradicate cancer cells and tumor tissue. Immunotherapy, in contrast to earlier surgery, chemotherapy, radiation, and targeted therapy, targets the body's immune system rather than tumor cells and tissues. Tumor immunotherapy has been practiced for more than 100 years. Today, it contains five main forms of treatment: cellular therapy, immunomodulators, monoclonal antibodies against oncolytic viruses, and cancer vaccines. Checkpoint inhibitors are the most widely used monoclonal antibodies.

Checkpoint inhibitors are part of immunotherapy that have been developed by many researchers. They can inhibit the proliferation and function of cells related to the immune response and reduce the antibody immune response. They are mainly used in anti-rejection organ transplants and autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, skin mycoses, inflammatory bowel diseases and autoimmune haemolytic anaemia. It first appeared in 1893, when William Coley, an orthopaedic surgeon in New York, discovered by chance that infection with *Streptococcus pyogenes* caused tumour regression in patients with sarcoma, which opened the way to tumour immunotherapy. Checkpoint inhibition is one of the popular drugs used to treat cancer over the past 20 years. In 1982, when Dr James P Alison was working at the System Cancer Center at the University of Texas, the T cell antigen receptor, which allows T cells to recognise an unusual protein on the surface of another cell, was identified. He believed that blocking the "off" signal on T cells could eliminate cancer, and this was also proven by another experiment on studies with anti-CTLA-4 antibodies in mice. This discovery led to a paradigm shift in immunotherapy research. Over the next 20 years, other receptors and ligands were discovered by researchers. In 1992, PD-1, which is the well-known receptor, was discovered by Tasuku Honjo, at first this programmed death receptor was not attached importance to other scientists. In 2006, Dr Jianping Chen organised the first clinical trial of the anti-PD1/PD-L1 antibody pathway. The first checkpoint inhibitor drug, Ipilimumab, was invented in 2011. 3 years later, the FDA approved Keytruda and Opdivo, anti-PD-1 antibodies. After these drug discoveries, checkpoint inhibitors became a hot spot in immunotherapy. On 1 October 2018, US immunologist James P Alison and Japanese immunologist Tasuku Honjo were awarded the 2018 Nobel Prize in Physiology or Medicine for their contributions to the field of anti-tumor immunity.

Currently, the FDA has approved 7 PD-1/PD-L1 inhibitors, involving more than 20 types of cancer. However, there are still some problems with this therapy. For example, some cancer patients develop resistance to the drugs that people currently use for therapy. So, scientists are trying to discover new

types of checkpoint inhibitors and in the future, new generation drugs could replace the old ones. Another problem is the overactivation of the immune system induced by checkpoint inhibitors, which can lead to T cells attacking self-antigens, resulting in a series of adverse immune-related events. Immune checkpoint inhibitor (ICI)-associated pneumonia is a rare but potentially fatal immune-related adverse event that occurs at any time during tumour immunotherapy.

This viewpoint focuses on the discussion of three different types of checkpoint inhibitors, including their background, mechanism, strength, side effects and the problems or challenges scientists face with checkpoint inhibitors.

2. Ipilimumab

On March 25, 2011, the FDA approved ipilimumab (trade name Yervoy) for the treatment of advanced melanoma, which is administered intravenously. It is a human cytotoxic CTLA-4-blocking antibody.

The mechanism of the checkpoint inhibitor is clear. On the surface of T cells, there are two types of $\alpha\beta$ and $\gamma\delta$ proteins, and the TCR is the complete protein complex. The α and β proteins are responsible for recognition, and $\gamma\delta$ and ζ are responsible for signal transmission [1]. The TCR on CTL binds with MHC I on APC, and the TCR on Th must bind with MHC II. Most $\alpha\beta$ T cells also express CD4 or CD8 costimulatory moieties, as CD8 molecules have been expressed on the surface of CTLs and CD4 molecules have been expressed on the surface of Th cells, which will help CTLs and Ths to function properly [2].

The immunoglobulin superfamily member CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), also known as CD152, is expressed and sends inhibitory signals to T lymphocytes. In contrast, CD28 can make T cells active. The crucial costimulatory molecules CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells interact to CTLA-4 and CD28. The former is more likely to bind the ligand because it has a higher affinity for the B7 molecule than the latter [3]. The details of how CTLA-4 works are controversial. Some evidence suggests that CTLA-4 collects phosphatases for the T cell receptor (TCR) to decrease signal strength. The new report suggests that CTLA-4 captures and removes B7-1 and B7-2 from the membranes of antigen-presenting cells, rendering them unable to trigger CD28.4

The protein has cytoplasmic tails, transmembrane domains, and a V-domain. A proline-rich motif that binds SH3 and the YVKM motif that binds PI3K, PP2A, and SHP-2 are both found in the intracellular domain. Its role as a direct dephosphorylator by TCR-proximal signaling proteins including CD3, SHP-2, and PP2A of LAT is one of its activities. Competition with CD28 will also have an impact on signaling.

