Proceedings of the International Conference on Modern Medicine and Global Health (ICMMGH 2023)
DOI: 10.54254/2753-8818/6/20230188

Immune escape mechanism of PD-1/PD-L1 in non-small-cell lung cancer (NSCLC) and its related drug treatment

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Abstract. In recent years, a variety of treatment methods for Non-small cell lung cancer (NSCLC) have been used, but most of them fail to show significant effect due to the late stage of diagnosis. At present, immunotherapy has become a new way of tumor therapy and attracted wide attention, among which programmed death molecule-1(PD-1) and programmed death ligand-1(PD-L1) have been proved to relate to immune escape in NSCLC, and relevant clinical drugs have shown a clear therapeutic effect. The related drugs can relieve the immune tolerance by blocking the pathway, and play a role in tumor killing. There are now various related drugs. Here, I review the progresses of the mechanistic role of PD-1 pathway in the tumor immune escape and effect of related drugs therapy.

Keywords: NSCLC, PD-1, PD-L1, immune escape, immunotherapy.

1. Introduction

In recent years, lung cancer has become a major threat to the health of the aged people in China especially the NSCLC (85%). Many patients were diagnosed in the advanced stage which leads to the poor effect of the surgical. Besides, the treatment is mainly radiotherapy or drug chemotherapy and the curative effect is not very satisfactory. Currently, it is known that exosomes and many cytokines can induce the formation of PD-1 in tumor cells to mediate immune escape in some malignant tumor such as melanoma and NSCLC. Therefore, blocking tumor-related PD-1 and PD-L1 or inhibiting their formation is anti-tumor.What's more, previous studies have shown that PD-1 has less toxic effects and better clinical therapeutic effect than other drugs using this mechanism. However,current studty shows a dilemma in clinical.The effective rate in patients is quite low when we just use a single drug,expecially in patients with PD-L1 comprehensive positive score(CPS) expression <50%.Therefore, the personalized combination therapy of tumor patients is very necessary.

2. Immune escape mechanism of PD-1/PD-L1 and theirs expression

T cell activation requires two activation signals: TCR and costimulatory molecules which can mediate T cell activation, tolerance, or apoptosis.After the costimulatory molecule PD-1 binds to the PD-L1, the downstream signaling pathway is inhibited by SHP-2, which affects the up-regulation of cell survival gene Bcl-XL and reduces the production of IL-2 and glucose metabolism.PD-1 can also inhibit the release of T cell cytokine and promote the apoptosis of T cell by inhibiting downstream

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PI3K/AKT signaling.EGFR-TKI, MAPK, P13K and other signaling pathways can also induce drug resistance and immune escape by increasing the expression of PD-1 and PD-L1[1].

TNM stage, tumor differentiation degree, lymph node metastasis and prognostic level were significantly associated the PD-1 expressing in CD3+ T cells. The pathological expression of PD-1 in NSCLC patients may become an auxiliary diagnostic indicator for the progression and prognosis of NSCLC in the future, and guide the using of related drugs.Studies have shown that high expression of PD-1 or PD-L1 are associated with lower survival and more rapid disease progression.The mechanism may be related to immune escape and low differentiation of tumor cells.

3. Immunotherapy of related drugs

3.1. Pembrolizumab/ Keytruda

Pembrolizumab is a monoclonal PD-1 antibody, which can enhance the killing ability of T cells by blocking the PD-1 binding, and is often used to treat malignant melanoma and middle and advanced NSCLC.When treating the patients who are TPS≥ 1%, the effect of pembrolizumab is much better than chemotherapy drugs.Especially for patients with TPS≥50% of PD-L1, it can effectively prolong the overall survival time[2].

When carboplatin or cisplatin plus pemetrexed is used to treat non-squamous cell carcinoma patients, if we combine it with pembrolizumab could prolong the OS, and the TRAEs don't increase in statistical significance [3].

The combination of niraparib and pembrolizumab enhanced the effect in patients against pembrolizumab, and the TRAEs do not increase significantly, but there was a small decrease in platelet count.And if the drug is discontinued ,the incidence of TRAEs is higher than when pembrolizumab is used alone.

Although platinum + paclitaxel + pembrolizumab could prolong PFS, the median TFS was almost the same, and the incidence of severe TRAEs withdrawal was higher than that of chemotherapy alone. Therefore, the appropriate group of patients receiving combination therapy should be carefully selected [4].

3.2. Nivolumab/ Opdivo

Nivolumab a drug that can bind to PD-1 to block its function and reactivate T cells to participate in the body's anti-tumor, which can be used for the advanced NSCLC. Using nivolumab alone obtain 18% ORR and 47% DCR, and the incidence of TRAEs is quite low in squamous cell carcinoma patients. The patients also have a good effect on the lesions of metastatic organs, among which the lymph nodes show the most obvious remission effect.

