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Application of Immunotherapy in the Treatment of Solid Tumors

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Abstract. Cancer is one of the major diseases that seriously threaten human life and health at present, and the number of deaths due to cancer every year ranks in the top 2 of all diseases. In recent years, the malignant tumor is increasing year by year, so it is necessary to explore new therapeutic methods. Immunotherapy of tumor cells is one of the hot topics in tumor therapy, which aims to destroy tumor cells by activating or regulating the immune system of patients. More and more tumor immunotherapy drugs have been successfully developed and marketed, bringing the hope of long-term survival to patients. However, like other tumor drug therapy, tumor immunotherapy has brought huge benefits to some tumor patients and made people full of expectations, but it also faces many difficulties and challenges in pre-clinical research and clinical application. This article summarizes the application and challenge of immunotherapy in solid tumors.

Keywords: Immunotherapy; cancer; challenge.

1. Introduction

Normal cells in the human body grow and divide to form new cells. Cells usually die after aging or damage in order to maintain the body's homeostasis. When the body's cells divide and spread without restriction, forming new organisms, it is called a tumor. According to 2020 data ,there were 4.57 million new cases and the deaths is 3 million in China. By 2040, new cases are expected to reach to 28.4 million worldwide, increasing cancer burden by 50% [1,2].

At present, tumor treatment mainly includes surgical resection, chemotherapy, radiation therapy, endocrine therapy, etc. Despite the continuous progress of diagnosis and treatment technology, tumor treatment still faces many challenges, such as the difficulty of early detection and diagnosis, high drug resistance and recurrence rate, strong invasiveness and metastasis ability, and significant treatment side effects. Therefore, the development of new, effective and safe anti-tumor drugs has become an urgent research demand. In recent years, with continuous deepening of oncology related research, immunotherapy has made breakthrough progress, based on the own immune system, give full play to the potential of immune in human body, and can effectively inhibit or even eliminate the tumor cells.

At the end of the 19th century, William B. Coley first tried to use immune system to treat the cancer. Then,after more than 100 years, the development of immunotherapy went through twists and turns until the drugs represented by immune checkpoint inhibitors changed the treatment pattern of a variety of tumors, thus opening the era of immunotherapy [3]. In this paper, immunotherapy in solid tumors were introduced, and the existing problems and solutions of immunotherapy were summarized, so as to provide references for clinical treatment of cancer.

2. Immune-checkpoint-inhibitor (ICI)

Under normal circumstances, immune checkpoints can maintain the body's immune tolerance by adjusting the intensity of the autoimmune response, which helps to protect the normal function of tissues and organs so that the body can achieve immune self-stability and avoid autoimmune diseases. PD-1 / L1 and CTLA-4 are the earliest ICI therapy used in clinic. PD-1 is mainly expressed on the surface of activated immune cells such as T cells, B cells, NK cells and dendritic cells. After binding with PD-L1, PD-1 inhibitors inhibit the activation of immune cells and protect tumor cells from attack.

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By reversing this inhibitory effect, PD-1 inhibitors promote immune cells to target tumors CTLA-4 is mainly expressed in activated the T cells and inhibits the proliferation by binding with leukocyte differentiation antigen 80 / leukocyte differentiation antigen 86(CD80 / CD86) [4].

A multi-cohort, phase II trial included 258 patients with the metastatic castration-resistant prostate cancer, including 133 PD-L1-positive patients in cohort 1, 66 PD-L1-negative patients in cohort 2, and 59 patients with predominantly bone metastases in cohort 3. To investigate the effects of pembrolizumab after docetaxel treatment. The results showed that the ORR of cohorts 1 and 2 were 5% and 3%, respectively, and the median OS of cohorts 1, 2 and 3 were 9.5, 7.9 and 14.1 months, respectively [5].

