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Immune checkpoint inhibitor combination therapy

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Abstract. In recent years, Immune checkpoint inhibitors (ICIs) are being approved for the treatment of a wide range of malignancies, and they are one of the most popular immunotherapies for tumours, bringing new hope to patients. However, single-agent ICI therapy has limited efficacy and is prone to drug resistance, and the objective remission rate of ICI alone is only 10-20% in some tumours, therefore, how to improve clinical efficacy is the key point of clinical research associated with immunotherapy. New research has found that the combination of ICIs with differing mechanisms not only improves efficacy, but also prolongs the anti-tumour effect, while an appropriate dosing regimen can effectively balance efficacy and safety. It is proposed to review the mechanism, pharmacokinetics and clinical research progress of ICI combination therapy.

Keywords: immune checkpoint inhibitors, combination therapy, programmed death, melanoma

1. Introduction

The immune system of the body regulates the tumour environment through immunosurveillance, among other things, the state of immune cells is regulated by a combination as activation receptors and inhibitory receptors expressing at their surface. Through the activation of inhibitory signals, Immune checkpoints like procedural drug cell kill-1/programmed cell killing ligand-1 (PD-1/PD-L1), cellular cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and lipid-activated LAG-3, which are able to negatively regulate activated immune cells and maintain organismal self-tolerance. However, in pathological conditions, tumour cells can achieve immune escape by increasing the expression of inhibitory immune checkpoints. Immune checkpoint inhibitors (ICIs) can effectively inhibit the proliferation of tumour cells and enhance the body's killing effect on tumours.

Tumour immunotherapy represented by immune checkpoint inhibitors (ICI) is a novel kind of tumour immunotherapy distinct to traditional radiotherapy and targeted therapy. A variety of ICIs have been approved by drug regulatory authorities in many countries for the treatment of different tumour types. Despite the fact that a subset of patients achieve durable remissions, the objective remission rate (ORR) of ICI alone is not high, and is only 10%-20% effective in selected first-line [1, 2]. How to make full use of this new therapeutic tool to benefit more patients is a hot topic for oncologists. Clinical studies have shown that combining multiple mechanisms improves the outcome of ICI [3-5]. Currently, procedural death [protein]-1 inventor is approved in the United States for use in conjunction with CTLA-4 inhibitors. Food and Drug Administration (FDA) for the management of irresectable or metastatic pigmented melanoma, primary intermediate- to high-risk advanced kidney cell cancers, and treated DNA

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defective misfit recovery/micro-satellite instability (dMMR/MR). high (dMMR/MSI-H) metastatic colorectal cancer (mCRC), sorafenib-treated hepatocellular carcinoma (HCC), and primary non-small cell lung cancer (NSCLC) patients. cancer (NSCLC) patients, and some efficacy has also been observed in other tumours such as gastric cancer. The aim of this paper is to review the mechanism and pharmacokinetics of ICI combination therapy and its efficacy and safety for different tumours.

2. Mechanisms of ICI combination therapy

2.1. Mechanism of action of anti-PD-1 and anti-CTLA-4 monoclonal antibodies

Ipilimumab is the first ICI in the anti-CTLA-4 monoclonal antibody (monoclonal antibody) class to be approved for use in cancer therapy. CTLA-4 is found in regulator T cells (Treg), activated CD4+ T cells, and depleted T cells with significant immunosuppressive effects. CD80/CD86 binds to CD28 and activates the immune response, but CTLA-4 competitively binds to CD28, isolating CD28 from APCs, which in turn affects their activation, induction of immune tolerance, and induction function. Using CTLA-4 as the target and CD28/CD80/CD86 as the entry point, monoclonal antibodies targeting CTLA4 can block this effect and re-establish the interaction of CD28 with CD80 and CD86, thus promoting the promotion of lymph node-specific T cell activation and multiplication. Monoclonal antibodies against CTLA-4 can also act locally in tumours, but their mechanism of action is unclear. In addition, binding by the all-human immunoglobulin G1 preparation, ibritumomab, to CTLA-4 membranes on the tissue of Treg cell faces also produces agent-dependent calibrated cell-mediated cellular cytotoxicity (ADCC)， by inducing macrophages in the tumour microenvironment, high CTLA-4-expressing Tregs are removed and low CTLA-4-expressing CD8+ effector T cells are retained, which in turn improves the efficiency of the anti-tumour immune response. Anti-CTLA-4 monoclonal antibody also stimulates the amplification of Th1-like CD4+ T cells at the initiation of the adaptive immune response and in its early stages, and promotes the formation of memory T cells and their migration to tumour tissues.