In Phase III clinical trials Checkmate017 and 057, patients treated with nivolumab and docetaxel obtained longer OS、PFS and less TRAEs [5].

Patients with resectable NSCLC who received Nivolumab plus platinum therapy or platinum-based therapy alone showed more effective disease remission, but the incidence of TRAEs increased significantly.In the Checkmate 227 clinical trial, nivoliumab + ipilimumab compared with platinum double-drug chemotherapy showed excellent OS prolongation effect regardless of PD-L1 expression. The most common adverse reaction was rash and most of them were easy to remission. Even patients who stopped taking the drug due to TRAEs also had long-term OS benefits.

3.3. Sintilimab

Sintillimab, a recombinant humanized anti-PD-1 monoclonal antibody, acts by the same mechanism as other PD-1 monoclonal drugs and is used for the treatment of Hodgkin's lymphoma and NSCLC. In the experiment, squamous cell carcinoma showed a better response than adenocarcinoma. The preoperative application of ChiCTR-OIC-17013726 showed its excellent auxiliary effect on excision therapy [6].

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The NCT02937116 trial, in which patients were grouped to receive Sintilimab plus cisplatin plus pemetrexed or gemcitabine, showed controllable toxicity and high anti-tumor activity.

In squamous cell carcinoma patients who don't have driver mutation, sintillimab plus paclitaxel/nab-paclitaxel plus platinum was better than sintillimab plus gemcitabine plus platinum.And the treatment was well tolerated but TREAs was more severe[7].

3.4. Atezolizumab/ Tecentriq

Atezolizumab acts as an antitumor agent by blocking PD-L1 receptor on tumor cells. Atezolizumab plus pembrolizumab has been the first-line monotherapy in patients with metastatic or advanced NSCLC and highly expressing PD-L1 according to FDA. Studies have found that first-line atezolizumab treatment for the patients with NSCLC is significantly improved against platinum-based chemotherapy for OS, which showing better efficacy and safety [8].

In the IMpower50 trial, it was also found that in NSCLC patients with EGFR mutation or metastasis, the combination of bevacizumab plus atezolizumab plus paclitaxel plus carboplatin (ABCP) provided a sustained extension of OS compared to bevacizumab plus paclitaxel plus carboplatin (BCP). Moreover, the effect of atezolizumab + paclitaxel + carboplatin (ACP) was not better than that of BCP in prolongating the survival of patients [9].

In CITYSCAPE experiment, a control experiment was conducted between treating with metastatic or relapsed NSCLC patients without driver mutation with tiragolumab plus atezolizumab and the treatment with atezolizumab in PD-L1 positive patients, and it was found that the combined treatment effect was superior and the safety was similar in terms of objective remission and median PFS. Two deaths from TRAEs in combination therapy which should be taken seriously.

3.5. Durvalumab/ Imfinzi

Durvalumab is the first one approved in China as an anti-PD-L1 drug, which can block the receptor of PD-L1 and break immune escape, and it is using for treating unresectable stage III NSCLC patients.In early experiments, it showed good therapeutic effect in NSCLC patients after platinum-based treatment plans, effectively prolongs median PFS and median distant metastasis or death events, and the occurrence of adverse events and their frequencies were similar[10].

The NCT02143466 trial showed that osimertinib combination durvalumab could due to a higher risk (35%) of TREAs and interstitial lung disease in patients [11]. Studies (NEPTUNE) have also found that durvalumab and other targeted drugs such as tremelimumab showed no significant OS improvement in patients with metastatic NSCLC(bTMB > 20), but the incidence of grade III/IV TRAEs decreased slightly[12].

4. Conclusion and discussion

Since the mechanism of PD-1 and PD-L1 was discovered, more and more clinical drugs have been put into use. Pembrolizumab, atezolizumab or pembrolizumab plus platinum and pemetrexed are used to treat of advanced non-squamous NSCLC without driver mutation as first-line treatment, and pembrolizumab, atezolizumab or pembrolizumab plus paclitaxel and platinum are used to treat advanced squamous NSCLC as first-line treatment. Nivolumab and tislelizumab are recommended for second-line treatment. Durvalumab after concurrent chemoradiotherapy is recommended for local advanced consolidation treatment. However, the use of immune checkpoint inhibitors is not recommended for mutation-positive patients.

Although immune checkpoint inhibitors have achieved good clinical therapeutic effect, there are still a small number of severe TRAEs, and some treatment have shorter survival after discontinuation than traditional therapies. Related mechanisms need to be further studied.

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