

Immune-checkpoint Inhibitor Treatment of Non-small Cell Lung Cancer Patients

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ABSTRACT

Lung cancer is the primary cause of mortality in the world. It is able to manipulate the host immune response system through many mechanisms, such as through alteration of cytokines structure, forming regulator T-cells, obstruction of cellular immunity function, and the interference of tumor antigen presenting process. The new therapy approachment is produced by stimulating anti-cancer immune response, therefore the growth of lung cancer is able to inhibit. Immune checkpoint inhibition is considered as therapy for non-small cell lung carcinoma (NSCLC) after the unsuccessful treatment by platinum-based chemotherapy. Recent study shows that immune checkpoint inhibition monotherapy is more distinguished as first line therapy than platinum-based chemotherapy. Nonetheless, the effect of immunotherapy is only available for small population (30%) which has more than 50% PD-L1 programmed by the tumor. Therefore, some strategies are investigated to solve this issue. Nowadays, immunotherapy is expected to overcome lung cancer which is still being investigated in many studies.

Keywords: immunotherapy, NSCLC, immune checkpoint inhibition

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INTRODUCTION

Lung cancer is the leading cause of death in developed countries in the world. In 2017, American Cancer Society found 222,500 lung cancer cases, 116,990 of whom were men and 105,510 women.¹⁻³

Lung cancer is distinguished to non-small cell lung cancer and small cell lung cancer. World Health Organization (WHO) classifies non-small cell lung cancer (NSCLC) into squamous cell carcinoma (25% of lung cancer), adenocarcinoma (40% of lung cancer), and large cell carcinoma (10% of lung cancer).³⁻⁵

The latest lung cancer therapy is currently related to the immune system. Lung cancer is able to manipulate the patient's immune response system through various mechanisms. A new therapeutic approach works by stimulating an anti-cancer immune response so that the development of lung cancer cells can be prevented.⁵⁻⁷

Lung Cancer Immunology

Lung cancer is lung tissue that proliferates uncontrollably. Genetic changes in cancer can be in the forms of mutations that cause an increase in protoonco-

genic function and mutations that cause loss of tumor suppressor gene function. Increased proto-oncogenic function will cause uncontrolled stimulation, division, and cell growth, whereas loss of tumor suppressor gene function causes cells to grow out of control, irreversible DNA damage, and disruption of checkpoint activation. Cell population that grows and is out of control, through the process of angiogenesis, will invade the normal surrounding tissue and metastasize to another place.⁸

Interaction Between Human Immune System and Lung Cancer Cell

There are three phases in immune-editing process, namely:⁸

1. Elimination Phase

Innate and adaptive immune work together to detect and destroy tumor cells. Cells involved: NK cells, NKT cells, $\gamma\delta$ cells, macrophages, and dendritic cells.

2. Equilibrium Phase

This phase is the longest phase of immune-editing. Due to the unstable selection of immunological which occurs continuously in cancer cells, eventually emerging variants of cancer cells

are able to escape from the immune response and subsequently entered escape phase.

3. Escape Phase

In this phase, cancer cells are immunologically successful in growing progressively. This happens because cancer cells undergo changes due to pressure by the immune system.

Basic Immunology

Human immune system is divided into two, namely innate immunity and adaptive immunity. Natural/innate/natural immunity is the default immunity that responds to foreign substances/pathogens even though the body has never been exposed to these substances. Innate immunity consists of epithelial barrier, phagocytes, natural killer cells, and complement proteins.^{1,9}

Adaptive immunity is a system that can recognize foreign substances that enter the body and can stimulate the development of immune responses that are specific to these substances.^{1,9}

Components of the adaptive immune system are B cells and T cells. B cells produce antibodies after being exposed to antigens from pathogens. When foreign antigens are presented to T cells, two types of effector T cells will form, namely CD4 + T- helper cells that facilitate the production of antibodies, and CD8 + T helper cells and cytotoxic cells that directly kill foreign cells (such as virus-infected cells or tumor cells). Adaptive immune response begins when tumor cell antigens are released by innate immune system and are taken by dendritic cells. These dendritic cells then migrate to lymph nodes; they carry these tumor antigens to T cells, so that T cells turn into cytotoxic T cells to destroy tumor cells.¹

