Immune Checkpoint Inhibitor Therapy: Application in Non-Small Cell Lung Cancer

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Abstract: Lung cancer is the most deadly disease in the world. The common treatment options include surgery, chemotherapy and radiotherapy, and targeted therapy can also be used selectively for those with positive driver genes. However, the 5-year survival rate of lung cancer patients is still low. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and there is an urgent need for new treatment methods in clinic. Immune checkpoint inhibitors have changed the treatment landscape for advanced NSCLC, showing advantages in first-line, second-line and even multi-line therapy for patients with NSCLC. In recent years, immunotherapy has provided a possibility for patients with NSCLC as a new and effective tumor treatment method. This review reviewed the mechanism of action, clinical application, immune escape mechanism and adverse reactions of immune checkpoint inhibitor therapy in non-small cell lung cancer.

1 INTRODUCTION

Lung cancer has become a global problem endangering human health, causing more than 1.6 million deaths every year. In recent years, targeted therapy has been proposed for patients with genetic dysfunction of NSCLC, but many patients do not have oncogenic factors such as epidermal growth factor and anaplastic lymphoma kinase, and drug resistance is inevitable (Low, et al., 2019). It has become a trend to study new therapeutic directions, and the development of immunotherapy has become a harbinger of the era of personalized medicine with the deepening of tumor immunology.

The application of Immune checkpoint inhibitors (ICIs) is a great leap forward in the immunotherapy of non-small cell lung cancer, such as antibodies to CTLA-4 or PD-1 or its death-ligand 1(PD-L1). Immune checkpoint inhibitors have been developed to target immune escape and immunosuppression of tumors (Galluzzi, Zitvogel, Kroemer, 2016). Unlike chemotherapy or targeted drugs that directly target malignant cells, immune checkpoint inhibitors are thought to stimulate immune-associated cell-mediated immune recognition and clearance, and work by modulating T-cell function and mechanisms related to targeted immune resistance, such as immunosuppressive factors in the tumor microenvironment. The interaction between PD-1 and the PD-L1/PD-L2 ligand inhibits T cell proliferation and promotes the secretion of cytokines related to immune response. Pd-l1 and PD-L2 ligands are expressed by antigen-presenting cells (APC) and can be expressed by tumor cells or other cells in the tumor microenvironment to promote tumor cell proliferation (Wang, et al., 2014). It is the monoclonal antibody against PD-1 or PD-L1 that blocks their interaction and rejuvenates T cells to eliminate cancer cells. Ctla-4 is mainly expressed in dendritic cells and inhibits the activation of CD28-dependent T cells, resulting in decreased levels of IL-2, IL-4, TNF-α and IFN-γ, and decreased proliferation of CD8+ and CD4+T cells. In addition, the interaction of CTLA-4 with CD80 and CD86 expressed by conventional T cells increases their inhibition of Treg mediation (Xiao, et al., 2020).

In recent years, targeted therapy has proposed new treatment options for patients with genetic dysfunction of NSCLC, but many patients do not have carcinogens such as epidermal growth factor and anaplastic lymphoma kinase, and drug resistance is inevitable (Low, et al., 2019). Approximately 60% of patients develop primary drug resistance during anti-PD-1 /PD-L1 therapy, and effective patients will also develop secondary drug resistance as NSCLC patients receiving targeted therapy. At present about the resistance mechanism of the immune checkpoint inhibitors may have the following several aspects:

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first, the effect of T cell activation depends on the local immune of the tumor microenvironment, first of all, the cancer cells of the immune cells to identify cancer cells around, so after lifting immunosuppression, these identifiable immune cells can effectively play a role of anti-tumor, i.e. thermal tumor. If the tumor is cold, due to the low degree of immune resistance in the immune microenvironment and the immunogenicity of the tumor itself is lower than that of the thermal tumor, there will be no immune cells to kill the tumor after the removal of immunosuppression (Arbour, Riely, 2019). Second, the TMB value of tumors. Studies have confirmed that low mutation load and poor immunogenicity of tumors will affect the development and maturity of effector T cells, affect the activation of T cells, and lead to the occurrence of drug resistance (Suresh, et al., 2018). Third, effect closely associated with APCs and T cell activation antigen presenting cells, dendritic cells, for example, by taking the tumor antigens, and to the effect of T cells, a process that strong induction and activation of the effects of tumor antigen specific T cells, which mediates antitumor effect, disrupting any link in the process is likely to lead to the occurrence of immune resistance. Fourthly, there are many immunosuppressive pathways in human body. In addition to pD-1 /PD-L1 signaling pathway and CTLA-4 signaling pathway, there are also TIM3 and LAG3, etc. It is assumed that these immunosuppressive pathways coexist in tumor tissues. If only one immunosuppressive pathway is blocked, the other immunosuppressive pathways will still be normal transduction. Even with compensatory enhancement, immunotherapy does not achieve ideal efficacy (Champiat, et al., 2017).