Although CTLA-4 monoclonal drugs started and clinical application is relatively early, the only CTLA-4 inhibitors approved by the US FDA are Ipilimumab and Tremelimumab. A clinical trial (MDX010-20) of Ipilimumab in combination with the melana-associated glycoprotein (HLA-A 0201) in the treatment of melanoma showed that both combination therapy and Ipilimumab monotherapy had better survival benefits than the control group, significantly extending the median OS. lpilimumab is approved as a single agent only in specific cases. At present, there are still problems such as the few types of drugs, the narrow range of indications, lack of optimal dose and soon [6,7].

3. Oncolytic Viruses

Oncolytic viruses (OV) are naturally occurring or modified to preferentially infect, replicate and lyse malignant tumor cells, and activate immune responses. An important property of oncolytic viruses is that they selectively replicate and induce cytopathic effects, making them very suitable for cancer immunotherapy. Therefore, the application scope of oncolytic virus in tumor therapy is gradually expanded, because it can trigger T cell response, and then trigger anti-tumor immunity. It is immunogenic in nature and therefore able to trigger an anti-tumor immune response. At present, more and more OV therapy trials for glioma are being extensively conducted at both preclinical and clinical levels [8].

DNX 2401 is with tumor selectivity and infectivity. In 2023, Nassiri et al. reported the results of a phase I and II clinical trial on DNX 2401, which included 49 patients with recurrent glioblastoma who were injected with different doses of DNX 2401 (5×108 ~5×1010 viral particles). The anti-PD-1 antibody Pembrolizumab was injected intravenously after oncolytic virus treatment. Median overall survival after treatment was 12.5 months (95% CI: 10.7 to 13.5), 12-month survival rate was 52.7% (40.1%~69.2%) and the objective remission rate was 10.4% (4.2%~20.7%), indicating a good survival benefit. The most common adverse events that are related to the treatment were cerebral edema, headache and fatigue. No dose-limiting toxicity [9,10].

Due to the heterogeneity of tumor tissue and the complexity of cancer cells, OVs alone cannot achieve optimal efficacy. Many studies have shown that OV combined chemotherapy can avoid the antiviral immune response of the body, resist the immunosuppressive tumor microenvironment, and regulate the immunogenicity of tumor cells. However, some scholars pointed out that the adverse reactions and risks of combination therapy should not be ignored, and high-throughput drug screening may be used as a way to find combination drugs. If tumor stem cells (CSCs) are more sensitive to the killing effect of oncolytic herpes simplex virus, combining drugs targeting CSCs will be an important way to improve the efficacy. However, most of above studies are from cell lines or animal tests, and further studies are needed before clinical application. In addition, the quality of technology patents in the field of OV in China still needs to be improved, and according to existing statistics, the patent operation of OV in China only accounts for 10.13%. Relevant departments need to increase financial support for relevant technologies to make up for the shortfall.

4. Tumor-infiltrating Lymphocytes(TIL) Cell Therapy

The core of this herapy is to extract tumor-infiltrating T lymphocytes from tumor tissues of patients, culture and expand them in vitro, and then inject them back into patients, so as to effectively attack solid tumors. When TIL reaches the tumor interior, it can directly kill tumor cells by releasing cytotoxins. In addition, TIL can regulate the immune function and improve the killing ability of the tumor cells. Second, most TILs target mutated tumor specific antigens rather than autoantigens, reducing the risk of autoimmunity after treatment. Compared with other T cell immunotherapies, auto TIL therapy has the unique advantages of recognizing broad spectrum antigens and reducing off-target toxicity [11].

In 1986, ROSENBERG and his team proved that TIL combined with the cyclophosphamide and IL-2 in the treatment of colon cancer mice achieved 100% cure of liver metastasis and 50% cure rate of lung metastasis, laying the foundation for the clinical application of TIL. In 1988, TIL therapy began corresponding clinical studies and achieved a 60% objective response rate in the metastatic melanoma [12].