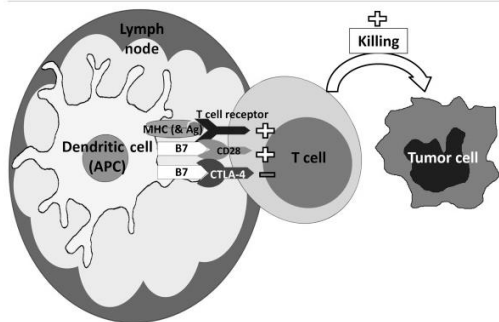


Figure 1. T cell activation phase and cytotoxic T lymphocyte antigen-4 (CTLA-4) immunologic checkpoint¹

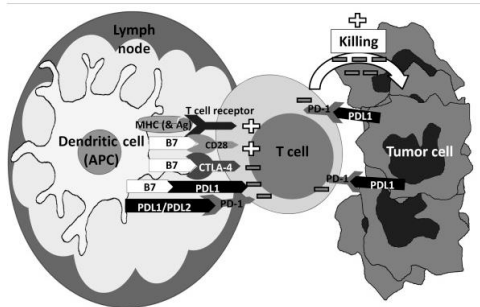


Figure 2. Relationship between T cell, dendritic cell, and tumor cell. T cells have various receptors including PD-1 and CTLA-4, while tumor cells also have receptors as a defense mechanism to activate T cell function.

The immune system has an important role in recognizing, controlling, and overcoming cancer, but cancer can induce immune suppression through several mechanisms, namely the secretion of immunosuppressive cytokines, loss of expression of major histocompatibility complex antigens, and interactions of Programmed cell death protein 1/Programmed cell death protein 1 ligands (PD-1/PD-L1) tumor cells with immune cells.

Cancer cells can prevent themselves from surveillance and destruction through resistance to adaptive immunity, which causes tumor-specific deactivation of tumor cells (Figure 2). Many types of cancer are found to express PD-L1 on the surface of tumor cells, which is a ligand of receptor PD-1 on T cells that have been known. The interaction pathway between PD-1 and PD-L1 causes downregulation and functional inhibition of T cells. There are two immune checkpoint inhibiting pathways that involve signaling via CTLA-4 or PD-1 with its ligands (Figure 1 and 2).

Immune Checkpoint Inhibitor

Cancer cells use several mechanisms to avoid immune response. One of them is through a pathway called an immune checkpoint that is able to influence and control the response of T lymphocytes. Tumor cells manipulate proteins in immune checkpoint pathway to avoid the immune response. The main known inhibitory pathways are the PD-1/PD-L1 pathway and the CTLA-4 pathway.⁵

a. Cytotoxic T-lymphocyte antigen-4 pathway

CTLA-4 pathway plays an important role in the activation of lymphocytes. Cytotoxic T lymphocyte antigen-4 (CTLA-4) is a receptor expressed on the surface of T cells during T cell activation phase. T cell activation requires the presentation of antigens in the context of major histocompatibility complex molecules and the stimulation of costimulatory signals by the B7 family of presenting cell antigens to interact with CD28 on T cells.¹

After T cell activation, CTLA-4 is translocated to the T cell plasma membrane. CTLA-4 binds members of the B7 family with a much higher affinity than CD28,b which decreases activated T cell function (Figure 3). CTLA-4 bdecreases T cell

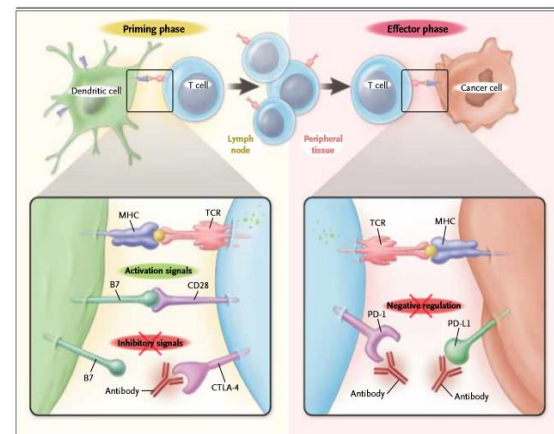


Figure 3. Blockade of PD-1 or CTLA-4 in Tumor Immunotherapy¹⁰

function that is activated not only by preventing stimulation of CD28 to its ligand, namely B7, but also by inducing the cessation of T cell function. Through this mechanism, CTLA-4 has an important role in maintaining homeostasis immunological normal.¹

