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Research Article

The Research Progress of Immunotherapy forAdvanced Lung Cancer

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Abstract: Lung cancer is one of the most fatal tumors at present. Although early lung cancer can be effectively intervened through surgery, the five-year survival rate is less than 55% because of its tendency for relapse and drug resistance. With the development of immunotherapy, such methods like activating the immune system and relieving immune tolerance have become the new direction in the systemic treatment of tumors. The newly discovered mechanism of immunostimulatory fatigue explains why immunotherapy is not very effective in some patients and finds that low-dose decitabine can relieve immunostimulatory fatigue. What's more, radiotherapy has a significant effect on the killing of local tumors, then disintegrated tumor cells can release antigens and further activate the body's immune system. Therefore, immunotherapy in combination with radiochemotherapy has shown great prospects of achieving efficacy on patients with lung cancer from systemic and local levels. This article describes the new progress of that method in treating lung cancer.

Key words: lung cancer, immunotherapy, immunostimulatory fatigue, radiotherapy, decitabine

0 Introduction

Lung cancer is one of the most fatal tumors at present. For patients who received local treatment in early stage, the 5-year survival rate is lower than 55%, and the 3-year distant metastasis rate is 20%-40%; For patients with distant metastasis or in stage III, the 5-year survival rate is less than 25%[1-3]. At present, For the medical treatment for non-small cell lung cancer without gene mutation, doctors mainly use standard first-line chemotherapy regimen which are based on platinum, but the efficacy of this method is only 15% to 30% [4-5]. The efficacy of paclitaxel-based second-line chemotherapy regimen is still not more than 25%[6] after adopting the first-line chemotherapy. Some studies have shown that in the advanced stage of non-small cell lung cancer, the efficacy of immunotherapy is better than that of the current second-line chemotherapy regimen and first-line chemotherapy regimen for patients with high expression of programmed cell death 1 ligand 1(PDCD1LG1, also known as PD-L1)[7].

With the development of lung cancer research and the continuous progress of immunotherapy, immunotherapy has become the main treatment method after surgery, chemotherapy, and radiotherapy. As the first choice for local treatment of advanced lung cancer, radiotherapy can greatly improve the local symptoms caused by tumors, and stimulate the immune system to attack tumors. And low-dose chemotherapy can promote the efficacy of immunotherapy. Therefore, the combination of the advantages of the three can play a synergistic effect. This article is to summarize the role of immunotherapy in the treatment of advanced lung cancer.

1 The application of immunotherapy

1.1 Mechanism of immunotherapy

Immunotherapy is an anti-cancer method that enhances the ability of the immune system to recognize and kill tumors. Ample evidence recently shows that immunotherapy can provide a promising method for the treatment of a variety of malignancies, particularly solid tumors, such as advanced melanoma, non-small cell lung cancer and hematologic malignancies. At present, several clinical trials are investigating how to use this treatment in a better way to standardize the treatment of lung cancer and achieve a better

therapeutic effect[8-9].

In brief, immunotherapy activates $CD4^+$ T cells and recruits $CD8^+$ T cells to attack tumor cells under the action of antigen-presenting cells. But in the tumor microenvironment, non-tumor immune cells and some tumor cells can suppress the immune system, which allows tumor cells to evade surveillance and attacks of the immune system, such as inhibiting the activation of T cells by using checkpoint pathways which prevent normal tissues from being attacked by the immune system. This also provides an idea for immunotherapy: by inhibiting the expression or binding of checkpoint pathways, release the factors that suppress the activation of T cells. And it has become the most promising therapeutic method at present[10].

1.2 The relationship between efficacy of immunotherapy and PD-1/PD-L1

Studies have shown thatfor patients with advanced non-squamous non-small cell lung cancer that have received the standard first-line chemotherapy regimen, the median survival time after using monoclonal antibody Nivolumab which can block programmed cell death 1 (PDCD1, also known as PD-1) is 12.2 months, and the median survival time for patients with standard second-line chemotherapy regimen (Docetaxel) is 9.4 months; while for patients with squamous non-small cell lung cancer, the median survival time after using PD-1 monoclonal antibody Nivolumab is 9.2 months, and the median survival time for patients with standard second-line chemotherapy regimen (Docetaxel) is 6 month. In this study, the total objective response rate is 19%. For the patients whose PD-L1 expression is above 1%, the response rate is as high as 38%, with a median survival time of 17.7 months; among patients with PD-L1 expression less than 1%, it is 9 months[11-12]. Therefore, the efficacy of PD-L1 antagonists is directly related to the expression of PD-L1. More than 50% of patients with NSCLC will have distant metastasis and receive chemotherapy. About 18% of patients will reach stage III b and will not be completely resected. These patients will undergo radical treatment combining radiotherapy with chemotherapy[13], and immunotherapy can significantly prolong the overall survival of these patients[14].