One agent, ipilimumab, is capable of acting. Patients with cutaneous melanoma who have regional lymph nodes greater than 1 mm receive adjuvant therapy for their condition. Patients have finished entire lymphadenectomy as well as full resection.

Additionally, there are other combinations involving other types of medications, with the interaction with nivolumab serving as a classic example. The major form of treatment for people with low-risk advanced RCC is advanced treatment of renal cell carcinoma. Patients having hepatocellular carcinoma are treated with sorafenib and ipilimumab in combination. This medication can receive expedited approval due to the general response rate and duration of response. The clinical advantage in the confirmatory studies may help in the effort to have this indication approved. Adult patients with metastatic non-small cell lung cancer typically get this therapy. Lacking EGFR or ALK genetic tumor abnormalities, patient's tumors express PD-L1. The preferred course of therapy for adult patients with unresectable malignancies is malignant pleural mesothelioma.

Pneumonitis (combination of nivolumab): the possibility that immune pneumonitis occurring is 1.9%-3.6% in all patients, and acute pneumonitis is rarer. anti-PD-1 and anti-PD-L1 monoclonal antibodies for patients with multiple malignancies includes nivolumab, ipilimumab, and

pembrolizumab for melanoma. Antibody-related pneumonitis is an immune-mediated toxic consequence that has contributed to drug-related fatalities [5].

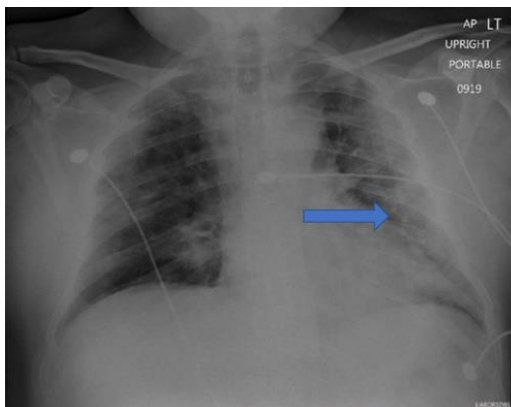


Figure 1. Body infiltrates may be seen on the patient's X-ray chest.

Blocking CTLA-4 receptors causes cytotoxic T cells to become more active, which has anticancer properties. There will be consequences to this. It can result in autoimmune side effects such as arthritis, inflammatory bowel disease, uveitis, dermatitis, and broad body rash [6].

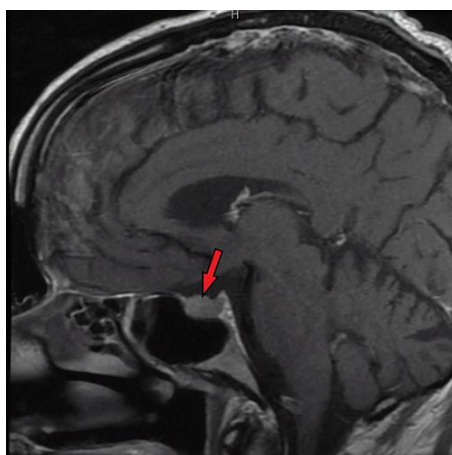


Figure 2. X-ray brain was with infiltrates in the patient's body [7].

Neutropenia: neutropenia is a case which is very serious and increase the risk of infection and death significantly. The evidences including normal erythropoiesis and thrombopoiesis level point out that there is great relationship between neutropenia and ipilimumab.

3. Nivolumab

By inhibiting the PD-1 pathway, the monoclonal antibody nivolumab, also known as Opdivo, is used to treat prime NSCLC. As a PD-1 inhibitor, nivolumab binds to PD-1, which is located on surface of B cells, inhibiting the immunosuppressive signaling cascade triggered by PD-1/PD-2 and restoring T cell antitumor activity.

The Mab OPDIVO pertain to a group of medications that bind to PD-1 or PD-L1, disrupting the PD-1/PD-L1 pathway, limiting the immune system's ability to respond, disrupting peripheral tolerance, and possibly causing unfavorable immunological-mediated responses.

