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Results of Radiotherapy Combined with Multiple Immune Checkpoint Inhibitors in the Treatment of Non-Small Cell Lung Cancer

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Abstract: Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers, and most of them have advanced stage, progression or metastasis at the time of diagnosis. Radiotherapy is one of the classical methods for the treatment of NSCLC. Immune checkpoint inhibitors (ICIs), the most common type of immunotherapy, have gradually developed into the preferred treatment for patients with advanced NSCLC. There are numerous clinical trials have demonstrated that radiation therapy can activate the body's immune system in the process of immune therapy, the effect of the combination of synergistic antitumor effect, can significantly improve the tumour local control, and improve the body's immune cells response "response, and through the joint model highlights the significant advantages in clinical research in China at present. However, the issues of radiotherapy dose, radiotherapy segmentation mode and timing of combined therapy are still controversial. This article reviews the mechanism, classification and distant effect of the combination of the two antitumor agents.

1. Introduction

At present, lung cancer is the malignant tumor with the highest morbidity and mortality rate in the world [1]. On average, hundreds of thousands of people die of lung cancer every year, and the number is on the rise every year. In lung cancer, about 4/5 patients have non-small cell lung cancer (NSCLC) [2]. Unfortunately, about 60% of patients are diagnosed at an advanced stage of the disease, and the primary treatment -- surgery -- is no longer considered. These patients can only consider radiotherapy, chemotherapy, immunotherapy and targeted therapy.

2. Radiotherapy

Radiotherapy is an effective treatment to prolong survival and improve local tumor control rate under certain conditions [3]. About two-thirds of cancer diagnoses are indicative of radiation therapy, which plays an important role in the radical treatment of early and advanced lung cancer and is more widely used in cases of cancer recurrence or metastasis [4]. In recent years, with the continuous development of radiotherapy technology, intensity modulated radiotherapy (IMRT) [5]

and image-guided radiotherapy (IGRT) have been widely used in the treatment of tumors in other parts of the chest [6]. It can provide effective dose of radiation to the tumor with sub-millimeter accuracy, and has a protective effect on normal tissues and organs around the tumor [7]. It is well known that cancer cells grow and divide faster than normal cells, and the proliferation and related abilities of cancer cells are positively correlated with radiosensitivity. The faster the development of cell proliferation ability, the higher the radiosensitivity [2, 8]. The main targets of lethal damage caused by radiotherapy are DNA fatal damage, including base damage, DNA strand break (single strand break and double strand break, and double strand break is the main fatal event) and DNA strand crosslinking. Radiotherapy primarily causes radiation damage to tumors, which can directly prevent the growth and division of cancer cells and lead to the death of cancer cells [9,10].

The antitumor mechanism of radiotherapy also includes cytotoxicity. Cytotoxicity is the killing effect of one cell on another. Radiotherapy can not only act on tumor cells, but also on tumor interstitial cells. On the one hand, it can kill both of them, and on the other hand, it can activate and induce their immune response. In other words, immunogenic death occurs in some tumor cells, forming "in situ vaccine", promoting the release of a variety of tumor itself and other related antigens to activate the corresponding acquired immune response, and finally playing an anti-tumor role through immune response [11,12].

3. Immunotherapy

In recent years, Immune checkpoint inhibitors (ICIs) are a promising new type of immunotherapy drugs, which have brought an expansion of ideas for the clinical research methods for the treatment of cancer patients and the research and development of clinical therapeutic drugs [13,14]. ICIs can block the activity of immune checkpoint related proteins, block the immunosuppressive signal, and enhance the immune response of T cells, so as to inhibit the immune escape of tumor cells, so as to realize the anti-tumor effect. Compared with radiotherapy and other monotherapy, ICIs significantly prolonged the overall survival (OS) and progression-free survival (PFS) of patients with stage IV NSCLC. For example, PD-1 /PD-L1 monoclonal antibody combined with radiotherapy has become an alternative treatment for patients with advanced non-small cell lung cancer. Some studies have also shown that radiotherapy combined with ICIs can promote the regulation of tumor microenvironment and improve the efficacy and sensitivity significantly. At present, ICI has been widely used in various tumor treatments and is called "broad-spectrum anti-tumor drugs" by some scholars [15,16].

