REVIEW

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Immunotherapy for Non-Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related mortality worldwide, and more than 80% of cases are of non-small cell lung cancer. Although chemotherapy and molecularly targeted therapy may provide some benefit, there is a need for newer therapies for the treatment of patients with advanced NSCLC. Immunotherapy aims to augment the recognition of cancer as foreign, to stimulate immune responsiveness, and to relieve the inhibition of the immune response that allows tolerance to tumor survival and growth. Two immunotherapeutic approaches showing promise in NSCLC are immune checkpoint inhibition and cancer vaccination. Although currently immunotherapy does not have an established role in the treatment of NSCLC, these patients should be enrolled in formal clinical trials.

Keywords: Carcinoma, Non-Small-Cell Lung; Immunotherapy; Cancer Vaccines

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, including the United States. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases. Among treatment for NSCLC, molecularly targeted therapy has been significantly developed in the last ten years. However, prognosis of NSCLC has been gradually improved. Conventional chemotherapy obviously has reached the limit. Additional benefits are also limited even though these are administered with bevacizumab, angiogenesis inhibitor.

New therapeutic approaches for patients with advanced NSCLC are required in order to improve the results of treatment. Accordingly, we would like to discuss the potential role of immunotherapy as a new therapeutic approach.

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Rationale

Immunotherapy is different from targeted therapy which is a type of treatment to block the process of cancer cell growth by selectively targeting rapid cell proliferation and interfering with growth and invasion of tumor.

The goal of immunotherapy is to help the immune system recognize cancer as foreign, stimulate immune responsiveness and relieve the inhibition of the immune system that allows tolerance of tumor survival and growth.

This approach is based on the assumption that the immune system plays a key role in surveillance and removal of malignant tumors and tumors have evolved to escape from the immune system. There are immunotherapies, such as interleukin-2 (IL-2), interferon, ipilimumab, sipuleucel-T and human papillomavirus vaccines, supporting this theory and those are used for the prevention or treatment for specific types of cancer.

Until recently, NSCLC has not been thought to be associated with the immune system and be destroyed by the immune system. Several immunotherapies, such as IL-2, interferon and bacillus Calmette-Guerin, were attempted but failed to control the immune system in the patients with NSCLC. Due to those results, immunotherapy was considered unsuccessful.

New drugs have been developed according to advances in understanding the immune system. Therefore, the promising results have been showed in clinical trials that evaluate the new immunotherapy. In particular, immune checkpoint inhibition and vaccination have attracted a fair amount of attention.

Immune Activation and Checkpoint Inhibition

1. Mechanism

For effective attack to tumor cells in immune system, the strategies, such as recognition of tumor cells, delivery of tumor antigen to T cell, T-cell activation and directly attack to cancer cells, are required.

Immune recognition is initiated by antigen presenting cells (APCs), such as dendritic cell and delivers tumor antigen to major histocompatibility complex (MHC) molecules on the surface of the cell. This process triggers the expression of B7 molecules on APCs and then, which migrate to the lymph nodes.

In the lymph nodes, APCs delivered tumor antigen by the interaction with antigen-specific T-cell receptor. If there is an interaction between B7 and CD28 on T cells, T-cell activation occurs and T cell moves out of the lymph nodes.

If activated T cells contacts with tumor cells and recognizes antigens related to MHC which expressed in the tumor, T cells are proliferated and release cytolytic enzymes (perforin and granzyme) and also secrete cytokines which assemble other members of immune system. As a result, tumor is destroyed but memory T cells are generated.

Various immune check points exist in order to protect (the body) from harmful inflammation and autoimmunity. The immune response is inhibited by these. In malignant tumor, these immune check points may promote immune tolerance and malignant tumor progression. In the clinical trial for the patients with NSCLC, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD1) are known as a check point.

CTLA-4 mainly has a role in regulating T-cell activity at early stages of T-cell activation and its expression on T cell increases after exposure to antigen. CTLA-4 is likely to compete with CD28 but binds to B7 with much higher avidity (than CD28). Also, it transmits an inhibitory signal to T cell and inhibits costimulatory signals, which are generated by the interaction of CD28 with B7 and necessary for T-cell activation.