A member of the immunoglobulin superfamily, PD-1, or can be named CD279, is an immunosuppressive molecule. It works by lowering the immune system's reaction to bodily cells. Both of the two minimal ligands for PD-1 are PD-L1 and PD-L2. Identical to PD-L2, PD-L1 and CD-80 are two or more of its ligands, while PD-L2 and RGMB are two or more of its ligands. It promotes T cell expansion, survival, and cytokine production [8]. PD-1 suppresses regulatory T cell apoptosis

and promotes antigen-specific T cell apoptosis in lymph nodes as two of its two methods for limiting healthy cell death.

The exterior IgV domain, the transmembrane region, and the intracellular tail compose form the 288 amino acid type I membrane protein known as PD-1. The immunoreceptor tyrosine-based inhibitory motif and the receptor tyrosine base switching motif both contain two phosphorylation sites in intracellula [9].

Nivolumab is a single agent which can be utilized. Adjuvant therapy is effective for adult melanoma patients who have undergone full resection and have involvement of lymph nodes or metastatic illness. Adult patients with metastatic non-small cell lung cancer who have developed the disease during or after receiving platinum-based chemotherapy must be treated. Before starting OPDIVO, patients who have genetic tumor abnormalities must show disease progression on an FDA-approved therapy for these abnormalities. It is suggested to treat adult patients with squamous cell carcinoma locating on the head or neck who have developed the illness while having platinum-based treatment or after it. Adult patients with classical Hodgkin lymphoma (cHL) who have relapsed, while progressed is an alternative, following autologous hematopoietic stem cell transplantation, brentuximab vedotin, or three or more lines of systemic therapy, including autologous HSCT, are indicated for treatment with classic Hodgkin lymphoma (cHL).

In addition, there are various combinations with other types of medications, the most prevalent of which is ipilimumab. Patients above the age of 18 who have metastatic or malignant melanoma are eligible for therapy. Prime therapy is prescribed for adult patients with metastatic non-small cell lung cancer who do not prosses that genetic tumor abnormalities of EGFR or ALK and whose tumors express PD-L1 (1%). Adult patients with unresectable malignant pleural mesothelioma are recommended to get malignant pleural mesothelioma as their first line of therapy.

Neoadjuvant treatment, sometimes referred to as adjuvant therapy, is suggested for adults with resectable non-small cell lung cancer. Gastric cancer, gastro-oesophageal junction cancer, and adenocarcinomas of the esophagus can all be treated with fluoropyrimidine and chemotherapy that involves platinum. Adult patients with these tumors who have established or metastatic cases are suggested to get these therapies.

Organizing Pneumonia: Organizing Pneumonia: This lung disease affects 5%–10% of patients, and it takes an average of 28 days to 2.8 months for symptoms to appear. Combination therapy poses a larger danger to patients than monotherapy does. Adverse effects may have an impact on many organs at once, changing how they present. Organising pneumonia, hypersensitivity pneumonia, diffuse alveolar injury, or nonspecific symptoms could be present [11].

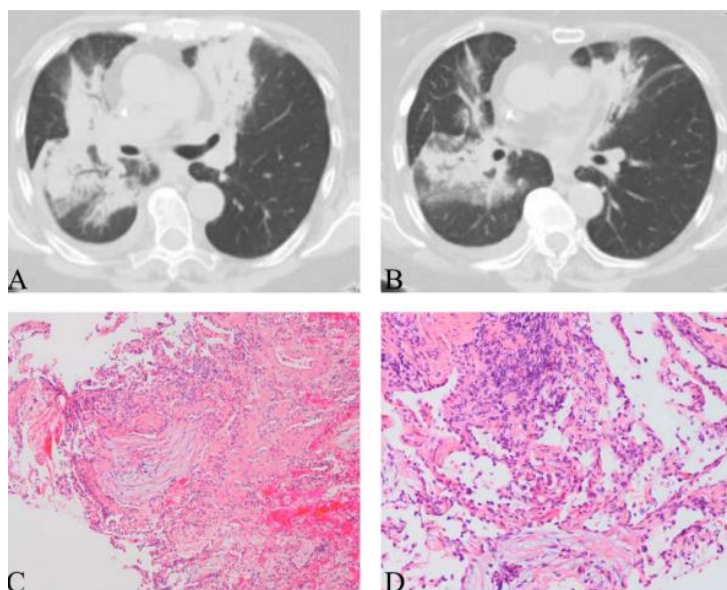


Figure 3. (A, B) CT chest scans revealing pulmonary infiltrates; (C, D) hematoxylin staining from a transbronchial lung sample displaying organized pneumonia [12].

Nivolumab-Induced Adrenal Insufficiency: less than 1% of patients may meet this event and it usually occurs about months after initiation of therapy. Common symptoms of this event include fatigue, hypotension, hypoglycemia, and hyponatremia.