The existence of immune detection points has both positive and negative effects. On the one hand, ICIs can prevent the immune system from aggressive attack on its own system, thus causing the occurrence of autoimmune diseases. On the other hand, tumor cells can also stimulate and activate pathways associated with immune detection points to achieve immune escape, avoiding recognition and attack by the immune system. We need to further discover immune detection sites, study their influencing pathways, intercept them on the pathways, block their progression, and then prevent the occurrence of immune escape, ultimately leading to the occurrence of anti-tumor events.

At present, the immune detection sites that have been discovered include CTLAA-4, PD-1/PD-L1, LAG-3, B7-H3, B7-H4, VIS-TA, CEACAM1, BLTA, etc. Ctla-4 mab, PD-1 mab and PD-L1 mab are the most widely used in the clinical treatment of lung cancer.

4. Radiotherapy Combined with Immunotherapy

4.1 Radiotherapy Combined with Single Antibody CTLA-4

Cytotoxic T lymphocyte-associated Antigen-4 (CTLA-4) is a transmembrane protein that is

expressed on the surface of activated CD4+ and CD8+ cells. The ligand B7 on the surface of T cells binds to the receptor CD28, which activates T cells to produce cytokines that promote proliferation and survival time. When CTLA-4 is activated, it has competitive inhibition with CD28 on the surface of T cells, and it is easier for CTLA-4 to bind to B7, thus preventing CD28 from binding to B7, reducing the activation of T cells, inhibiting their proliferation, and finally blocking the immune effect and reducing the anti-tumor effect [17,18].

Both Ipilimumab and Tremelimumab are monoclonal antibodies to CTLA-4, which can bind to CTLA-4 and prevent the binding between CTLA-4 and B7, and positively regulate the activity of T cells and the proliferation ability, thus promoting the anti-tumor effect. In addition, Golden reported that ipilimumab combined with radiotherapy not only reduced tumor size but also had a distant effect, and tumors outside the primary tumor showed signs of regression. It is sufficient to infer a synergistic effect between the two. However, the specific mechanism is not completely clear and needs further clinical trial verification [19].

4.2 Radiotherapy Combined with PD-1/PD-L1 Antibody

Under normal conditions, PD-1 is expressed on the surface of T cells and binds to its ligand, PD-L1, to prevent the over-activation of T lymphocytes from causing autoimmune diseases. However, studies have shown that there is a phenomenon of high expression of PD-L1 between tumor cells, which is easier to bind with PD-1 on the surface of T cells, hiding tumor cells and avoiding recognition by the immune system, thus inhibiting the activation of T cells, reducing their proliferation, weakening the anti-tumor immune response and causing immune escape [20, 21].

The antibodies to PD-1 are Nivolumab and Pembrolizumab, Antibodies to PD-L1 include Atezdizumab, Durvalumab and Avelumab. Pd-1 /PD-L1 antibody cuts off the PD-1 pathway and enhances the anti-tumor immune response. Further clinical trials show that radiotherapy combined with PD-1/PD-L1 antibody has a significant effect on the treatment of advanced NSCLC. In addition, patients with negative PD-L1 expression after radiotherapy in the clinical sample of NSCLC had higher objective response rate (ORR) and disease control rate. Therefore, radiotherapy can increase the sensitivity of NSCLC patients to PD-1/PD-L1 inhibitors.

4.3 Immune Distancing Effect

In the course of radiotherapy combined with immunotherapy for tumor patients, radiotherapy can induce the occurrence of immune distant effect. For example, CTLA-4 antibody or PD-1 antibody can be used as immune checkpoint inhibitors. By enhancing the activity of T lymphocytes, ctLA-4 antibody can not only act on the primary tumor, but also kill tumor cells at non-primary sites, thus exerting immune distant effect. Most distant effects are reported to occur after radiotherapy, and different immunomodulators participate in different ways and different mechanisms to promote distant effects. Factors influencing the distant effect such as the number of radiotherapy, segmentation, type of immunotherapy, timing of combination, and different types of tumor are still being studied.

5. Conclusion

Tumor immunotherapy is one of the hot issues in the field of clinical treatment of cancer in China at present. Combined with radiotherapy, tumor immunotherapy can not only improve the survival rate of patients, but also open up new ideas for the prospect of tumor treatment. However, in the research process of combination therapy, there are still many problems, such as precise treatment of tumor, accurate screening of tumor patients, accurate grasp of treatment timing, toxic

and side reactions after various combination reactions and the mechanism of each reaction are not completely clear, indicating that there is still a long way to go in the treatment of tumor.

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