Another immunosuppressive molecule, PD-1 is generally found on the surface of circulating tumour-specific T cells, tumour-infiltrating lymphocytes, and other cells in the tumour microenvironment, it bound to procedural death ligand-1 (PD-L1) expressing at the tumour cell or tumour-infiltrating immune cell surface and delivered immunosuppressive signals. Monoclonal antibodies against PD-1 or PD-L1 block this pathway, promoting the expansion of CD8+ effector T cells and their immune response to tumours.The PD-1/PD-L1 signalling pathway is inhibitory to other immune cells (e.g. DCs, B-cells, etc.),Thus, single clone versions of PD-1/PD-L1 are equally lethal.

2.2. Anti-PD-1 and anti-CTLA-4 combination

Combination of two immune checkpoint antibodies with different targets maximises immune escape of tumour cells, and thus better exert the anti-tumour effect. The association of a PD-1 antibody (navulizumab) and a CTLA-4 antibody (ibritumomab) for the management of metastatic malignant melanoma was the first antibody combination therapy to receive FDA approval. The 5-year overall survival was 52% in the combination group versus 44% in the natalizumab group and 26% in the ibritumomab group, resulting in a significant improvement in the efficacy of ICIs. In additional to combinations of marketed antibodies, combinations of novel antibodies have shown excellent anti-tumour effects. In a clinical trial of BMS's LAG-3 monoclonal antibody rilimumab and nabulizumab for advanced melanoma, Mean interim progression-free survival was 10.1 versus 4.6 months in the combination group, and one-year progression-free survival was 7.7 per cent in the combination group versus 36.0 per cent in the navulizumab group, which demonstrated the superior antitumour effects of LAG-3 monoclonal antibody and nabulizumab. The combination of LAG-3 monoclonal antibody and nabulizumab showed good therapeutic effects, and the treatment regimen has been cleared by the U.S. Food and Drug Administration for the treatment of metastatic malignant melanoma.

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2.3. Synergistic effects of anti-PD-1 and anti-CTLA-4

Both CTLA-4 and PD-1 pathways play the role of "brakes" in anti-tumour immunity, but they differ in their mechanism of action, main sites of action (lymph nodes and tumour microenvironment) and the stages of immune response affected (T-cell activation and effector phases), and thus simultaneous blockade of both pathways is likely to exert a synergistic effect [1]. Therefore, simultaneous blockade of these two pathways is likely to exert a synergistic effect [1]. In animal experiments, compared with blocking PD-1 alone, Improvement of the immune response to tumours in conjunction with anti-CTLA-4 monoclonal antibody and promotion of memory T-cell production, thereby preventing tumour recurrence in micee, and the effects of promoting tumour regression, decreasing Treg cells, and enhancing the infiltration of local lymphocytes in tumours have been cumulative, and the effects of depletion-like CD8+ T cells have been reduced, and the activated CD8+ effector T cells and Th1-like CD4+ effector T cells have been increased [2-5]. CD4+ effector T cells increased. Flow cytometry profiling demonstrated that anti-PD-1 monotherapy induced the multiplication of only PD-1+ CD8+ T cells, whereas the combination therapy group induced the increase in proliferation by PD-1+ and PD-1 low-expressing CD8+ T cells.