4. Atezolizumab

In 2016, the FDA granted atezolizumab approval for the treatment of patients with NSCLC whose disease worsened during or after platinum-containing chemotherapy. Patients with EGFR or ALK genetic tumor abnormalities must demonstrate disease progression on an FDA-approved treatment for these aberrations before beginning atezolizumab. A PD-L1 inhibiting antibody has already received accelerated FDA clearance for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed following platinum-containing chemotherapy.

Programmed death ligand 1 (PD-L1), also known as CD274. It is the ligand for PD-1, so its function is the same as that of PD-1. PD-L1 is a transmembrane protein, by coding for the CD274 gene, inducing expression in T cells, B cells and dendritic cells, macrophages, mast cells, bone marrow mesenchymal stem cells between sources and non-haematopoietic cells on the surface, in interferon and other inflammatory factors stimulate the response of tumor tissue and other tissues are likely to increase rapidly. When activated, the PD-1/PD-L1 pathway suppresses the immune system in cancer, pregnancy, tissue transplantation and autoimmune diseases. In addition, PD-L1 can also bind to CD80 and competitively inhibit the CD80 and ligand activation pathway, becoming another mechanism by which PD-L1 inhibits T cell activity.

It's feasible to use a signaling agent like atezolizumab. Adjuvant treatment for non-small cell lung cancer is recommended for adult patients with secondary stage to tertiary stage non-small cell lung cancer, which PD-L1 is present on 1% of tumor cells, as confirmed by an FDA-approved test, is administered after resection and platinum-based chemotherapy. Additionally, it is recommended as a first-line therapy for adult patients with metastatic non-small cell lung cancer whose tumors exhibit high PD-L1 expression and no tumor genetic mutations, as determined by test.

There are actually many combinations with other medication classes. When coupled with bevacizumab, paclitaxel, and carboplatin, one is authorized for prime therapy of adult patients with metastatic non-squamous NSCLC who do not have EGFR or ALK genetic tumor mutations. Treatment for small cell lung cancer with atezolizumab, carboplatin, and etoposide is possible.

Myocarditis caused by atezolizumab is caused by a type of infiltrative cardiomyopathy known as cardiac amyloidosis, in which wrong protein aggregates form insoluble amyloid fibrils that deposit extracellularly in cardiac tissue. There are many different types of amyloidosis, with light chain (AL) and transthyretin (TTR) amyloidosis being the most prevalent types. Over 80-year-old patients develop cardiac TTR amyloidosis in about 25% of cases. In clinical trials, atezolizumab shown effectiveness against a variety of cancers, including non-small-cell lung cancer, paving the way for its clinical application. Only 0.27%–1.14% of patients receiving ICIs experience this reaction, which is extremely uncommon. In the majority of reported cases, steroid therapy has been used to treat it [14].

Atezolizumab-Induced Sarcoidosis: There have been numerous cases of sarcoidosis that have been brought on by PD1 or programmed death-ligand-1 inhibitors, such as atezolizumab. The downregulation of induced peripheral tolerance is one theory that could explain the situation. The pathogenic process is not well understood, yet. It has been suggested recently that this might be because scars contain antigens or foreign materials that can react by inducing the formation of granulomas. Foreign issues present in those locations can also be taken into account [15].

5. Limitation and new improvement of checkpoint inhibitor drugs

Recently, as many patients already have the resistance to the inhibitor drug, researchers start to find out other combinations to treat different cancers and further research in the drug efficiency. For

example, there is the research of short-course nivolumab and low-dose ipilimumab for prime treatment of melanoma in metastatic uveal melanoma which represents 5% of all melanoma and most (50%) of it will metastasize.¹⁶ Recently, as many checkpoint inhibitors drugs are, more and more rare side-effect is discovered by researchers, such as immune reconstitution syndrome after nivolumab for progressive multifocal leukoencephalopathy.¹⁷ Apart from that, there are new generation of drugs. For example, relatlimab is the first LAG-3 inhibitory mab to enter the clinic, and Bristol-myers Squibb announced the first results of its phase 2/3 trial of RELATIVITY-047

6. Conclusion

As the outbreak in medicine, the checkpoint inhibitors now have become the one of the most important therapies to cure cancer. Normally speaking, different types of checkpoint inhibitors usually use in combination like nivolumab and ipilimumab, which can use in advanced treatment renal cell carcinoma, and they can treat vary cancer diseases. However, those drugs have many side-effects. Until now, many unusual side-effects are being discovered by researchers, some of them have only around ten cases, but they still have large academic value. All in all, new checkpoints are discovered such as LAG-3 therefore many new drugs are in the clinical trial phase. In the future, more cancer patients can get more effective treatment, and cancer will be completely cured by human.

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