At present, immunotherapy for NSCLC has achieved good results in phase I /II clinical trials: improved tumor response rate, small toxic and side effects, and easy tolerance by patients, which will develop a new field for NSCLC treatment. Immune checkpoint inhibitor therapy achieves anti-tumor effect by inhibiting immune checkpoint activity, releasing immune brake in tumor microenvironment and reactivating the immune response effect of T cells to tumor, which also makes it a new weapon against tumor. Clinically, some patients can achieve lasting clinical results and remain free of any tumor-related clinical symptoms for several years.

This review mainly includes the following parts: mechanism of action, clinical application, immune escape mechanism and main adverse reactions of immune checkpoint inhibitor therapy in non-small cell lung cancer.

2 MECHANISM OF IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

Lung cancer can be divided into primary lung cancer and secondary lung cancer, according to etiology, while NSCLC is the most common type of primary lung cancer. Among them, non-small cell lung cancer (NSCLC) accounts for about 85% of primary lung cancers (Brahmer, et al., 2018). The overall five-year survival rate of lung cancer patients in the past 40 years is still less than 21% (Lu, Yang, Huang, et al., 2019). Unfortunately, about 60% of patients are diagnosed at an advanced stage and lose the opportunity for surgical treatment. The only treatment options for these patients are chemotherapy, radiotherapy and targeted therapy. It is reported that the 5-year survival rate of NSCLC is only 17%, and the 5-year survival rate of advanced NSCLC is less than 5% (Siegel, Miller, Jemal, 2017).

Table 1: Basic information on non-small cell lung cancer.

Type	Adenocarcinoma	Squamous cell carcinomas	Large cell carcinoma
Incidence rate	About 50%	About 30%	About 5%
Features	The most common type of lung cancer, especially in non-smokers. Targeted drugs are suitable for most patients in China.	Squamous cell carcinoma usually grows slowly. Surgery is an option for early detection.	Relatively rare, but malignant degree is generally higher, easy to metastasize.
Metastatic	Moderate	Moderate	Strong
Main treatment modalities	Surgery, chemotherapy, radiation, targeted drugs	Surgery, chemotherapy, radiation	Surgery, chemotherapy, radiation

The body resists tumor formation through acquired immunity. Tumor cells avoid detection and attack by the body's immune system through allowing tumor cells to escape the immune killing impact and advance to growth and metastasis, according to immunology. Antigen uptake, processing, and presentation by antigen-presenting cells start the immune response. APC binds to major histocompatibility complex (MHC) molecules and transfers antigen to the t-cell surface receptor. Furthermore, T cells' CD28 receptor binds to APC's CD80/CD86 ligand, causing both signals to activate T cells (Reck, Heigener, Reinmuth, 2016). As demonstrated in Figure 1, lung cancer cells' immunological escape weakens the immune response primarily through the immune checkpoint pathway, which includes CTLA-4 and PD-1.

2.1 Anti-CTLA-4 Antibody

CTLA-4 is a CD28 homologous analogue. CTLA-4 is more compatible with CD80/CD86 than CD28, hence CTLA-4 preemies CD80/CD86 by competitive action. CTLA-4 can also suppress the production of CD80 / CD86 on APC or remove it via cytoendocytosis, preventing CD28 from attaching to T cells and inhibiting T cell activation (Qureshi, Zheng, Nakamura, et al., 2011). In the process of T cell activation and immune response activation, CTLA-4 acts as a negative regulator. Antibodies against CTLA-4 can disrupt inhibitory signals, causing T cells to activate and proliferate, thus restoring their function.

