Checkpoint Inhibitor Pneumonitis Induced by Anti-PD-1/PD-L1 Therapy in Non-Small-Cell Lung Cancer: Occurrence and Mechanism

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Immune checkpoint inhibitors (ICIs), particularly those targeting programmed death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1), enhance the antitumor effect by restoring the function of the inhibited effector T cells and produce durable responses in a large variety of metastatic and late patients with non-small-cell lung cancer. Although often well tolerated, the activation of the immune system results in side effects known as immune-related adverse events (irAEs), which can affect multiple organ systems, including the lungs. The occurrence of severe pulmonary irAEs, especially checkpoint inhibitor pneumonitis (CIP), is rare but has extremely high mortality and often overlaps with the respiratory symptoms and imaging of primary tumors. The development of CIP may be accompanied by radiation pneumonia and infectious pneumonia, leading to the simultaneous occurrence of a mixture of several types of inflammation in the lungs. However, there is a lack of authoritative diagnosis, grading criteria and clarified mechanisms of CIP. In this article, we review the incidence and median time to onset of CIP in patients with non-small-cell lung cancer treated with PD-1/PD-L1 blockade in clinical studies. We also summarize the clinical features, potential mechanisms, management and predictive biomarkers of CIP caused by PD-1/PD-L1 blockade in non-small-cell lung cancer treatment.

Keywords: programmed cell death 1, programmed cell death ligand 1, immune checkpoint inhibitors, immune-related adverse events, checkpoint inhibitor pneumonitis, non-small-cell lung cancer

1 INTRODUCTION

Although the incidence and mortality of lung cancer has shown a significant decline according to recent studies, it still exceeds the vast majority of cancer types (1). According to the International Agency for Research on Cancer, lung cancer is the most common malignant tumor with the highest mortality. Non-small-cell lung cancer (NSCLC) is the major histological subtype of lung cancer, accounting for approximately 85% of all lung cancers (2). Anti-programmed death 1 (PD-1) and
anti-programmed death ligand 1 (PD-L1) monoclonal antibodies (mAbs) have profoundly produced durable anticancer responses in patients with a variety of solid tumors, including NSCLC. The U.S. Food and Drug Administration has approved three PD-1 inhibitors (nivolumab, pembrolizumab and cemiplimab) and two PD-L1 inhibitors (atezolizumab and durvalumab) for the treatment of NSCLC with different stages (3–6).

However, accompanied by a promising survival advantage, PD-1/PD-L1 inhibitors are related to a broad spectrum of toxic effects known as immune-related adverse events (irAEs), including skin rash, colitis, hepatitis, endocrinopathies, and pneumonitis (7). In clinical trials, adverse events are reported and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) from the U.S. National Cancer Institute, and immune-related pulmonary adverse events are graded from grade 1 to grade 5 depending on the symptoms from mild to serious (8). Most irAEs are mild and tolerable, while some of them can be fatal. In recent years, pulmonary adverse events caused by PD-1/PD-L1 inhibitors have been gradually reported, and some rare severe events even lead to death (9). It is worth noting that checkpoint inhibitor pneumonitis (CIP) accounts for 35% of PD-1 and PD-L1 inhibitor-related deaths (9). In addition, the incidence of CIP induced by anti-PD-1/PD-L1 is higher in patients with NSCLC than in patients with other cancers (3, 10). Pneumonitis can be mediated by various factors, such as radiotherapy, chemotherapy, targeted therapy, infection, and nonanticancer drugs (3). Thus, the diagnosis of CIP needs to be distinguished from hyperprogression, pseudoprogression, and other types of pneumonia (11). Further characterization of the unique clinical and radiographic features is needed to aid in the diagnosis of CIP. The incidence, risk, clinical characteristics and mechanism of CIP for anti-PD-1/PD-L1 monotherapy or a combination with other therapies (radiotherapy, chemotherapy or targeted therapy) may differ, which might influence the subsequent treatment options and prognosis of CIP (12). The clinical features and mechanisms of CIP induced by anti-PD-1/PD-L1 therapy in non-small-cell lung cancer have not been fully elaborated. In this review, we summarize recent discoveries on CIP introduced by anti-PD-1/PD-L1 treatment, especially in patients with NSCLC, and aim to provide a reference for clinical diagnosis and preclinical mechanistic research. We will also elucidate the incidence, time to onset and characteristic manifestations of CIP, as well as discuss the management and predictive biomarkers of CIP.

