Emerging Vaccine Immunotherapy In NSCLC: The Adverse Reactions of Recent Clinical Trials and Future Directions

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Abstract. Lung cancer is the most common primary malignant tumour of the lung today and can be classified into two types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), depending on their histopathological characteristics. The incidence and mortality rates of lung cancer are currently extremely high and, on the rise, worldwide. However, normal scientific methods are not sufficient enough to cure lung cancer, but only to monitor the spread of cancer cells and inhibit them to a certain extent, so it is urgent to find effective treatments for lung cancer. This article focuses on the mechanisms of cancer vaccines for non-small cell lung cancer and a review of recent vaccine immunotherapy for lung cancer. This article also discusses some clinical adverse reactions, in order to provide a reference for vaccine immunotherapy in the future.

Keywords: Vaccine immunotherapy, Non-small cell lung cancer, Clinical trial.

1. Introduction

Lung cancer is still the most common cancer in the world it is estimated that there are over 2 million people diagnosed with lung cancer and 1.76 million patients died due to lung cancer every year [1,2]. Although the rate of new cases and death rate of lung cancer in the United States are decreasing year by year, Lung cancer continues to be the most detected and the deadliest cancer, at 43.2% and 32.8% respectively in 2018 [3–5]. Meanwhile, China also suffers from lung cancer and has become the country with the newest cases of lung cancer. This has not only caused pain to the patients but also placed a heavy economic burden on their families and China [3]. Meanwhile, in these lung cancer patients, non-small-cell lung carcinoma (NSCLC) and small-cell carcinoma (SCLC) are the major subtypes of lung cancer that cause death. It is worth noting that the proportion of non-small-cell lung carcinoma is much higher than the proportion of small-cell carcinoma, the former accounted for 85% of lung cancer, while SCLC accounted for only 15%, which means the proportion of NSCLC patients is about 5.7 times that of SCLC [2,6,7]. NSCLC is also of great interest because of its low cure rate, high recurrence rate, and short survival [8,9]. However, unfortunately, after several years of research, there is still no a well treatment with fewer adverse reactions developed [8], and NSCLC still needs to be tackled.

Cancer immunotherapy is a form of treatment that uses immune cells and enhances their function to eliminate cancer. It helps the immune system to identify and attack specific cancer cells, boosts immune cells to destroy cancer, and also provides the body with additional substances to enhance the body's immune response. To date, lung cancer immunotherapy has been developed in various forms, such as tumour vaccines, cytokines, immune checkpoint inhibitors and more [10]. Among these, tumour vaccines can be divided into two categories: preventive and therapeutic. The preventive category, such as hepatitis B vaccine and HPV vaccine, can be used to prevent cancer by preventing the infection of cancer-causing viruses. Therapeutic vaccines, on the other hand, are designed to activate cellular immunity in the body by introducing tumor-associated antigens, thereby achieving a
therapeutic effect. Lung cancer vaccines are evolving and learning from immune checkpoint inhibitors and have been refined to achieve better therapeutic results [11].

However, the researchers did not observe a large number of exciting results in clinical trials, and many trials discontinued serious adverse reactions and low efficacy. Based on the basic research and development of vaccine immunotherapy and the adjustment of drug regimens, researchers have synthesized more kinds of vaccines and designed more reasonable drug use schemes. The discussion of the results of these clinical trials could provide some meaningful references for the drug regimen and patient standards of the next clinical trials. In this review, we will discuss the progress of current clinical trials of vaccine immunotherapy for NSCLC and the main adverse reactions that lead to the discontinuation of clinical trials, and propose some potential ways to reduce adverse reactions.

2. Immunological mechanisms of vaccine immunotherapy for NSCLC

The formation of cancer is a complex process, and the molecular mechanisms involved are not yet precisely understood. However, the development of NSCLC can be influenced by many external factors, such as smoking, which is one of the most important factors. Cigarette smoke could cause DNA damage and miRNA dysregulation, which is related to the development of NSCLC [12].

Tumour vaccine was proved to be an effective immunotherapy. The three main categories of vaccine therapy for NSCLC currently include antigen-specific vaccines, tumour cell vaccines and peptide/protein vaccines [13].

TG4010 is a suspension of recombinant modified cowpox virus capable of encoding MUC1 tumour-associated antibody and interleukin 2 (IL-2) [14]. MUC1 is a class of high molecular weight glycoproteins that are expressed in T cells, B cells and dendritic cells [15], but in the tumour cells of NSCLC, MUC1 expression is abnormal and can reach more than 100-fold of what it would normally be. It is the abnormal expression of MUC1 in tumour tissue that makes it a potential biological marker of tumours and is now used in the diagnosis and biological treatment of tumours. MUC1 is capable of providing antigenic stimulation to mediate cellular responses and IL-2 acts to optimize antigen presentation to T cells. In addition, viral vectors could also increase the immune response.

Transforming growth factor beta (TGF-β) is an immunosuppressive cytokine with a broad spectrum of inhibitory effects on the immune response through different mechanisms. In advanced tumours, TGF-β has instead a tumour-promoting effect by regulating genomic instability, epithelial mesenchymal transition and immune evasion, making blockade of TGF-β signaling an effective approach to treating tumours. Belagenpumatucel-L is a therapeutic, genetically modified allogeneic tumour cell vaccine that inhibits the production of TGF-β2 mRNA. Because it can effectively block TGF-β signalling pathway, it is also used in the treatment of NSCLC [16].

IDO is an important immunomodulatory molecule in the tumour microenvironment, mostly acting as a negative immunomodulator. The activation of IDO-specific cytotoxic CD8+ T cells in the tumour microenvironment by the IDO1 antigen introduced by the peptide vaccine will remove IDO-positive cancer cells and immunosuppressive cells from the microenvironment, thus reversing the microenvironmental state and enhancing the anti-tumour immune response [17]. Combining IDO with immunotherapy and chemotherapy can be more effective in treating cancers such as NSCLC, and the combination of IDO peptide vaccine and PD-1 inhibitor is currently being used in clinical trials [18].

