

EDITORIAL

Immunotherapy in non-small cell lung cancer: The past, the present, and the future

Lung cancer is a malignant tumor with the highest morbidity and mortality in the world. Non-small cell lung cancer (NSCLC) is the most common pathological type; however, the effects of NSCLC treatments are unsatisfactory. Tumor immunotherapy represented by immune checkpoint inhibitors (ICIs) has a bright future in this background.

The past: The discovery of immune checkpoint inhibitors

Since 1998, the Food and Drug Administration has approved a series of tumor immunotherapies, such as cytokines, Provenge, anti-CTLA-4 antibodies (ipilimumab), and chimeric antigen receptor T-cell therapy. During the 2000s and 2010s, these tumor immunotherapies were only applied to a few types of tumors, and there were a number of failures. In 2017, ICIs, represented by PD-1/PD-L1, were approved for use in different cancer treatments.

In the past, it was thought that immunotherapy would strengthen immunity, but this has proven to be ineffective. The current theory is that tumors develop because of defects in the immune system, and the goal of immunotherapy should be to look for loopholes rather than reinforcing immunity. Immunotherapy today is successful because we have been able to address immune deficiency in patients with lung cancer. A high expression of PD-1/PD-L1 and the suppression of T cells are observed in these patients. This is managed with the administration of PD-1/PD-L1 inhibitors. Therefore, immunotherapy needs to determine the site of a patient's immune deficiency and then look at how to address the deficiency. Only in this manner can the efficiency of immunotherapy be improved.¹⁻³

Tumor immune responses are often selectively suppressed around tumor tissues without systemic immune inhibition. Immunotherapy does not work in many patients, not because the immune response cannot be systematically activated, but because the immune response is not activated around the tumor tissue. In addition, when treated with tumor vaccine or cell therapy, a large number of effector T lymphocytes can be detected in the blood, but the tumor continues to grow, which is the result of immunosuppression in the tumor microenvironment. Immune checkpoint is the brake pad of the immune pathway, which will suppress T lymphocytes when activated. The PD-1/

PD-L1 inhibitor inhibits this checkpoint, thereby releasing T cells and restoring its function, enabling them to recognize and kill tumor cells.^{1,4} Anti-PD-1/PD-L1 therapy has three unique characteristics: it can normalize tumor immunity, selectively target the tumor microenvironment, and reshape the immune response in the tumor microenvironment.

However, patients may also have many other suppressor molecules. Only 25–30% of tumors use the PD-1/PD-L1 pathway to suppress the immune response, whereas other tumors use other molecular pathways or mechanisms to escape the immune response, which we currently know little about.^{1,4}

The present: The application of immunotherapy

Since 2015, the FDA has approved the use of four different ICIs for the treatment of NSCLC, including anti-PD-1 nivolumab and pembrolizumab and anti-PD-L1 atezolizumab and durvalumab.

At present, two thirds of NSCLC patients in China have negative driver gene mutations, thus progress in this field will significantly guide clinical practice in lung cancer in China. For advanced NSCLC, the status of immunotherapy has risen from a second-line to a first-line scheme, and the application method has been expanded from single to combined drug use.^{2,5} In the case of lung squamous cell carcinoma, KEYNOTE-407 findings suggest that pembrolizumab combined with carboplatin and paclitaxel or albumin-paclitaxel can significantly improve patient survival, and this combination regimen was recommended as the first choice for patients with lung squamous cell carcinoma without pembrolizumab contraindication in the latest National Comprehensive Cancer Network (NCCN) guidelines (version 1, 2019) (Type I evidence).⁶

What are the advantages of immunotherapy in NSCLC? First of all, it is more effective. The five-year survival rate of advanced NSCLC is < 5% with traditional treatment. But immunotherapy with PD-1/PD-L1 antibodies alone can lead to a five-year survival rate of 16%. The efficiency will be greatly improved if the dominant population is included or if a drug combination is used. Secondly, the duration of the curative effect is long. Immunotherapy can significantly prolong the overall survival of patients and thus benefit the population. Thirdly, the side effects of

immunotherapy are relatively mild. The actual incidence of severe side effects above grade 3 and 4 is < 10% and fatal adverse reactions are lower. Finally, immunotherapy has longer effectiveness. Patients with two consecutive years of treatment can benefit for a long period of time after withdrawal.

The future: The development of immunotherapy

First-line treatment of advanced non-small cell lung cancer

First-line treatment means that immunotherapy is the first choice for patients with advanced NSCLC. A large amount of experimental data has shown that immunotherapy is superior to chemotherapy in many aspects in the dominant population with positive tumor biomarkers and in the process of combination therapy.⁷

Patients with positive driver genes: Limited efficacy

In NSCLC patients with positive driver genes, even if the patients have high PD-1/PD-L1 expression and can be treated with PD-1/PD-L1 inhibitors, the curative effect is still limited according to first-line and second-line immunotherapy statistics.

Neoadjuvant immunotherapy

Preoperative immunotherapy is superior to chemotherapy in terms of toxicity and pathological effectiveness. Immunotherapy can be performed before surgery as part of neoadjuvant treatment combined with chemotherapy and better results can be obtained. At present, we have only witnessed the dawn of neoadjuvant immunotherapy. Confirmatory data from stage III randomized controlled trials are still required to ascertain whether immunotherapy can be used as standard therapy.⁷

Immunotherapy in lung cancer is one of the most promising research directions in the field of cancer treatment.

The ultimate goal is to screen for patients who would benefit from specific immunotherapy and to effectively treat more people who could benefit from it. Only with in-depth understanding of the mechanism involved in tumor evasion from the immune system and the tumor-related immune microenvironment can we combine methods of immunotherapy, radiotherapy, chemotherapy, and targeted therapy to improve the outcomes of lung cancer treatment. There is still a long way to go in the fields of treatment modes, molecular markers, combined therapy, and the overall management of immunotherapy.

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