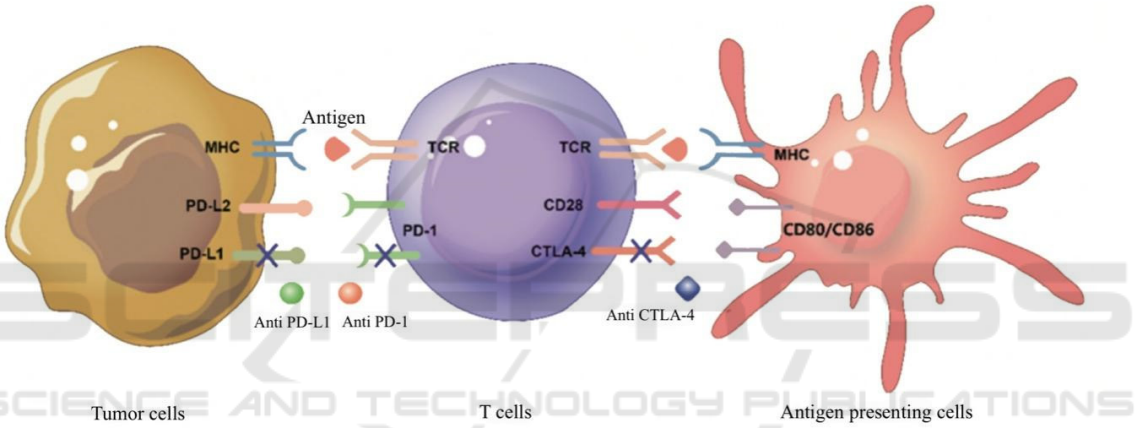

Fig. 1 T cell activation mechanism and immune checkpoint inhibitor action mechanism.

2.2 Anti-PD-1 /PD-L1 Antibody

PD-1, a type I transmembrane glycoprotein, was first identified in isolation of mouse T cells involved in programmed cell death. PD-L1 and PD-L2 are the two ligands for PD-1. In normal tissues, the expression of PD-L1 regulates the expression of the tissue's own immune response after a prolonged inflammatory response to tissue injury. T cells, B cells, macrophages, vascular endothelial cells, islet cells, and other cells all express PD-L1. PD-L2 is mostly expressed in macrophages and B cells, with a low level of basic expression (Sharpe, Pauken, 2018). Tyrosine residues in the cytoplasmic domain are phosphorylated after PD-L1 interacts to ligands, and protein-tyrosine phosphatase (PTP) is recruited. Signal kinases in signaling pathways are dephosphorylated as a result of this PTP. The signal transduction of CD28 receptor positive activation is inhibited (Akinleye, Rasool, 2019). PD-1 signaling inhibits T cell activation and proliferation by lowering activating transcription factors (TFs) such as activating protein 1 (AP1), activating T cells (NFAT), and NF-κβ (Wu, Gu, Chen, et al., 2019).

3 CLINICAL APPLICATION OF IMMUNE CHECKPOINT INHIBITORS IN NON-SMALL CELL LUNG CANCER

3.1 Immune Checkpoint Inhibitor Monotherapy

As the rise of immunotherapy and multiple ICI approved for monotherapy, some studies reported that CTLA-4 antibodies (Ipilimumab, Tremelimumab) and human anti-PD-1 / PD-L1 antibodies

(pembrolizumab, Nivolumab, Atezolizumab) was effective in the treatment of NSCLC in recent years. Pembrolizumab monotherapy, based on KEYNOTE024 and 042, is utilized as a first-line treatment for PD-L1 positive NSCLC patients, particularly those with high PD-L1 expression (Mok, Wu, Kudaba, et al., 2019). After the CheckMate 017 and CheckMate 057 studies compared to docetaxel, nivolumab was authorized for second-line therapy of advanced relapsed or refractory NSCLC (Borghaei, Paz-Ares, Horn, et al., 2015). The efficacy of Atezolizumab in lung cancer was revealed in a Phase II trial of POP-lar, and this benefit was particularly pronounced in patients with high PD-L1 expression (Fehrenbacher, Spira, Ballinger, et al., 2016). The OAK Phase III experiment was later confirmed. Regardless of PD-L1 expression status, atezolizumab was approved for treatment in previously treated patients with metastatic NSCLC (Brahmer, Govindan, Anders, et al., 2018).

3.2 Immune Checkpoint Inhibitors Combined with Chemotherapy

Pembrolizumab plus chemotherapy significantly improved ORR compared to chemotherapy alone and pembrolizumab, regardless of PD-L1 expression, following KEYNOTE 021 first successful combination of platinum-based chemotherapy with ICI in patients with advanced NSCLC. The risk of tumor progression and death was cut in half (Langer, Gadgeel, Borghaei, et al., 2016), and immunotherapy was switched to a combination treatment. The objective response rate of Nivolumab combined with conventional chemotherapy was as high as 47% in CheckMate 012 (Rizvi, Hellmann, Brahmer, et al., 2016), with a 2-year OS rate of 62% for Nivolumab(5mg/kg) plus paclitaxel-carboplatin. Pembrolizumab plus pemetrexed and platinum-based patients with previously untreated metastatic non-squamous NSCLC without *EGFR or ALK* mutations had a median progression-free survival of 8.8 months in Keynote-189 (Gandhi, Rodriguez-Abreu, Gadgeel, et al., 2018).

