Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/44/20240484

Research progress of PD-1/PD-L1 inhibitors combined with other drugs in the treatment of tumors

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Abstract. Cancer as the first killer of the influence of human life and health, researcher use a variety of ways to cure cancer, but has been no effective treatment, along with the innovation of new biotechnology, researcher discovered the cancer cells rely on the "Warburg" effect in the human body metabolism. And understanding the PD-1L receptor on the surface of tumor cells can help tumor cells to achieve immune escape, which is not easy to be recognized and killed by the PD-1 receptor on the surface of immune cells. After understanding this process, researchers have developed PD-1/PD-L1 receptor inhibitors to help cure cancer by targeting this mechanism, which is also part of immunotherapy. Among the drugs on the market today, it has been confirmed that PD-1/PD-L1 is effective in the treatment of non-solid tumors and a small number of solid tumors. However, because of the characteristics of most solid tumors, PD-1/PD-L1 is limited to play a role, so researchers try to develop PD-1/PD-L1 combined with other drugs to treat more solid tumors. In the literature cited in this article, it can be seen that the combination of PD-1/PD-L1 with other drugs is effective, but the adverse reactions will also increase. This article will discuss the effectiveness of PD-1/PD-L1 combined with other drugs in detail.

Keywords: PD-1/PD-L1, CTLA-4, nivolumab, Durvalumab, Docetaxel, Bevacizumab.

1. Introduction

Malignant tumor is a serious disease that endangers human life and health today. A lot of resources and funds have been spent worldwide to try to cure this disease, but so far there is no particularly effective method. Surgery, chemotherapy and radiotherapy are often used to reduce the likelihood of death from cancer. However, due to obvious adverse reactions, poor prognosis, and the influence of the grade of differentiation of cancer cells, the survival of patients is greatly reduced [1]. Therefore, there is an urgent need for an efficient method to treat malignant tumors. With the continuous progress of biotechnology, immunotherapy against cancer has become the hot focus of people's treatment of cancer today. Immunotherapy refers to its purpose of controlling and eliminating tumors by restarting and maintaining the The Cancer-Immunity Cycle, so as to restore the normal anti-tumor immune response [2].

Because immunotherapy has strong directivity, small adverse reactions, and can significantly improve the survival cycle of patients, the study of immunotherapy has gradually become a hot topic in global cancer treatment [3]. Among them, PD-1/PD-L1 has become a popular target in immunotherapy, which uses the PD-1/PD-L1 binding reaction between cancer cells and T lymphocytes to design drugs to achieve the purpose of treating cancer.

The difference between PD-1/PD-L1 antibody drugs and traditional targeted therapy is that targeted therapy blocks a certain carcinogenic site of the tumor at the gene and molecular level, so that tumor

DOI: 10.54254/2753-8818/44/20240484

cells die specifically and achieve the purpose of inhibiting tumor growth [4]. PD-1/PD-L1 binds to specific sites on T lymphocytes or cancer cells, so that immune cells in the human body can successfully recognize cancer cells for killing. In general, blockade of PD-1 and PD-L1, two immunosuppressive signaling pathways, can disable tumor immune escape and achieve the purpose of treatment.

PD-1/PD-L1 monoclonal antibodies have a good therapeutic effect on non-solid tumors, but for solid tumors, the treatment effect is unsatisfactory due to the dense shape of solid tumors and the large tumor microenvironment [5]. Therefore, some research institutions have tried to use combination drugs to treat solid tumors. The treatment of tumor by combination therapy is due to the joint action of multiple drugs, so the therapeutic effect of combination therapy is often better than that of single drug therapy [6]. This idea is also used in the design of PD-1/PD-L1 combined with other drugs. This article will discuss the metabolic mechanism of tumor cells and the PD-1/PD-L1 pathway between T cells, as well as the therapeutic effect of PD-1/PD-L1 combination therapy and current research progress.

2. Metabolic Pathways of Tumor Cells and Their Immune Environment

In the metabolism of substances in tumors, tumor cells rely on special metabolic methods to construct tumor micro-environment (TME) changes, so that the immune response of macrophages and T cells related to tumor killing can be inhibited [7], promote tumor tissue growth, and play an important role in tumor cell metastasis and angiogenesis [8].However, under the continuous tumor antigen stimulation and immune activation reaction, the relevant effector cells in the microenvironment are in a state of exhaustion or remodeling, and the inhibitory immune microenvironment makes the immune cells unable to play their normal function, making the malignant growth of the tumor more serious[9].