2 OCCURRENCE OF CIP DURING PD-1/PD-L1 BLOCKADE

2.1 Incidence and Timeline

Pulmonary irAEs are more common in patients with NSCLC than in patients with other cancers, with an incidence of 3% to 5% according to clinical trial data (3, 10, 13). Without the exclusion criteria of clinical trials, the incidence of CIP can be much higher in the real world. In a retrospective study of 205 patients with NSCLC, 19% of them encountered CIP during PD-1/PD-L1 blockade. PD-1/PD-L1 inhibitors show a higher incidence of CIP than other ICIs, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, and are responsible for 35% of CIP-related deaths (9, 14). The incidence of CIP can vary when different PD-1/PD-L1 inhibitors are used (4, 10, 15–27) (Table 1). However, in general, PD-1 inhibitors account for a higher incidence of all-grade (3.6% vs. 1.3%) and high-grade (1.1% vs. 0.4%) CIP than PD-L1 inhibitors based on a clinical trial of NSCLC (28). A multicenter, open-label, global, phase 3 trial compared the effect and safety of cemiplimab single-agent therapy with platinum-doublet chemotherapy in the first-line treatment of advanced NSCLC patients with a PD-L1 expression level of 50% or higher. The results showed that the incidence of immune-related pneumonitis in NSCLC patients receiving cemiplimab therapy was 2.3% (22).

There is a lower incidence of pneumonitis in PD-1/PD-L1 inhibitor monotherapy than in concurrent or sequential chemotherapy (29), radiotherapy (30) or immunotherapy (3, 17, 27, 31). In a randomized phase III clinical trial, the incidences of any-grade and high-grade CIP in NSCLC patients receiving durvalumab plus tremelimumab, a CTLA-4 inhibitor, were higher than those with durvalumab monotherapy (6.7% vs. 2.2% for any-grade CIP and 2.2% vs. 1.1% for high-grade CIP) (27). This may be attributed to the overlapping pulmonary toxicity of different treatments. In addition, there are no reliable criteria to distinguish CIP from radiation pneumonitis and radiation recall pneumonitis, which may affect the diagnosis of CIP (32, 33). Concurrent or sequential combination therapy is common in the clinic and may account for the higher incidence of treatment-related pneumonitis in the real world (34–36).

The median time to onset of pulmonary adverse events can vary. A report showed that the median time to onset of pneumonitis was 2.8 months, with a wide range from 9 days to 19.2 months (3). The onset time may be affected by the selection of the ICI agent (15, 16, 18, 34–37) (Table 2). In a randomized, open-label, international phase 3 study, the median onset time to pneumonitis was 15.1 (2.6–85.1) weeks and 31.1 (11.7–56.9) weeks in patients with advanced squamous and nonsquamous NSCLC who received nivolumab, respectively (15, 16). In another randomized controlled trial, the median onset time was 8.1 (0.6–56.1) weeks in advanced NSCLC patients treated with pembrolizumab (18). The treatment strategy may also influence the onset time. A shorter median onset time was reported in patients with combination immunotherapy compared with monotherapy (2.7 months (9 days to 6.9 months) vs. 4.6 months (21 days–19.2 months), P=0.02) (3). In retrospective studies that enrolled only NSCLC patients, the onset of CIP occurred earlier when PD-1/PD-L1 inhibitors were combined with other treatments (Table 2). More high-grade CIP onset occurs within the first 100 to 200 days of immunotherapy (38). Naidoo et al. reported a type of CIP called chronic CIP, which refers to a kind of clinical pneumonitis persisting or worsening with steroid tapering and necessitating ≥12 weeks of immune suppression after ICI discontinuation. The incidence of chronic pneumonitis is
## TABLE 1 | Important clinical trials that reported checkpoint inhibitor pneumonitis (CIP) in NSCLC patients with PD-1/PD-L1 blockade.