Overall, 69.2% of patients survived for 12 months. IMpower132 found that Atezolizumab in combination with chemotherapy improved PFS more than chemotherapy alone, while imPOWER150 found that Atezolizumab in combination with bevacizumab and standard chemotherapy improved OS regardless of pD-L1 expression or genetic changed status of EGFR or ALK (Socinski, Jotte, Cappuzzo, et al., 2018). In patients with metastatic non-squamous non-small cell lung cancer who do not have *EGFR or ALK* genetic abnormalities, the FDA has approved Atezolizumab in combination with bevacizumab and conventional chemotherapy as a first-line treatment.

3.3 Combination Therapy with Immune Checkpoint Inhibitors

The CheckMate 012 experiment began attempting dual ICI medication therapy based on the various modes of action of the PD-1 and CTLA4 pathways. In the first-line therapy of NSCLC patients, Nivolumab plus Ipilimumab has a tolerable safety and therapeutic effect (Hellmann, Rizvi, Goldman, et al., 2017). The CheckMate 227 study also found that, regardless of PD-L1 status, the median PFS in the dual ICI group (Nivolumab plus Ipilimumab) was 7.2 months compared to 5.4 months in the high-TMB chemotherapy group. The ORR was also greater, at 45.3% vs. 26.9%. 252 patients with recurrent stage IIIB/IV NSCLC treated with Nivolumab in combination with Ipilimumab were divided into three groups based on pD-L1 expression levels of less than 1%, 1%, and more than 1% in CheckMate 568 (Ready, Hellmann, Awad, et al., 2019). ORR rates were 15%, 30%, and 41%, respectively, and ORR increased as TMB increased. However, in a Phase Ib trial (NCT02000947) involving 102 patients with advanced NSCLC who received Durvalumab, an anti-PD-L1 antibody, and Tremelimumab, an anti-CTLA-4 antibody, 29 patients (28%) were stopped due to treatment-related adverse events, and 37 patients (36%) had treatment-related serious adverse events (Antonia, Goldberg, Balmanoukian, et al., 2016). Group according to PD-L1 expression, 118 patients were separated into two groups (>25% and <25%) in the phase III clinical trial (NCT02453282). There was no statistically significant difference in OS and PFS whether Durvalumab (or Durvalumab + Tremelimumab) or chemotherapy was given in addition to the machine (Rizvi, Cho, Reinmuth, et al., 2018). D + T was administered in combination with chemotherapy in a Phase Ib trial (NCT02537418), and 17 of 24 patients with advanced NSCLC achieved remission, with an ORR of 52.9%. The efficacy of D + T combination with platinum therapy will be further investigated in the ongoing Phase II clinical trial (NCT03057106) and Phase III trial (NCT02542293). The trial's primary goal is OS, with secondary endpoints including PFS, ORR, quality of life, and safety, with the particular effect yet to be determined.

3.4 Immune Checkpoint Inhibitors Combined with Indoleamine 2,3-dioxygenase 1(IDO-1) Inhibitors

IDO-1 is a metalloproteinase that can catalyze the metabolism of tryptophan into canisuric acid. IDO-1 oxidizes tryptophan to N-formylcanisuric acid and then converts it into catabolites (Prendergast, Mondal, Dey, et al., 2018). When tryptophan is consumed, the activity of T-cell-activated kinase PKC-θ decreases, and the tryptophan catabolites promote the differentiation of CD4+T cells into Treg cells by binding to the aromatics receptor, while limiting the differentiation of CD4+T cells into Th17 cells, inhibiting the immune system (Zhu, Dancsok, Nielsen, 2019). Multiple quantitative immunofluorescence was used to measure the levels of PD-L1, ID-1, B7-H4 and different tumor-infiltrating lymphocyte (TIL) subtypes in 552 patients with stage I to IV lung cancer, and the increase of PD-L1 and ID-1 was consistent with significant B and T cell infiltration, with limited co-expression (Schalper, Carvajal-Hausdorf, Mclaughlin, et al., 2017). The echo-202 / Keynote-037 trial used the IDO-1 inhibitor EpACa-dostat in combination with Pembrolizumab in NSCLC, resulting in an ORR of 35% and a DCR of 60% in 40 assessable patients. The most common adverse reactions were fatigue (19%), arthralgia (9%), and elevated AST (9%). E+P was generally well tolerated and effective in the treatment of advanced NSCLC (Mitchell, Hamid, Smith, et al., 2018).