1.3 Other immunotherapy methods

In addition to the above methods, there are other ways of immunotherapy, such as adoptive therapy. It extracts effector T cells in the body, and edit them to make it possible to identify the relevant tumor antigens. After in vitro amplification, the cells are returned back to the patients to inspire the killing effect on tumor cells[15]. However, due to the immune tolerance and immune escape mechanisms of tumors, it has a little efficacy, so this article will focus on the relationship between checkpoint inhibitors and radiochemotherapy.

2 Application of radiotherapy in the treatment of advanced lung cancer

2.1 Local effects of radiotherapy

Palliativeradiotherapy plays an important role in the treatment of advanced non-small cell lung cancer patients. Although advanced NSCLC is a systemic disease, patients sometimes need a more rapid and reliable treatment than systemic therapy for local tumors which affect the quality of life of patients. Radiotherapy can greatly alleviate the patient's discomfort. Especially in the treatment of metastatic central system, many drugs can not break down the blood-brain barrier, so it is necessary to adopt both systemic treatment and radiotherapy at the same time for advanced non-small cell lung cancer.

2.2 Effects of radiotherapy on the immune system

Studies have suggested that after radiation therapy, disintegrated tumor cells can release and expose new antigens, and these new antigens can alter the microenvironment of tumor cells and systemic immune response[16]. Therefore, there is possible to use radiotherapy to release new tumor antigens to activate the local and systemic immune systems. At the same time, use checkpoint inhibitors to stimulate the tumor immunotherapy to obtain a better therapeutic effect. The abscopal effect of this kind of radiotherapy has also been observed in some of the previous studies[17]. A number of preclinical studies have shown that radiotherapy has a positive effect on the immune system. The survival rate can increase 50% in in situ malignant glioma models [18] with stereotactic radiotherapy in combination with checkpoint inhibitors. Some experts like Sharabi[19] have used PD-1 antibody combined with radiotherapy in mice of breast cancer or melanoma to increase the penetration of T cells to tumor cells and the presentation of antigens by dendritic cells in lymph nodes. More and more researches have shown that radiotherapy can enhance

the efficacy of immunotherapy by directly raising tumor-associated antigens, increasing the expression of MHC class I molecules on the cell surface, and increasing the number of $CD8^+$ T cells[20-21]. In addition to the surface expression of MHC class I receptors, radiotherapy may also stimulate the immune system by activating dendritic cells and increasing antigen cross-presentation[22].

3 Immunostimulatoryfatigue

The above studies have shown that PD-1/PD-L1 antagonists can activate the immune system by relieving immune non-response mechanisms of tumor cells, and localized radiotherapy can further activate the immune system by destroying tumor tissue and making disintegrated tumor cells release new antigens, so as to achieve a very good efficacy. However, even if the immune escape mechanism is released and the T cells are fully exposed to antigens, some patients are still unable to effectively activate the immune system during this treatment. This phenomenon is called immunostimulatory fatigue, and the solution to immunostimulatory fatigue is of great clinical value.

3.1 The mechanism of immunostimulatory fatigue

Studies have shown that the phenotypic and functional changes of $CD8^+$ T cells are accomplished through the methylation of DNA when such cells are activated into effector cells[23]. Therefore, in order to study whether the adjustment of effector T cells function is also accomplished by methylation of a certain gene and whether this gene methylation is related to immunostimulatory fatigue, the researchers designed a rapid experiment: study $CD8^+$ T cells of wild type and mutant type without methylation in mice. People found that the wild-type effector $CD8^+$ T cells were significantly depleted both in quantity and function compared with mutant $CD8^+$ T cells during chronic inflammation. To investigate whether this property could persist in an environment fully exposed to antigens, the researchers studied wild-type and mutant $CD8^+$ T cells in these mice 2 months later, and found that the ability of cells to secrete interferon and interleukin-2 of wild-type $CD8^+$ T was significantly impaired during chronic inflammation, whereas the variants did not change significantly. Subsequently, another experiment was conducted to determine the degree of methylation of genes in $CD8^+$ T cells of wild-type and mutant type , and it showed that the degree of methylation of the wild-type was higher. To test whether methylation of $CD8^+$ T cells would occur in a tumor environment, the researchers performed the above experiments using chronic tumorigenic mouse models (Tramp-C2) and obtained similar conclusions[24]. Therefore, it is considered that $CD8^+$ T cells without methylation is less prone to exhaustion, and there are different ways of methylation for the failure and activation process of effect T cells.

3.2 PD-1 antagonistic therapy can not alter the methylation of fatigue-related genes and the methylation can be inherited.