Compared with normal cells, cancer cells exhibit a rather high glucose uptake rate under the condition of sufficient oxygen, while in normal cells, the glycolysis process is inhibited in this environment, which is called the “Warburg” effect [10]. The "Warburg” effect is used to understand the metabolic mechanism of tumor cells. It can help experts better design drugs. “Warburg

"Effect refers to the ability of tumor cells to metabolize energy by glycolysis even under aerobic conditions. With the enhancement of glycolysis, the tumor microenvironment is characterized by hypoxia, high acid, and increased immunomodulatory metabolites, leading to better proliferation of cancer cells [11]. In the tumor microenvironment, the increased production of lactate due to the increased role of glycolysis leads to the increase of hypoxia-inducible factor-1a (HIF-1a) in tumor cells and bone marrow derived macrophages. Overexpression of HIF-1a in the tumor microenvironment upregulated genes involved in glycolytic metabolic pathway, such as PKM2, PDK1 and GLUT1. PKM and HIF-a1 can bind to the PD-L1 promoter to cause PD-L1 expression on cancer cells [12]. The general role of PD-L1 is to combine with PD-1 on T lymphocytes and transmit signals to T lymphocytes to prevent excessive immune response [13]. Tumor cells use this mechanism to escape T lymphocyte killing by over-expression of PD-L1. In addition, PD-1 on T lymphocytes increases the concentration of SH2 domain containing phosphatase 1/2 by increasing the concentration of SH2 domain-containing phosphatase 1/2. SHP1/2 further activates the downstream T cell receptor cascade signaling pathway, inhibits the killing effect of T lymphocytes on tumor cells and the proliferation of T lymphocytes, and promotes the apoptosis of T lymphocytes. Thus, tumor cells escape from the killing effect of T lymphocytes [14]. In this process, immunosuppressive cells hinder the killing of T cells to cancer cells. In the tumor microenvironment, regulatory T cells (Tregs) are common immunosuppressive cells, and low Tregs can play a good role in tumor cell cure [15].

3. Mechanisms of PD-1/PD-L1 Action

programmed cell death protein 1 (PD-1) is an immune checkpoint molecule on the surface of T cells, Its main function is to receive PD-L1 (Programmed cell death 1 ligand 1) signal to suppress the excessive immune response of T lymphocytes [13]. Also exists in macrophages, PD-1 B lymphocytes and dendritic cells express, confirmed that the PD-1 in the important position of inhibiting immune reaction.

Programmed cell death 1 ligand 1 (PD-L1), a ligand that normally protects cells under special circumstances, is highly expressed in cancer cells and alternatively activated macrophages (M2-TAMs)

DOI: 10.54254/2753-8818/44/20240484

[16] associated with cancer cell proliferation. Activate PD-1 on the surface of T lymphocytes, inhibit the killing of T lymphocytes, and even cause the apoptosis of T lymphocytes [17].

At present, the treatment methods for tumor immunity are mainly Immune checkpoint inhibition and adoptive cell therapy. PD-1/PD-L1 as the most representative of immune checkpoint has always been the hot spot of the tumor immune research field. As immunosuppressive sites that regulate the effector function of T lymphocytes, immune checkpoint exists in the whole process of tumor immunity in the form of co-suppressive molecules [18].

Based on the special mechanism of the immune checkpoint between PD-1/PD-L1, experts use the principle of the combination of monoclonal antibodies and tumor cell surface targets to develop PD-L1 and PD-1 monoclonal antibodies. As immune checkpoint inhibitors, PD-1 inhibitors increase the attack of T cells on tumor cells by reducing PD-1/PD-L1 binding to generate signals. Recovery of T cell immune mechanisms [19]. And PD-L1 inhibitors is the use of PD- L1 targeted drug molecule and the tumor cell surface, make tumor cells on T cell immunosuppression is abate, to achieve the effect of killing tumor cells [20].

4. Introduction of PD-1/PD-L1 Monoclonal Antibody Drugs on the Market

4.1. nivolumab (PD-1 Monoclonal Antibody)

Nivolumab, a newly developed PD-1 inhibitor, is a humanized IgG4 monoclonal antibody designed to bind to PD-1 and block the interaction between PD-1 and its ligands, which can disrupt the PD-1-mediated immune suppression response and inhibit tumor cell proliferation.

Taking the experiment of nivolumab injection in the treatment of gastric cancer as an example, this experiment was treated with placebo, and the observation group was treated with nivolumab injection. Compare two groups of patients survival, and other observation index. The test conforms to the WHO criteria in solid tumors, clinical results and statistical analysis effectively.