CTLA-4 also regulates tumor immunity through Treg which shows high CTLA-4 levels. CTLA-4-expressed-Treg can trigger a lack of immune system response to tumor antigens. Tregs have been shown to exist in tumors and coexist with prime effector T cells. Thus, blocking Treg function through anti-CTLA-4 antibodies has the potential to eliminate Treg suppression and enhance antitumor immunity.¹

b. PD-1 / PD-L1 pathway

PD-1 is expressed by active CD4 + and CD8 + T lymphocytes, natural killer T cells, monocytes, and active dendritic cells. PD-1 is a negative regulator of T cell activity that limits T cell activity, especially in the effector phase, when interacting with two ligands, PD-L1 and PD-L2. When engaged through ligands, PD-1 inhibits the kinase signaling pathways that normally cause T cell activation.^{4,5}

Monoclonal antibodies anti-PD-L1 has properties similar to anti-PD1. Monoclonal antibodies anti PDL1 blocks the interaction between PD-1 receptor with PDL1. Some of these antibodies include BMS-936559 and MPDL3280A which have been tested in patients with solid tumors, including lung cancer.⁵

Immune Checkpoint Inhibitor Development

Nivolumab targets PD-1 receptor. The study of 129 patients with pretreated NSCLC who entered an increase in phase I dose of the nivolumab cohort trial of 1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously (IV) every 2 weeks showed that the overall survival rate for 1, 2, and 3 years were 42%, 18% and 24%, while results of 56%, 42%, and 27% respectively were indicated at doses of 3 mg/kg (n = 37) used for further clinical development. The response rate with NSCLC squamous (16.7 %) and NSCLC non-squamous (17.6%).^{1,6}

NSCLC squamous phase II trials, the response rate in patients with PD-L1 tumor expression <5% was 14%, while in patients with PD-L1 expression ≥ 5% is 24%. Phase III trials were performed on 272 NSCLC squamous patients who developed disease during or after first-line chemotherapy. Patients were randomized to receive nivolumab 3 mg/kg every 2 weeks, or docetaxel 75 mg/m² every 3 weeks. The average rate of overall survival was 9.2 months with nivolumab compared to 6.0 months with docetaxel (HR = 0.59, p <0.001). The one-year survival rate was 42% with nivolumab compared to 24% with docetaxel. The response rate was 20% with nivolumab compared to 9% with docetaxel (p = 0.008). The median of PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR = 0.62, p <0.001). PD-L1 expression did not show prognosis or prediction of treatment benefit. USA FDA gave approval to nivolumab as a treatment for metastasis NSCLC squamous patients with development on or after platinum-based chemotherapy in 2015.^{1,6}

In CheckMate 057 study, the nivolumab response rate compared to docetaxel was 19% versus 12% (p = 0.02). Based on the data, FDA approved nivolumab for the treatment of NSCLC metastatic patients with a progressive response on or after recent platinum-based chemotherapy. This agreement extends the indication of nivolumab in NSCLC to include non-squamous histology.^{1,6}

Research studies are conducted to evaluate the efficacy and safety of nivolumab monotherapy in patients with NSCLC who have recently undergone chemotherapy. The objective response was 31% (8/26) in PD-L1 positive patients and 10% (2/21) in PD-L1.1 negative patients.⁶

Nivolumab has been combined with platinum-based chemotherapy or anti-CTLA4 immunotherapy as a first-line treatment for advanced NSCLC, or with epidermal growth factor receptors (EGFR), but the research is still ongoing.^{1,6}

Pembrolizumab is a humanized IgG4 antibody that targets the PD-1 receptor. A study was conducted on 495 NSCLC patients who received pembrolizumab and found patients with RR 19.4% with a response duration of 12.5 months and overall surveillance of 12.0 months. US FDA has approved pembrolizumab for the first-line treatment of patients with NSLCC metastasis in patients who have tested positive PD-L1. Pembrolizumab can be given in tumors that are known to be progressive both during and after platinum-based chemotherapy.¹

A study found that a combination of anti-PD-1 and anti-CTLA-4 treatments had demonstrated effectiveness and toxicity that can be tolerated in patients with melanoma, so a study was conducted to evaluate pembrolizumab and ipilimumab in NSCLC patients. In this study, patients with NSCLC received pembrolizumab and ipilimumab every 3 weeks for four cycles followed by maintenance therapy for pembrolizumab. Preliminary data indicate pembrolizumab and ipilimumab have the effectiveness to suppress tumor growth with acceptable side effects of toxicity.⁶

The study of immunotherapy in NSCLC patients with metastatic brain found that pembrolizumab showed good results.^{1,6}