In 2022, the results of Phase II clinical trial (C-144-01, advanced mucosal melanoma,n=153) showed that the overall survival rate at 1, 2, 3 and 4 years was 54.0%, 33.9%, 28.4% and 21.9%, respectively, confirming its durable antitumor activity. On February 16, 2024, FDA accelerated the approval of Lifileucel for advanced melanoma after the anti-PD1 /PD-L1 treatment, which is the first approved TIL therapy in the world and also for the solid tumors [13-15].

A clinical trial of TIL therapy for osteosarcoma (ChiCTR1900026789) was reported at the 24th National Congress of Clinical Oncology. Through September 6, 2021, the study enrolled 12 subjects with stage IV lung metastasis of juvenile osteosarcoma. In the early stage, various treatments including surgery, chemotherapy, antirotinib and anti-PD-1 antibodies developed after treatment, and there is no effective treatment at this stage. Twelve subjects achieved disease stabilization and prolonged survival after receiving TIL treatment, which verified the efficacy and safety of TIL in treating advanced osteosarcoma [16].

5. Current Challenges

In clinical practice, it will be found that immunotherapy will produce some atypical reactions. For example, according to the traditional evaluation criteria for the efficacy of solid tumors, it may not be accurate enough, resulting in impaired survival. For example, the evaluation criteria are difficult to cover all populations, or the evaluation methods are still limited to imaging methods. Traditional CT and MRI only rely on the change of tumor size and whether new lesions appear to judge the treatment effect. The future direction is to use changes in tumor metabolic characteristics to judge anti-tumor effects, such as PET/CT, or to use more precise radionuclide imaging related to immune cell metabolism to judge therapeutic efficacy

At the same time, immune regulation in tumors also requires the assistance of the peripheral immune system. Changes in metabolic pathways and epigenetic modifications can also affect tumor cells and immune cells, and also affect the interaction between them to change the immune state of tumors. Therefore, it is expected that the breakthrough of basic research will bring new breakthroughs in tumor immunotherapy. In addition, many scientists are also working on the development of small molecule immunosuppressants. Compared with antibody-based drugs, the intervention targets of small molecule inhibitors are more diverse, the pharmacokinetic characteristics are easy to adjust and improve, and oral administration can be achieved, with better patient compliance and lower production cost, which can reduce the burden of patients [17].

The unsatisfactory efficacy observed in clinical trials is related not only to the characteristics of the drug, but also to the criterion of efficacy. Some tumors under the current early prevention and early treatment measures, the survival of patients has been greatly improved, so as a clinical trial efficacy criteria will undoubtedly increase the difficulty of clinical trials. How to make better use of artificial

intelligence, find some new algorithms, and find more rapid and effective clinical efficacy indicators is also the direction of many researchers' efforts.

Cost and price is an unavoidable problem, but also the most concerned by patients, some early patients are limited by its expensive price, only when there is no alternative therapy is forced to choose immunotherapy, China in the field of immunotherapy relatively developed countries are still in its infancy, need to increase basic research and development support, break the foreign intellectual property monopoly situation, This is the key to support the future research and development of immunotherapy [18].

6. Conclusion

Immunotherapy is playing an increasingly important role in today's solid tumors, although the use of the immune system to treat tumors has a long history, but modern tumor immunology still belongs to the emerging field of tumor therapy, hoping that new therapeutic targets will continue to emerge, from which more methods can be found to defeat tumors.

As a foundation for tumor immunotherapy, a better understanding of immune cells in the tumor microenvironment is critical for interpreting immunotherapy mechanisms, searching for predictive biomarkers, and identifying novel therapeutic targets in order to enable individualized therapy. At the same time, in order to further improve the effectiveness of tumor immunotherapy, it is also necessary to explore the combination of immunotherapy and traditional therapy to reduce the occurrence of tumor drug resistance. Of course, how to modify immunotherapy and select combined strategies to improve safety and efficacy while reducing adverse reactions is the key to making breakthroughs in the field of tumor research in the future and realizing accurate tumor treatment.

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