The T cell immunostimulatory fatigue described above is present in chronic inflammation or long-term antigenic stimulation, and also in the micro-environment of long-term stimulation of lung cancer tissue. Methylation of DNA plays a key role in immunostimulatory fatigue. Hence, whether the use of PD 1/PD-L1 antagonists can relieve immune tolerance of tumor cells and activate T cells activity has become the focus.

The researchers used PD-1/PD-L1 antagonists in micewith wild-type $CD8^+$ T-cells that had been infected for long periods of time, then continuously tested the degree of methylation of immunostimulatory fatigue-related genes. The results showed that this treatment increased the number of GP-33 and polyclonal $CD44^{hi}PD\text{-}1^+$ $CD8^+$ T cells in mice, but at the same time, the methylation status of these T cells did not change[24]. In other words, the methylation of immunostimulatoty fatigue-related genes is in a very stable state and can be inherited for many generations, and PD-1/PD-L1 antagonists cannot eliminate the methylation status of this kind of genes.

3.3 The effect of low dose chemotherapy on immunostimulatory fatigue

There is an important relationship between gene methylation of T cells and immunostimulatory fatigue. So people wonder whether it is possible to use drugs to inhibit methylation to regenerate fatigued T cells if the methylation of T cells can be inhibited. The researchers used the commonly used DNA demethylation drug--decitabine in wild-type mice infected with virus for a long time, with PD-1 antagonists at the same time. According to the longitudinal analysis of the number of virus-specific $CD8^+$ T cells in the peripheral blood of these mice, it was found that after using both kinds

of drugs, the increase of GP-33-specific cells was more marked than that of either of the above-mentioned drugs alone [24].

This study is of vital significance for tumor immunotherapy. Currently, both methylation inhibitors and PD-1 antagonists have come into the market in the United States. Based on the above experimental results, they are expected to be jointly applied to increase T cells activity. It will be a promising new direction for the future, although final tests need to be done on human body.

4 The Opportunities and challenges of combined application

For patients with advanced non-small cell lung cancer, especially those with brain metastases, radiotherapy has become an important topical treatment because some drugs cannot overcome the blood-brain barrier and some tumor cells have drug resistance. However, advanced lung cancer is a systemic disease. If the treatment can mobilize the immune system from the whole body level and relieve immunostimulatory fatigue through low-dose decitabine, the synergistic effect it generates may further improve its efficacy and reduce the complications. It is also necessary to see the risks of radiochemotherapy combined with immunotherapy, such as skin rash, thyroid and pituitary dysfunction, colitis, nephritis, hepatitis and other common adverse reactions[14], and even severe pneumonia has been heard[25]. It is due to the use of radiation therapy that may superimpose toxicity or body load, which has attract people's attention. In an ongoing study of Phase I treatment of patients with metastatic solid tumors treated with sterotactic radiotherapy combined with Ipilimumab, none of the patients developed severe pneumonia; there was also a phase I study of patients with metastatic melanoma showing that 10 had radiation damage to the lungs among the 22 patients treated with radiation therapy in combination of Ipilimumab, but no immunotoxicity injury related to treatment was higher than grade 4 during the study period (occurred within 30 days of the use of Ipilimumab)[26-27]. The main adverse reactions of chemotherapy are suppression of bone marrow hematopoietic function and reduction of leukocytes, which is contrary to the direction of immunotherapy. But in the course of comprehensive immunotherapy, low-dose chemotherapy is used instead of standard chemotherapy regimens to relieve immunostimulatory fatigue and improve efficacy. However, there are no relevant reports on that and its dosage and safety need to be further confirmed.

5 Conclusion

The rapid development of immunotherapy plays an important role in supplementing existing treatments. Combined radiotherapy has great potential benefits for systemic and local treatment of patients with advanced lung cancer. Under ideal circumstances, high-dose radiation can reduce local progression. And its abscopal effect combined with immunotherapy can improve the distant metastasis rate of lung cancer, and the discovery of immunostimulatory fatigue mechanism and the application of decitabine will help people to better use immunotherapy. However, the poor prognosis of patients with advanced lung cancer is still a problem in the medical community. Therefore, how to reduce the recurrence rate of the whole body and prolong the survival period is very important, which is also a huge challenge at present.

After solving the above problems, it is necessary to improve the system for assessing the efficacy. The delayed results of immunotherapy may require the discovery of more targeted and effective evaluation indicators or systems, such as circulating tumor DNA, to assess the effectiveness of treatment. Although there are many concerns and things need to be explored in the current immunotherapy combined with radiotherapy approach, this treatment can treat lesions from both local and systemic levels and reduce the recurrence rate of lung cancer, so it has great prospects and hope.

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