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Development of PD-1 / PD-L1 in the treatment of liver cancer

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Abstract: Liver cancer as the world ' s top five high incidence of malignant tumors, in the world, about 700,000 new cases of liver cancer patients each year, 1200000 deaths, in China, the incidence of liver cancer is also increasing year by year. As an immunotherapy, PD-1/PD-L1 inhibiting agent have shown certain advantages in the therapy of a variety of malignant tumors, but the quality of clinical treatment needs to be improved. Studies have shown that anti-angiogenic drugs and related treatments can synergistically improve the anti-cancer ability of PD-1/PD-L1 inhibitors. By combing the principle and application status of programmed death-1 and programmed death ligand-1 inhibitors for liver cancer, it is expected to improve the prognosis of patients with advanced lung cancer, and to explore the concurrent immune-related adverse reactions and efficacy evaluation indicators, so as to better apply in clinical practice and achieve satisfactory therapeutic effects.

Keywords: Liver cancer; PD-1/PD-L1; Antiangiogenic drugs; Drug combination; Immune adverse reactions.

1. Introduction

1992 Kyoto University, Japan, Department of Medicine scholars in the study of programmed cell death in the process by subtractive hybridization isolated PD-1 gene. 2000 Kyoto University School of Medicine and Harvard University School of Medicine published a joint study found that PD-1 ligand PD-L1 is a member of the B7 gene family, PD-L1 involved in mediating T lymphocyte receptor-mediated cytokine secretion and cell proliferation inhibition. As a very important immunosuppressive receptor, PD-1 can be developed into activated T cells, natural killer cells (NK cells), macrophages, dendritic cells and other cells. After binding to its ligand (PD-L1), it can inhibit the killing activity of T cells against malignant tumor cells, inhibit the immune response, and enable malignant tumor cells to obtain immune escape.

2. The Mechanism

PD-1 of T cells from patients with liver cancer binds to its programmed PD-L1 and convenes Scr homology 2 domain containing protein tyrosine phosphatase-2 (SHP-2). Inhibition of downstream phosphoinositide 3-kinase-protein kinase B signal transduction pathway. This inhibits the killing activity of T cells against malignant tumor cells, so that liver cancer cells can obtain immune escape, so that the immune activity of T cells can be restored, which can effectively kill liver cancer cells.

3. Research status

In 2017, a phase I/II clinical study, Checkmate040, showed that the median overall survival (mOS) and objective response rate (ORR) performed better in the Nivolumab than Sorafenib. Therefore, Nivolumab has become the first liver cancer immunotherapy drug, and US Food and then the Drug Administration approved it as the second-line solution of liver cancer. Some scholars have explored the killing effect of hepatocellular carcinoma cell line Hep G2 in vitro and its anti-tumor effect in vivo by constructing PD-1 knockout and phosphatidylinositol proteoglycan-3 (GPC3) modified CART (GPC3-PD1gRNA-CART) cells. Experiments in animal models of liver cancer have proved that PD-1 knockout can reverse the functional inhibition of CART cells. GPC3-PD1gRNA-CART cells can solve the problem of tumor escape and can effectively target tumor cells. Their research provides a technical basis for the subsequent treatment of liver cancer.

4. Drug combination

4.1. Combined anti-angiogenic drugs

Liver cancer is a malignant tumor mainly supplied by arterial blood. It has obvious vascular proliferation. In the meantime, angiogenesis is important in the occurrence and progress of malignancy. Previously, anti-vascular drugs have a wide and profound impact on the treatment of other malignancy, such as carcinoma of uterine cervix and malignant melanoma. This confirms that anti-angiogenic drugs can reverse the key mechanism of vascular endothelial growth factor (VEGF) -mediated immunosuppressive response to inhibit the maturation of dendritic cells (DC) and increase immunosuppressive cells in tumor microenvironment (TME). Antiangiogenic drugs inhibit the proliferation of malignant tumor blood vessels and prolong the survival of patients with malignant tumors. Currently known anti-angiogenic drugs used in clinical treatment are lenvatinib, sorafenib, cabozantinib, regorafenib, ramucirumab and so on. Gu Weiqin et al. combined with lenvatinib and PD-1 inhibitors in the treatment of advanced liver cancer, found that combined with lenvatinib can improve the liver function of patients with liver cancer and improve the survival rate of patients.