3. Current research progress of vaccine immunotherapy for NSCLC

Over the past five years (2017–2021), 15 lung cancer vaccine research projects have been reported worldwide [19–33]. Most of the projects are in Phase I to II trials, only one is in the experimental development phase and the other is in the improvement phase. Because non-small-cell lung carcinoma is a major subtype of lung cancer, most lung cancer vaccine research has focused on non-small-cell lung carcinoma.
Although there is no proven vaccine available as a powerful treatment for NSCLC, it is reassuring to note that many of the 15 lung cancer vaccines performed well. A novel autologous modified-DC vaccine, studied by Ge et al., performed well in a Phase I trial in which half of the patients did not relapse and only two were reported to have died during follow-up, and the vaccine is effective in improving the quality of life of patients. If it can prolong the Time To Progress (TTP) and Progress Free Survival (PFS) in follow-up clinical trials, it has the potential to become one of the effective means for the treatment of NSCLC [21]. The IDO peptide vaccine has been shown to improve survival in phase I clinical trials over five years, non-small-cell lung carcinoma increases the overall six-year survival rate for patients with stage 3 and stage 4 to 20 percent [23]. Using UV1 Vaccine, a Second Generation Telomerase Based Vaccine, there was a significant increase in PFS and OR (Overall Survival) after treatment in advanced NSCLC patients, especially with a 4-year survival rate of 34%, and the immune responses triggered by UV1 are dynamic and long-lasting, meaning that the UV1 vaccine if successfully tested in subsequent clinical trials, could become one of the more effective treatments [19]. In addition, the performance of the modified TG4010 vaccine was also excellent, TG4010 expressed MUC1-specific CD8 + response, and there was epitope diffusion, which is very helpful to the cure and prognosis of advanced NSCLC patients [31].

The combination of the vaccine and other therapies works better than the drugs alone. In 2020, Ott et al. reported the combination of NEO-PV-01 vaccine and PD-1 therapy for NSCLC, bladder cancer and melanoma, and PD-1 epitope proliferation was consistent with vaccine-mediated tumour cytotoxicity, specific and persistent T cell response to new antigen epitopes [26].

4. Adverse reactions of vaccine immunotherapy for NSCLC

In a considerable number of tumour vaccines in clinical trials, the adverse reactions associated with their use are troublesome, which weakens the safety to a certain extent and slows down the process of clinical application.

It was found that clinical trials at an early stage showed a wide range of vaccine-related adverse reactions. A clinical study of personalized dendritic cell vaccine showed that the adverse reactions in clinical trials were I/II grade, including local skin reactions and untreated epidemic low fever[32]. The phase I trial of the Hu-rhEGF-rP64k/Mont vaccine showed that the patients were well tolerated, and the main adverse events were dizziness, injection site reaction, tremor, and some adverse events such as neutropenia and leukopenia. In this experiment, 14 cases (66.67% of 48 cases) reported adverse events, mainly in grade I/II, and 1 case in grade III. The researchers believe that the adverse reactions in some of these cases may be related to previous chemotherapy [33]. Another phase I trial of intratumoural injection of autologous DC (AdCCL21-DC) overexpressing CCL21 found that influenza-like symptoms and bloody sputum, nausea and fatigue were common symptoms. Three of the 17 patients had four possible vaccine-related adverse events, which the researchers did not believe to be clearly linked to the dose or plan[24]. These vaccines in the early stages of clinical trials tend to show more but mild adverse reactions, but their efficacy remains to be seen.

Vaccine immunotherapy in combination with known drugs is a potential way to enhance efficacy, but it also has a greater risk of toxicity to some extent. The combination of tecemotide and bevacizumab was evaluated as safe, but 27 of 68 patients developed grade 3 toxicity during the first phase of the evaluation. the most common adverse reactions were leukopenia, lymphocytopenia, and neutropenia. In the later experiment, 11 patients had grade 4 toxic reactions and 1 patient had fatal adverse reactions due to sepsis [27]. Although these adverse reactions do not affect the overall safety of the treatment, they may include mechanisms that damage the immune system in the body. In the future drug design and treatment design, personalized drug use can be designed according to the patient's basic medical history and medication history, which may reduce the level or frequency of adverse reactions.
5. Conclusion

This article analyzes the last five years of lung cancer vaccine researches which reveals that there are not many cancer vaccines available for the treatment of NSCLC, but there are several promising vaccines, such as the IDO peptide vaccine, the UV1 vaccine and the modified TG4010 vaccine, which have shown excellent performance in clinical trials in terms of improved survival rates and longer survival. Notably, the effects of combining vaccines with other therapies or drugs are also impressive, and some vaccines, such as NEO-PV-01, have shown substantial improvements in their efficacy when combined with other therapies. These facts suggest that lung cancer vaccines may be a promising treatment option for lung cancer in the future, and that combination therapy may be a better way to treat lung cancer.

We are also concerned about the adverse reactions associated with the use of the vaccine. Although some of these mild adverse reactions do not hinder the progress of clinical trials, paying attention to the widespread adverse reactions of other vaccines is equally important in improving the efficacy and safety of vaccine immunotherapy. Reasonable screening of patients participating in clinical trials can help to reduce the occurrence of adverse reactions, similarly, taking personalized drug administration for different patients and reasonably balancing the relationship between cancer vaccine and basic medication may be a potential way to improve the efficacy. We expect that future clinical trials of vaccine immunotherapy for NSCLC will continue to produce encouraging results.

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