3. Pharmacokinetics/pharmacodynamics of anti-PD-1 and anti-CTLA-4 combination therapy

Pharmacokinetic/pharmacodynamic (PK/PD) studies showed no significant change in the rate of excretion of ibritumomab in the body when nabulizumab (Nivolumab) was combined with CTLA-4 monoclonal antibody (Ipimab). Nabulizumab combined with ibritumomab resulted in a 17% higher clearance after 6 weeks of treatment than nabulizumab alone; the combination of ibritumomab 3 mg/kg,3 weeks resulted in a 29% higher clearance rate compared to the control group; clearance was not significantly different in both groups between ibutilimumab 1 mg/kg and ibutilimumab 1 mg/kg later on 1 mg/kg after 3 weeks of use. Investigations in different populations showed no statistically significant differences in PK/PD values between Asians and Chinese using nabulizumab, pembrolizumab (an anti-PD-1 monoclonal antibody) or ibritumomab compared to non-Asians. The phase I and II CheckMate-672 trials were conducted in Chinese patients with solid tumours to evaluate the effects of 1 dose of 3 mg/kg nabulizumab and 6 weeks of 1 mg/kg ipimizumab; 3 mg/kg nabulizumab and 1 mg/kg ipimizumab once every 3 weeks, for a total of 4 courses of therapy; followed by 240 mg of nabulizumab administered for 2 weeks. Preliminary results suggest that the PK/PD profile of nabulizumab in combination with Ipimizumab is comparable to other previous phase I therapies. Data were similar to the PK data of each monotherapy in other previous phase I studies.

4. Conclusion

For tumour patients who meet the indications, the application of ICI combination therapy with different mechanisms has potent and durable anti-tumour efficacy. Monoclonal antibody co-delivery regimen against PD-1 and CTLA-4 approved in clinical practice, which has the advantages of fewer side effects and is safe and manageable, providing a new treatment option for patients with advanced tumours. How to better utilise the advantages of ICI combination therapy and at the same time reduce its adverse effects has been a hot topic of researchers' attention in recent stages. Recent animal studies have shown that prophylactic application of TNF inhibitors improves the therapeutic benefit of anti-PD-1 antibodies with CTLA-4 monoclonal to colitis, and the relevant phase I clinical trials are underway. Inhibitors, and other novel immunological agents under development also remain to be seen whether they can synergise with existing ICIs and improve anti-tumour effects with a controlled safety profile. In addition, many patients may have good initial efficacy at the start of immune-combination therapy but eventually progress, so potential mechanisms of resistance to ICI monotherapy and combination therapy, including inactivation of interferon gamma signalling due to mutations in the genes JAK1/JAK2, decreased expression of class I major histocompatibility complex antigens due to truncating mutations in the antigen presenting protein, β2-microglobulin decreased expression of up-regulated T-cell activation inhibitory receptors (V domain-containing immunoglobulin T-cell activation inhibitory receptor, VISTA) also deserve further investigation. In addition to the above points, it is necessary to explore the most appropriate

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immunotherapy drugs and dosage regimens for different tumour types and disease characteristics in more clinical trials in the future, as well as to search for more precise biomarkers to select the population that may have more benefits.

References

[1] HAYASHI H, NAKAGAWA K. Combination therapy with PD-1 or PD-L1 inhibitors for cancer[J]. Int J Clin Oncol, 2020, 25(5): 818-830.

[2] MALHOTRA J, JABBOUR S K, AISNER J, et al. Current state of immunotherapy for non- small cell lung cancer[J]. Transl Lung Cancer Res, 2017, 6(2): 196-211.

[3] LARKIN J, CHIARION-SILENI V, GONZALEZ R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma[J]. N Engl J Med, 2015, 373(1): 23-34. \

[4] WOLCHOK J D, CHIARION-SILENI V, GONZALEZ R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma[J]. N Engl J Med, 2017, 377(14): 1345-1356.

[5] OVERMAN M J, LONARDI S, WONG K Y M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer [J]. J Clin Oncol, 2018, 36(8): 773-779.