Atezolizumab (MPDL3280A) is a human IgG1 monoclonal antibody that targets PD-L1. The POPLAR study with sample of 287 showed that atezolizumab significantly improved OS. In this study, NSCLC patients who had received previous therapy were given atezolizumab 1200 mg IV every 3 weeks or docetaxel 75 mg/m² IV every 3 weeks, then the expression of PD-L1 was evaluated using the SP142 antibody test. The results of this study found that OS with atezolizumab was 12.6 months and with docetaxel only 9.7 months.^{1,6}

Based on BIRCH research, it was found that atezolizumab has high effectiveness in patients with NSCLC with high PD-L1 expression regardless of treatment history.^{1,6}

Durvalumab (MEDI-4736) is a fully human monoclonal antibody IgG1 that targets PD-L1. Based on the research of Phase I and II, it was found that

durvalumab have a higher response rate in NSCLC squamous (21%) than NSCLC non-squamous (10%).^{1,6}

Avelumab (MSB0010718C) is a fully human monoclonal antibody IgG1 that targets PD-L1. Avelumab is also capable of inducing cytotoxicity of cells mediated by antibody.^{1,6}

Many studies have been conducted to evaluate the effectiveness of the treatment of patients with progressive advanced NSCLC after platinum-based chemotherapy. Objective responses were observed in 22 (12%) patients. The median PFS was 2.7 months. RR in PD-L1 positive patients (n = 118) was 14.4 % and 10.0% in PD-L1 negative patients (n = 20).^{1,6}

Combination Therapy for Non-small Cell Lung Cancer

a. Combination of Anti-PD1 or anti-PD-L1 with chemotherapy

Chemotherapy and radiation modulate the immune response to tumors, and chemotherapy can induce the expression of PD-L1 in tumor cells. Preliminary clinical data for a combination of chemotherapy with anti-PD1, such as nivolumab and pembrolizumab, or anti PD-L1, such as atezolizumab, have been reported to have promising efficacy as first-line therapy and have a good safety profile.⁶

The group receiving the combination therapy in the study of KEYNOTE 021 has better RR and PFS than only pembrolizumab.⁶

Ipilimumab and tremelimumab are monoclonal antibodies recombined against cytotoxic CTLA-4. Based on studies in NSCLC patients, there was no significant benefit in patients who received chemotherapy before ipilimumab, especially patients with NSCLC squamous.

b. Combination of anti-PD-1/PD-L1 Antibodies with anti-CTLA4 antibodies

Preclinical studies initially suggested that the combination of blockade lines CTLA-4 and PD-1 will produce a synergistic antitumor activity. In patients with metastatic melanoma after administration of the combination therapy of nivolumab and ipilimumab, there was a reported increase in activity relative to each single therapy. The same combination shows antitumor activity with a longer response and a safety profile that can be handled in recurrent NSCLC.⁶

Research conducted on NSCLC collected 17 advanced NSCLC patients who had undergone a phase I multicohort KEYNOTE 021 study and were given pembrolizumab and ipilimumab as second-line therapy. The combination of these two therapies resulted in a RR of 55% (9% complete response) while disease control was found in all patients (100%) with grade 3 side effects of 11%. This study shows the results of the strong antitumor activity of pembrolizumab combined with ipilimumab in repetitive NSCLC patients.⁶

The magnitude of the clinical benefit with combination therapy is enhanced by the higher expression of PD-L1. An interesting finding was

found in two cohort studies, in patients with PD-L1 expression, more than 1% had RR 57% compared to 92% in 12 patients with PD-L1 expression $\geq 50\%$.⁶

In Phase 1b studies, 102 advanced NSCLC patients who had not received immunotherapy, a combination of durvalumab and tremelimumab was tested. Serious side effects were found in 36% of patients and resulted in 28% of patients stopping therapy. Based on available clinical and safety data, durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg every 4 weeks were chosen for dose expansion. Among 63 patients who responded, ORR was 23% , and antitumor activity was found independent of PD-L1 status.⁶

c. Combination of Immunotherapy with Targeted Therapy

Targeted therapy is recommended as NSCLC first-line therapy with EGFR mutations. In pre-clinical studies, it was considered promising by combining PD-1 and EGFR-TKIs inhibitory therapy.