3.5 Immune Checkpoint Inhibitors Combined with Radiotherapy

Massive radiotherapy can destroy intracellular DNA, effectively delay tumor metastasis, and reduce local compression symptoms in patients with advanced NSCLC; on the other hand, tumor cells killed by radiotherapy will release a significant number of new antigens to stimulate the body's immune response. As a result, immunocheckpoint inhibitors combined with radiation have emerged as a new effective therapeutic strategy for advanced NSCLC. Pembrolizumab (0.2 g/kg every 3 weeks) or radiation (8 Gy 3 times) followed by Pembrolizumab were given to 76 patients with relapsed metastatic non-small cell lung cancer (treatment group). The experimental group's ORR was 36% vs. 18% at 12 weeks, their PFS was 6.6 vs. about 2 months, and their median overall survival was 15.9 vs. 7.6 months. For patients with PD-L1 negative tumors, a subgroup study revealed that increasing the radiation dose was more effective. The findings revealed that a small amount of radiation before to Pembrolizumab treatment improved the therapeutic outcome (Theelen, Peulen, Lalezari, et al., 2019). Patients with advanced NSCLC who received intravenous Pembrolizumab following local ablation had a median PFS of about 20 months and an overall mean survival rate of 90.9% at 1 year in the NCT02316002 study. Pembrolizumab after local ablation increases PFS without impairing mass of life in patients with advanced lung cancer, according to a study (Bauml, Mick, Ciunci, et al., 2019). However, several issues remain with this treatment, including the best dose and timing for ICI-related radiation, the impact of PD-L1 status, and how to incorporate immune checkpoint inhibitors into these combinations. More experimental research is needed to find the best therapy combination.

3.6 Immune Checkpoint Inhibitors Combined with Targeted Therapy

First-line targeted therapy with tyrosine kinase inhibitors (TKI) is preferred for sensitive NSCLC patients with driver gene mutations such as *EGFR, BRAF*, *ALK*, or *ROS1*. Due to the drug resistance of targeted therapies, a combination of ICI and TKI was tested. Although there were some favorable signs in some subgroups, overall clinical efficacy was poor, and adverse events were common (Berghoff, Bellosillo, Caux, et al., 2019). When TKI therapy is ineffective or the response to TKI drugs is intolerable, ICI is indicated.

4 IMMUNE ESCAPE AND IMMUNOSUPPRESSION IN NSCLC

Immune escape is a major feature of cancer, in which tumors lose expression of their antigens, negatively collectively regulate major histocompatibility complex (MHC) molecules, reduce antigen presentation ability, do not express effector T lymphocyte costimulatory molecules or overexpress molecules that inhibit the activity of these lymphocytes. In addition, immunosuppressive factors can be produced by promoting T regulation of gonorrhoetic cell differentiation (Tregs) and increasing the number of myeloid suppressor cells (MDSCs) (Spagnuolo, Gridelli, 2019), expressing immune checkpoints to inhibit immune cell function, leading to immune cell failure and apoptosis, and thus

avoiding the host's immune surveillance (Theelen, Jong, Baas, 2020). The checkpoint signals PD-1 and CTLA-4 block T cell activation and allow malignancies to evade the adaptive immune response (Somasundaram, Burns. 2017). PD-1 is a negative costimulatory receptor, mainly expressed on the surface of activated T cells and belonging to the CD28 family. After binding with PD-L1 and PD-L2, the main ligands on T cells or antigen-presenting cells (APC), PD-1 reduces the activity of T lymphocytes to avoid being eliminated by the immune system (Economopoulou, Mountzios, 2018). The CTLA-4 expression on regulatory T cells causes a decrease in T cell activity and an increase in the system's immunosuppressive activity.

5 ADVERSE REACTION ANALYSIS

5.1 Completion of Immunotherapy

During the period of 70 patients receiving immunotherapy for non-small cell lung cancer, 2 patients were discontinued due to adverse reactions. One patient died, and the remaining 67 patients continued treatment. Among the 70 patients, 67 patients were followed up for 6 months, with a follow-up rate of 95%. Among them, 18 cases received 2 cycles of treatment, 12 cases received 3 cycles of treatment, 8 cases received 4 cycles of treatment, 14 cases received 5 cycles of treatment, 6 cases received 6 cycles of treatment, 4 cases received 7 cycles of treatment, and 8 cases received 8 cycles of treatment (Fu, Wang, 2020).