4.2. Combined treatment

The immune microenvironment of liver cancer is very complex, and the effect of combined therapy with anti-angiogenic drugs alone is finite. Therefore, it is necessary to introduce combined immunotherapy for clinical diagnosis and treatment. For patients with advanced liver cancer, the effect of combined immunotherapy is higher than that of single drug therapy to a certain extent. Combined immunotherapy can act on multiple targets at the same time, improve the treatment efficiency and improve the anti-tumor ability of patients. Immune checkpoint inhibitors-combined with vascular endothelial growth factor (VEGF) monoclonal antibody, tyrosine kinase inhibitor (TKI) and other treatment regimens have obvious clinical therapeutic benefits. VEGF binds to its endothelial cell surface receptors, which can induce endothelial cell proliferation and promote angiogenesis. VEGF and its acceptors are significantly aggrandized in patients with hepatocellular carcinoma (HCC), which are associated with micro vessel density, tumor invasiveness and poor prognosis. At the same time, atelizumab-combined bevacizumab (' A + T ') compared with sorafenib, in advanced liver cancer clinical therapeutic effect of phase III clinical trials IMbrave150, compared with sorafenib, ' A + T ' joint scheme can lengthen the survival time of patients with liver tumor, tumor response rate increased more significantly. Zheng Liyun and other scholars according to the treatment method is divided into TACE group and combined group. The patients were followed up to compare the tumor control rate (DCR), median survival time (OS) and progression-free survival (PFS). The results showed that DCR in combination group was higher than that in TACE group. The median PFS of the combined group was longer than that of the TACE group, and the median OS of the combined group was longer than that of the TACE group. The ultimateness shows that PD-1 inhibitor can effectively enhance the curative effect of TACE in the therapy of patients with massive liver cancer. PD-1 inhibitor combined with TACE is effective and feasible in the treatment of massive liver cancer.

5. Immune-related adverse reactions

Unlike chemotherapy, the clinical adverse reactions of PD-1/PD-L1 immune checkpoint inhibitors are mostly organ damage caused by immune activation. In addition to acting on specific organs, PD-1/ PD-L1 immune checkpoint inhibitors cause systemic non-specific symptoms due to the release of cytokines. For example, during the treatment of liver cancer, patients may have symptoms of pneumonia such as fever and chills, and even die of multiple organ failure after one week of liver cancer treatment. In addition, common adverse reactions that may occur during the treatment of liver cancer include: infusion-related adverse reactions, endocrine, digestive tract, skin, and multiple organ toxicity. In the process of using PD-1 immune checkpoint inhibitors and anti-vascular inhibitors to treat liver cancer, clinical results of different disease progression will occur. If the liver tumor increases during the treatment, there will be 'super-progression' results. A study has elucidated the mechanisms of possible tumor progression after combination therapy with PD-1 immune checkpoint inhibitors and antiangiogenic drugs, including the activation of oncogenic pathways following synergistic blockade of PD-1/PD-L1 and the activation of PD-L1 ligand-positive M2 macrophages, which directly or indirectly contribute to tumor progression. Therefore, treatment between anti-vascular inhibitors and immune checkpoint inhibitors has an inhibitory effect.

6. Conclusions

The application of PD-1/PD-L1 immune checkpoint inhibitors in the treatment of malignancy such as liver cancer, lung cancer, also breast carcinoma has received extensive attention. In clinical treatment, the clinical remission rate of single drug treatment is low (ORR). Combined therapy will become a key research direction in future immunotherapy research. At the same time, it should be noted that immune-related adverse reactions are still a major problem encountered in clinical treatment. How to accurately detect, prevent and control immune-related adverse reactions still requires in-depth research to find markers of immune-related adverse reactions that can be detected in time, and to prove that the treatment is effective. This also shows that PD-1/PD-L1 inhibitors still have great limitations in practice, and it is hoped that there will be a significant breakthrough in the study of immune checkpoint inhibitors in the future.

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