In contrast to CTLA-4, PD1 inhibition occurs primarily in tumors and it acts mainly in lymphoid organs. PD1 expression increases on activated T cell. In addition, PD1 recognizes tumors by T-cell receptor and influences inactivation of T cell, involving programmed death ligand 1 (PDL1). For the primary mechanism of tumor PDL1 expression (PDL1 expression on tumors), it is assumed that the inflammation is induced in tumor microenvironment, which mediated by interferon-γ. Another hypothesis is oncogene linked to PDL1 tumor expression, regardless of tumor inflammation.

2. CTLA-4 antibodies: ipilimumab

Ipilimumab is IgG1 CTLA-4 monoclonal antibody and extends the period of survival in patients with metastatic melanoma. Phase III study for patients with metastatic squamous cell NSCLC who have never received chemotherapy has been conducted. The study design is to compare the standard therapy of carboplatin and paclitaxel versus concomitant administration of ipilimumab (NCT01285609).

This study is based on the results of the phase III study comparing the standard therapy of carboplatin and paclitaxel versus concomitant administration of ipilimumab in patients with metastatic squamous cell NSCLC who have never received chemotherapy[1]. In subtype analysis of this study, patients with squamous cell carcinoma, who received concomitant administration of ipilimumab, showed the primary benefit. In addition, another clinical trial with ipilimumab administration with chemotherapy or immunotherapy, comparing to the standard second-line chemotherapy, is ongoing.

3. PD1 and PDL1 antibodies

The initial findings of study were highly promising because patients with chemotherapy-refractory metastatic NSCLC had responded to the immunotherapy using PD1 and PDL1 antibody for a long time. The phase III study for patients with metastatic NSCLC is ongoing and the concomitant administration is also being evaluated. Research for biomarker that may influence the treatment response such as PDL1 expression on tumors has been proceeding additionally.

4. PD1 blocking antibodies

1) Nivolumab: Nivolumab is an IgG4 monoclonal antibody to PD1 and two phase III clinical trials with it as a second-line therapy for patients with advanced NSCLC are ongoing. In the phase I clinical study, nivolumab was administered intravenously to 306 patients, who have different types of tumor, every two weeks for a maximum of two years and the dose was gradually increased[2,3]. As a result of this study, favorable outcomes were presented. One hundred twenty-nine patients with NSCLC, who received the treatment previously, were included in this study. These patients had received chemotherapy several times and especially, 54% of them had done at least three kinds of chemotherapy due to advanced stage cancer. Overall response rate was 17% and the median duration of response was 47 weeks. Other 10% of patients showed

stable disease for six months and their median survival time was 9.6 months. Thirty-seven patients who received it at doses of 3 mg/kg presented 24% of response rate and 14.9 months of median survival.

Initially, squamous cell carcinoma had been considered to show better response to nivolumab. However, that result was not clear at the follow up. Only 14% of patients had the 3 or 4 stages of drug toxicity and autoimmune toxicity was also rarely occurred. Nivolumab related pneumonia was observed in 8 patients (6%). PDL1 expression on tumors was evaluated in 63 of 129 patients with NSCLC. Although 49% of them were PDL1 positive, it was not associated with the cell type of NSCLC. The response rate was 16% in PDL1 positive tumor and 13% in PDL1 negative tumor[4].

2) Lambrolizumab: Lambrolizumab (MK-3475), an IgG4 monoclonal antibody to PD1, is known as 'breakthrough therapy' for the treatment of patients with advanced melanoma and this status was granted by Food and Drug Administration (FDA) on January 2013.

Preliminary results of phase I cohort study of lambrolizumab for the patients with NSCLC were reported by World Conference on Lung Cancer meeting in 2013[5]. Its effectiveness was evaluated in 38 patients who treated previously due to advanced NSCLC. As a result of evaluation, 9 patients (24%) showed at least partial response and the median survival time was 51 weeks. Mostly, they endured the treatment well except two cases of a pneumonitis and a pulmonary edema.