5.2 Distribution of Species and Classification

5.2.1 Type Analysis of Adverse Reactions

The incidence rate of anorexia and tiredness symptoms was 100% (70 instances), which differed from the findings of Gettinger et al (Gettinger, Horn, Gandhi, et al., 2004). And could be due to the fact that there were 70 patients receiving combination treatment. With a 1% incidence of bad cardiac reactions, one patient died, demonstrating that while the incidence of adverse cardiac reactions is modest, the fatality rate is significant. The other 19 cases had a 1%-5% incidence of adverse reactions, which were common adverse reactions to immunotherapy and had a low incidence.

5.2.2 Distribution of Adverse Reactions

Three patients (4%) had grade 4 adverse events, including one with liver function injury and another with fever. All of the patients were given drug withdrawal, and one of them died as a result of cardiac complications. There were 17 cases of grade 1-2 adverse reactions (24%), demonstrating that immunotherapy adverse reactions are uncommon. Mild adverse reactions were the most common, while severe adverse reactions were uncommon, although severe adverse reactions had major repercussions for patients (Fu, Wang, 2020).

The safety and observable qualities of epidematic-free treatment have been proven in terms of the types and amount of adverse reactions, however life-threatening and life-threatening adverse reactions do occasionally occur, necessitating medical intervention (Table 1) (Fu, Wang, 2020).

Table.2: Analysis of adverse reactions to immune checkpoint inhibitor therapy in 70 patients with non-small cell lung cancer (cases, %) (Fu, Wang, 2020).

Project	Level 1	Level 2	Level 3	Level 4	Total	Incidence rate (%)
Hypothyroidism	2	-	-	-	2	3
Rash	4	-	-	-	4	7
Fever	5	-	-	1	4	7
Hepatic	5	-	-	1	4	7
Interstitial pneumonia	2	2	-	-	4	7
Neurotoxicity	1	-	-	-	1	1
Cardiac toxicity	-	-	-	1	1	1
Loss of appetite and fatigue	70	-	-	-	70	100

5.2.3 Analysis of Adverse Reaction Time during Treatment

In the first two cycles of combination chemotherapy, seventy patients with NSCLC experienced anorexia and fatigue. There was a total of 20 additional adverse events, with 18 patients (90%) having immune-related adverse reactions in the first four cycles. All immune-related side effects occurred within the first six cycles of treatment, demonstrating that immune checkpoint inhibitor-related side effects began early in the drug administration (Fu, Wang, 2020). There was no link between the duration of medicine and the outcome (Table 2).

Table.3: Time of adverse reactions to immune checkpoint inhibitor therapy in 70 patients with non-small cell lung cancer (cases, %) (Fu, Wang, 2020).

Project	The first cycle	The second cycle	The thrid cycle	The fourth cycle	The fifth cycle	The sixth cycle
Hypothyroidism	1	-	-	1	-	-
Rash	-	2	-	2	-	
Fever	2	-	1	1	-	-
Hepatic injury	-	1	2	1	-	-
Interstitial pneumonia	-	2	-	1	1	-
Neurotoxicity	1	-	-	-	-	-
Cardiac toxicity	-	-	-	-	1	-
Loss of appetite and fatigue	40	30	-	-	-	-
Total	44	35	3	6	2	-
Incidence rate (%)	62	50	4	8	3	-

6 CONCLUSION

Immune checkpoint inhibitors have changed the treatment landscape of advanced NSCLC, showing advantages in first-line, second-line and even multi-line therapy for patients with NSCLC.Despite the fact that immunotherapy has demonstrated remarkable efficacy in patients with non-small cell lung cancer, there are still a number of pressing issues to be addressed, including the lack of biomarkers that can predict immunotherapy on their own, the difficulty of preventing immune-related side effects, and the emergence of drug resistance. This paper summarized the mechanism of ICI in NSCLC, clinical application, immune escape mechanism and the occurrence of adverse reactions, with the purpose of summarizing the latest progress of this immunotherapy and making prospects. Future immunotherapy research for non-small cell lung cancer should concentrate on increasing sensitivity to tumor-specific antigens, developing additional effective targets and more reliable biomarkers, and balancing efficacy and toxicity between monotherapy and combination therapy.

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