Compared with placebo, nivolumab treatment had a significantly higher response rate. The median OS was 5.26 months for nivolumab and 4.14 months for placebo, and the 24-month OS rates were 10.6% and 3.2%, respectively. The treatment effect was better than placebo [21]. The trial also looked at serum tumor markers and adverse effects in different groups of patients, and nivolumab tended to perform better. This study preliminary shows that nivolumab can significantly improve the survival of patients, down-regulate the levels of serum tumor markers, and the adverse reactions are well tolerated, which is worthy of clinical promotion. This study also indicates that the treatment effect of monoclonal antibody developed for PD-1 is effective.

Nivolumab single resistance in non-small cell lung cancer treatment is played very well, multicenter, single-arm II CheckMate 063 study [22] in 117 cases of always had at least two system after treatment progress of III B / IV squamous NSCLC patients, The results showed that 17 of 117 patients achieved objective response. At the time of analysis, 11 patients had lesions reduced by at least 50%, 36% patients were evaluated as stable disease (SD), and the mPFS was 1.9 months.In another phase II clinical trial [23], 100 patients with stage IIIB/IV squamous (44 cases) and non-squamous (56 cases) NSCLC were enrolled, and their overall objective response rate (ORR) was 20.0% and mOS was 13.9 months. All the above phase II clinical trials suggest that nivolumab has good efficacy and safety in the treatment of patients with advanced NSCLC.

The phase 3 CheckMate 017, CheckMate 057, and CheckMate 078 trials evaluated nivolumab as second-line therapy. CheckMate 017 and CheckMate 057 were international multicenter studies, including 272 squamous and 582 non-squamous NSCLC patients, respectively. The results of CheckMate 017 study [24] showed that the mOS of nivolumab group and chemotherapy group were 9.2 months and 6.0 months, respectively, the 1-year OS rate was 42% and 24%, and the mPFS was 3.5 months and 2.8 months. In CheckMate 057 [25], the mOS were 12.2 and 9.4 months, respectively, and the 1-year OS rates were 51% and 39%, although the superiority of nivolumab (2.3 months) over docetaxel (4.2 months) was not supported in terms of PFS. But nivolumab single more than 1 year of PFS rate resistance group was obviously higher than that of the west he group (19% vs. 8%). The results

DOI: 10.54254/2753-8818/44/20240484

of this series of clinical trials have established nivolumab as the standard treatment in the second-line treatment of advanced NSCLC, and even challenged the first-line treatment.

4.2. Durvalumab Monoclonal Antibody (PD-L1 Monoclonal antibody)

Durvalumab monoclonal antibody (Durvalumab) is a humanized immunomodulator belonging to the class of anti-PD-L1 monoclonal antibodies. The mechanism mainly includes two aspects: the first is to block the interaction between PD-L1 and PD-1, thereby activating immune cells; The second is through the enhancement effect of cytotoxic T cell destruction, to kill tumor cells.

Durvalumab single resistance for an resection III stage non-small cell lung cancer, small cell lung cancer treatment, can be used as monotherapy. In 2020, researchers reported on the PACIFIC research 4 years follow-up data. The trial demonstrated an excellent performance of Durvalumab in the treatment of unresectable stage III non-small cell lung cancer.

OS was 49.6% with Durvalumab versus 36.3% with Durvalumab over 4 years. In other words, half of the patients treated by Durvalumab sheet resistance to consolidate lived for 4 years. This is a very significant number in unresectable stage III NSCLC, which fully reflects the advantage of long-lasting immune efficacy in stage III consolidation treatment. In contrast, Durvalumab consolidation therapy was associated with a 3-fold improvement in PFS of 17.2 months versus 5.6 months in the placebo group [26]. The results show that Durvalumab is effective in the treatment of tumors as a PD-L1 monoclonal antibody, which also proves that the idea of designing monoclonal antibodies to treat tumors by targeting PD-L1 is correct.

4.3. PD-1/PD-L1 monoclonal antibodies were used in combination with other drugs

A large number of medical practice and medical institutions have shown that single-agent treatment of advanced cancer is often difficult to achieve the desired therapeutic effect, and the same result is also the case for PD-1/PD-L1 inhibitors, so researchers intend to combine PD-1/PD-L1 inhibitors with other drugs to try to obtain better therapeutic effects. Results show that the PD-1/PD-L1 inhibitor combination with other drugs, good cure effect for patients.

4.4. Results of Docetaxel combined with PD-1/PD-L1 inhibitors

For the treatment of negative advanced non-small cell lung cancer, the single-agent use of PD-1/PD-L1 and Docetaxel is still not ideal. In order to increase the efficacy, combination therapy is very important. A large number of studies have shown that the combination of chemotherapy drugs and PD-1 and PD-L1 can produce good efficacy. In this study, 118 patients were selected to receive treatment. Among them, the observation group (n=69) was treated with Docetaxel and PD-1/PD-L1, and the control group (n=49) was treated with Docetaxel alone. This trial used RECIST 1.1 as the reference standard, and the test process was in accordance with the law of statistical data, and the valid test result [27] was obtained.