| Registration number | Published year | Treatment | Enrollments | NSCLC stage | Incidence, n (%) | Reference |
|---------------------|----------------|-----------|-------------|-------------|------------------|-----------|
| NCT01642004         | 2015           | Nivolumab  | 131         | III IIIB or IV | 6 (5.0) 1 (1.0) | (15)      |
| NCT01673867         | 2015           | Nivolumab  | 287         | III IIIB or IV | 8 (2.8) 3 (1.0) | (16)      |
| NCT02477826         | 2018           | Nivolumab  | 391         | IV           | 9 (2.3) 6 (1.5) | (17)      |
| NCT02477826         | 2018           | Nivolumab + Ipilimumab | 576      | IV           | 22 (3.8) 13 (2.3) | (17)      |
| NCT01296827         | 2015           | Pembrolizumab | 550     | III IIIB or IV | 21 (3.8) 11 (2.0) | (19)      |
| NCT01905857         | 2018           | Pembrolizumab | 682     | II/III IIIB or IV | 26 (3.8) 12 (1.8) | (19)      |
| NCT02142738         | 2016           | Pembrolizumab | 154     | III IIIB or IV | 9 (5.8) 4 (2.6) | (20)      |
| NCT02220894         | 2019           | Pembrolizumab | 636     | III IIIB or IV | 53 (8.3) 22 (3.5) | (21)      |
| NCT02775435         | 2018           | Pembrolizumab + Carboplatin + Nab-paclitaxel | 278     | III IV | 18 (6.5) 7 (2.5) | (13)      |
| NCT02008227         | 2017           | Atezolizumab | 609     | III IIIB or IV | 6 (1.0) 4 (0.7) | (4)       |
| NCT02409342         | 2020           | Atezolizumab | 286     | IV           | 11 (3.8) 2 (0.7) | (23)      |
| NCT02657434         | 2021           | Atezolizumab + Pemetrexed | 291    | IV           | 18 (6.2) 6 (2.1) | (24)      |
| NCT02367781         | 2019           | Atezolizumab + Carboplatin + Nab-paclitaxel | 473     | IV           | 25 (5.3) 2 (0.4) | (25)      |
| NCT02125461         | 2017           | Durvalumab  | 475         | III           | 51 (10.7) 8 (1.7) | (26)      |
| NCT02453282         | 2020           | Durvalumab  | 369         | IV           | 8 (2.2) 5 (1.4) | (27)      |
| NCT02453282         | 2020           | Durvalumab + Tremelimumab | 371     | IV           | 25 (6.7) 11 (3.0) | (27)      |

NSCLC, non-small-cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.
aPatients enrolled in and received ICI treatment.
bIncludes 7 immune-related pneumonitis and 1 immune-mediated pneumonitis.
cIncludes 1 immune-related pneumonitis and 1 immune-mediated pneumonitis.

## TABLE 2 | Study that reported the onset time of checkpoint inhibitor pneumonitis (CIP) in NSCLC patients with PD-1/PD-L1 blockade.

| Published Year | Treatment | Study type | Enrollment | NSCLC stage | Incidence, n (%) | Median time to onset, week(range) | Reference |
|----------------|-----------|------------|------------|-------------|------------------|-----------------------------------|-----------|
| 2015           | Nivolumab | Prospective, RCT | 131       | III IIIB or IV | 6 (5.0) 1 (1.0) | 15.1 (2.6–85.1) | (15)      |
| 2015           | Nivolumab | Prospective, RCT | 287       | III IIIB or IV | 10 (3.5) 4 (1.4) | 31.1 (11.7–56.9) | (16)      |
| 2015           | Pembrolizumab | Prospective, RCT | 550       | III IIIB or IV | 21 (3.8) 11 (2.0) | 8.1 (0.6–56.1) | (18)      |
| 2017           | Nivolumab (mono or combined with chemotherapy) | Retrospective | 111 | IV or recurrent | 8 (7.2) 4 (3.6) | 5.2 (2.3–24) | (3-4)     |
| 2018           | Nivolumab/Pembrolizumab/Durvalumab (mono or combined with other ICI/chemotherapy) | Retrospective | 205 | all | 39 (19.0) 24 (11.7) | 11.7 (2.9–26.1) | (35)      |
| 2020           | Nivolumab (mono or combined with chemotherapy) | Retrospective | 901 | all | 94 (10.4) 39 (4.3) | 8.4 (0–75.1) | (36)      |
| 2020           | Nivolumab/Pembrolizumab/Durvalumab (mono or combined with chemotherapy) | Retrospective | 205 | all | 5 (2.4) 2 (1.0) | 52.9 (34–86.6) | (37)      |