5. PDL1 blocking antibodies

1) MPDL3280A: MPDL3280A, a monoclonal antibody to PDL1, is designed to avoid antibody dependent cell mediated cytotoxicity of activated T cell. Preliminary results of phase I cohort study of MPDL3280A was reported by annual American Society of Clinical Oncology meeting and World Conference on Lung Cancer meeting in 2013[6,7]. MPDL3280A was administered intravenously every three weeks for a year. The dose was increased gradually but did not reach the maximum tolerated dose. Fifty-three patients received this treatment and 23% of them responded to it in evaluation of efficacy. As a result of evaluation of toxic reaction for 85 patients with NSCLC, 11% of them experienced side effects. Nobody had pneumonitis but hyperglycemia and dyspnea were reported.

2) BMS-936559: BMS-936559 is a human IgG4 monoclonal antibody to PDL1. For patients with NSCLC, melanoma and renal cell carcinoma, the phase I clinical study with this medicine was performed[8]. They received BMS-936559 every 2 weeks for a maximum of 2 years. Ten percent of 49 patients with NSCLC showed a partial response and 12% of them did stable condition at least for 24 weeks.

3) MEDI4736: MEDI4736 is an IgG4 monoclonal antibody to PDL1 and preliminary report about the phase I clinical study was presented at 2013 European Cancer Congress[9]. Dose limiting toxicity was not appeared and pneumonitis was not observed in 11 patients who were evaluated for safety. Among 11 patients with NSCLC who were evaluated for efficacy, 3 achieved partial response, 2 stable disease, and 1 progression of disease.

Vaccination

NSCLC shows potentially genetic variation that may be recognized as a foreign substance by immune system. Vaccine increases the exposure to these antigens and promotes the activation of immune cells.

1. Melanoma associated antigen-A3 vaccine

Melanoma associated antigen (MAGE)-A3 is expressed normally in germ cells of testis and trophoblasts of placenta and also, expressed in 30% to 50% of all tumors, including NSCLC. GSK1572932 is a recombinant DNA vaccine composed of MAGE-A3 and immunoadjuvant AS15. There is the phase III study of GSK1572932[10,11]. In this study, this medicine was administered with adjuvant chemotherapy and supplements to 2,270 patients with early NSCLC. Disease free survival time is the primary end point and the preliminary results will be reported in 2014.

2. Tecemotide

MUC-1 is a cell-surface glycoprotein overexpressed or abnormally glycosylated in epithelial malignancies, including NSCLC. Tecemotide is a vaccine composed of BLP25 MUC-1 lipopeptide, monophosphoryl lipid A, cholesterol, dimyristoyl phophatidylglycerol and dipalmitoyl phosphatidylcholine.

Phase III study of Tecemotide for patients with advanced partially NSCLC (stage III) was performed for the purpose of the treatment and if the patient completed the chemotherapy, it was used for adjuvant chemotherapy[12,13]. Prior to initial vaccination, low-dose cyclophosphamide was administered in order to augment the effect of vaccine. This study evaluated the median survival and there is significant difference compared to the placebo group. However, as a result of subgroup analysis, the survival was more improved in patients, who treated by concurrent chemoradiation than sequential therapy when comparing those treatment groups to the placebo group (median, 30.8 months vs. 20.6 months; hazard ratio, 0.78; 95% confidence interval, 0.64–0.95).

3. Belagenpumatucel-L

In order to avoid the immune surveillance, tumor cells sometimes release transforming growth factor beta (TGF-β) around tumors and protect themselves from the immune

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recognition or attack. TGF-β suppresses the activation of T and B cells, dendritic cell maturation and antigen presentation, natural killer cells and lymphokine activated killer cells, but induces immunosuppressive T regulatory cells. Belagenpumatucel-L is an allogeneic tumor cell vaccine, composed of irradiated NSCLC cell lines, to block TGF-β secretion. The phase III study of belagenpumatucel-L maintenance therapy compared to placebo began enrolling patients with NSCLC who responded to the first-line chemotherapy or presented stable condition[14,15].

4. Other vaccines

A lot of phase III studies with respect to various vaccines are ongoing. Also, many studies for development of new vaccines and for vaccines combinated with other immunobiologics, chemotherapeutic agents and target agents have been proceeding. DNA and RNA sequence analysis and the development of new drugs are thought to be capable of the invention of a personalized vaccine composed of several types of antigen expressed by tumor characteristics of each individual patient.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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