All patients received at least 2 cycles of treatment and were followed up. As of June 22, 2021, the 1-year progression-free survival rate of the observation group was 15.6%, and the 1-year progression-free survival rate of the control group was 7.7%. Docetaxel combined with PD-1/PD-L1 inhibitors compared with PD-1/PD-L1 inhibitors as a second-line treatment for stage IV NSCLC can significantly benefit patients in DCR and PFS, with low toxic and side effects, and is safe and controllable.

4.5. PD-1/PD-L1 inhibitors were used in combination with Bevacizumab

Combined with Bevacizumab single fight PD-1/PD-L1 inhibitors to curative effect for the analysis for the treatment of unresectable hepatocellular carcinoma. Several studies have shown that the combination of PD-1/PD-L1 and Bevacizumab can show advantages in the treatment of unresectable liver cancer compared with other groups of drugs, and the survival time of patients is compared. PD-1/PD-L1 OS and PFS period are higher than the other three kinds of drugs. Of the drug in the actual treatment compared with other three drugs can show a certain treatment advantage, but due to less for experimental samples, PD-1/PD-L1 joint Bevacizumab single resistance [28] treatment effect still needs further research.

DOI: 10.54254/2753-8818/44/20240484

4.6. Efficacy of PD-1/PD-L1 combined with CTLA-4

To prevent a single immunosuppressant drug for cancer cells develop resistance and disease development, researchers have tried using PD-1/PD-L1 and CTLA-4 double immune inhibitors to treat tumor. Clinical studies on PD-1 / PD-L1 combined with CTLA-4 dual immunotherapy for solid tumors have been carried out. In theory, PD-1/ PD-L1 and CTLA-4 combination therapy can block the two pathways of anti-tumor immune response at the same time, and should have better efficacy than single therapy. According to a large number of data analysis and clinical treatment experience analysis, different cancer types and different drugs used during the use of different methods of treatment, and the healing of patients and survival time are comprehensively compared.

Results show that compared with PD-1/PD-L1 use, PD-1/PD-L1 and CTLA 4 combination therapy can significantly improve the DCR in patients with solid tumor (RR = 1.22, 95% CI (1.03, 1.44), P = 0.02). PD-1/PD-L1 and CTLA- 4 combination therapy can significantly improve patients with solid tumor ORR [RR = 1.2995% CI (1.14, 1.46), P < 0. 01). Subgroup analysis of safety indicators showed that there was a significant increase in the incidence of grade 3-4 adverse reactions and discontinuation of treatment in patients with melanoma, and there was no significant difference in the incidence of all grade adverse reactions and mortality. It significantly increased the incidence of all grade and 3-4 grade adverse reactions, mortality and discontinuation of treatment in patients with lung tumor. Compared with PD-1/PD-L1 alone, PD-1/PD-L1 combined with CTLA-4 significantly increased the incidence of grade 3-4 adverse events and the discontinuation rate of treatment in patients with other solid tumors [29].

In general, the use of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors can significantly increase the ORR, DCR and PFS advantages of patients, but the adverse reactions during the treatment are also obvious. Comprehensive, using two immune inhibitors to provide new ideas for cure cancer treatment.

5. Conclusion

In general, researchers have developed immunotherapy drugs such as PD-1/PD-L1 inhibitors by studying the microenvironment of tumor cells and the immune effect between tumor cells and T lymphocytes, which has made great progress in the direction of immunotherapy. At the same time, researchers have also introduced the conventional treatment idea of combination drugs into the application of PD-1/PD-L1 inhibitors. It can greatly improve the survival time of patients and improve the quality of health. However, because PD-1/PD-L1 is still present, anti-PD-1 /PD-L1 monoclonal antibodies also have inevitable defects, such as long half-life, and their immunogenicity is easy to lead to drug-induced immune-related adverse events, which are also reflected in PD-1/PD-L1. Nephrotoxicity reported so far includes acute interstitial nephritis, minimal change disease, and immune complex glomerulonephritis, which increase with the frequency of PD-1/PD-L1 drug use [29]. In addition, hypothyroidism and hyperthyroidism are common adverse reactions [30][31]. However, in general, the initial research progress of PD-1/PD-L1 combination therapy has been effective. More treatments of immunotherapy combined with other anti-tumor drugs need to be further studied by researchers.

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