Based on a retrospective study of 125 NSCLC patients, patients with positive PD-L1 were more sensitive to EGFR-TKIs than negative PD-L1, and this affected the response rate ($p = 0.01$); in addition, positive PD-L1 was often associated with histology adenocarcinoma ($p = 0.05$).¹¹

Other retrospective studies of 56 patients with EGFR mutations in pulmonary adenocarcinoma showed longer PFS ($p = 0.001$), and longer OS ($p = 0.004$) after being treated with TKI in positive PD-L1 patients.¹¹

National Comprehensive Cancer Network Guidelines for Non-Small Cell Lung Cancer with Positive PD-L1 Expression

Human immune checkpoint inhibitors PD-1 and PD-L1 are useful for increasing anti-tumor immunity. PD-1 receptors are expressed by cytotoxic T cells. Nivolumab and pembrolizumab inhibit PD-1 receptors. National Comprehensive Cancer Network (NCCN) recommends examining PD-L1 expression before giving first- line therapy to NSCLC metastasis patients with negative or unknown results in EGFR, BRAF, V600E, ALK and ROS1 mutations.¹²

a. First Line Therapy

Pembrolizumab (category 1) as first-line therapy for non-squamous or squamous NSCLC patients with positive PD-L1 expression of $>50\%$ accompanied by negative/unknown mutations of EGFR, BRAV V600E, ALK, ROS1.¹²

b. Subsequent Therapy

- Pembrolizumab

NCCN recommends pembrolizumab (category 1) as a subsequent therapy for patients with non-squamous/squamous NSCLC metastasis with PD-L1 expression of $>1\%$. FDA approved the administration of pembrolizumab as subsequent therapy in NSCLC patients with progressive results after receiving platinum-based chemotherapy provided that the tumor was found to produce PDL1.¹²

- Atezolizumab is recommended as a subsequent therapy for patients with non-squamous metastases and squamous cells in NSCLC.¹²

Side Effect of Immunotherapy

The side effects are called immune related adverse events (irAEs).¹²⁻¹⁴

1. Side effects that often happens
 - a. Systemic side effects
Decreased appetite, nausea, vomiting, fatigue and cough.¹³
 - b. Dermatology
Measuring the severity of toxicity of the skin leads to the common terminology criteria for adverse events (CTCAE) classification.¹⁵
 - c. Colitis
Diarrhea is most often found in patients using CTLA-4 inhibitor therapy. Most often found in the initial 6 weeks of treatment.^{13,16}
2. Side effects that rarely happens
 - a. Hepatotoxicity
Complaints were found in patients using PD-1 inhibitor therapy and CTLA-4 inhibitors.¹⁷
 - b. Ophthalmology
In severe cases, oral corticosteroid administration can be considered.¹³
 - c. Renal
Renal insufficiency is reported in patients receiving CTLA-4 inhibitors (ipilimumab) and PD-1 inhibitors (pembrolizumab).¹³
 - d. Pancreas
Increased serum amylase and lipase levels were found with the use of CTLA4 and PD-1 inhibitors.¹³
 - e. Neurological disorder
Myasthenia gravis, aseptic meningitis, enteric neuropathy and transverse myelitis, and Guillain Barre Syndrome (GBS).¹³
 - f. Lung disease
Diseases that have been reported on the use of CTLA-4 inhibitor (ipilimumab) are sarcoidosis and pneumonia, while the use of agents PD-1 inhibitor (pembrolizumab) reported the occurrence of pneumonitis even though the incident very rarely happens.¹³
 - g. Hematology
Side effects were reported after the use of CTLA-4 inhibitors: red cell aplasia, neutropenia, thrombocytopenia and Acquired hemophilia A.¹³
 - h. Endocrine disorders that can occur are hypophysitis, hypothyroidism, and adrenal insufficiency.¹³

SUMMARY

Lung cancer is able to manipulate the patient's immune response system through various mechanisms, including through changes in the composition of cytokines, the emergence of regulatory T cells, inhi-

bition of cellular immune function, and disruption of tumor antigen presentation process. The new therapeutic approach works by stimulating the anti-cancer immune response so that the development of lung cancer cells can be avoided. Immunotherapy in lung cancer is an inhibition of immunological tolerance to lung cancer (immune checkpoint inhibition) that is able to affect and control the response of T lymphocytes. Immune check point inhibition can be considered as a therapy for NSCLC after failing with platinum-based chemotherapy. Recent studies have shown that immune check point inhibition monotherapy is superior in first-line treatment than platinum-based chemotherapy. However, the benefits of immunotherapy can only be felt for a small proportion of the population (30%) whose tumors program PD-L1 was above 50%. Therefore, several strategies are under investigation. One option for patients with PD-L1 expression lower than 50% might be a combination of immunotherapy with platinum-based chemotherapy or with immunotherapy with a different target.

Currently, immunotherapy is a ray of hope in overcoming lung cancer. However, all of these strategies and studies are still in the research stage and are quite expensive in addition to have side effects.

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