NSCLC, non-small-cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.
aPatients enrolled in and received ICI treatment.
bIncludes patients with interstitial lung disease (2 in a1, 1 in a2, all in a3).
cInterquartile range of onset time.
A retrospective study on Chronic pneumonitis (clinical pneumonitis persisting or worsening with steroid tapering and necessitating ≥12 weeks of immune suppression after ICI discontinuation).
dInitial pneumonitis grade.
approximately 2.4% in patients with NSCLC, and the onset time of chronic CIP is variable (range: 238–606 months) and occurs at a median time of 370 months after ICI start (37). In summary, the onset time of CIP shows various timespans and may be affected by many factors, including treatment regime (Figure 1).

2.2 Risk Factors

Checkpoint inhibitor pneumonitis may be the preferred attack in patients with features of lung deterioration conditions, including aging, smoking status, prior treatment, combinations with other drugs, primary tumor type, and previous lung disease. A previous study found that patients aged >70 years were more common in a CIP group than in a non-CIP group (P = 0.025) (39), which may be due to decreased lung function and increased medical complications in the elderly. In a study by Suresh et al. (35), a higher incidence of CIP was observed in males than in females and in squamous cells than in other histological types. Notably, smoking may also play a role in the development of CIP. Former/current smokers were found to have a higher incidence of pneumonitis than nonsmokers (P=0.03) (40). The incidence of CIP is also influenced by treatment strategy. Currently, a significant number of patients with locally advanced unresectable or metastatic NSCLC receive treatment with radiotherapy alone or concurrent chemotherapy before receiving immunotherapy (41). Multiple clinical studies have shown that the incidence of CIP was numerically higher in patients receiving chest radiotherapy than in those receiving nonchest/no radiotherapy (40, 42–45). Some researchers consider this kind of pneumonitis radiation recall pneumonitis (RRP) introduced by immunotherapy, while the criteria for identifying CIP and RRP are still unclarified (33). However, radiation parameters did not correlate with the development of pneumonitis (40). As mentioned above, PD-1 inhibitors are related to a higher incidence of CIP both for any grade or ≥ grade 3 compared with PD-L1 inhibitors. PD-1/PD-L1 blockades are usually combined with chemotherapeutic drugs, tyrosine kinase inhibitors, or additional immune-targeted drugs. The combination of PD-1/PD-L1 inhibitors with a variety of different drugs was also associated with pneumonitis risk, indicating the superposition effect of multiple drugs on pulmonary toxicity (10, 17, 31, 45, 46). Patients with epidermal growth factor receptor (EGFR) mutations are more likely to undergo pneumonitis during the combination therapy of sequential PD-(L)1 blockade followed by later osimertinib (47). The risk of CIP was also closely associated with preexisting lung disease, including pulmonary infection (48), pulmonary emphysema (49), chronic obstructive pulmonary disease (COPD) (50), asthma (50), interstitial lung disease (ILD) (51), pulmonary fibrosis (52), pneumothorax, and pleural effusion (45). Interestingly, a recent study found that tumor invasion into the central airway was strongly associated with early-onset CIP in patients with NSCLC (53). The presence of extrathoracic metastasis was related to a lower incidence of ICI-related pneumonitis (39). In addition, according to a recent study, a high baseline absolute eosinophil count (≥0.125 ×10⁹ cells/L) was correlated with an increased risk of CIP and with a better clinical outcome (54). A higher baseline level of anti-CD74 autoantibody is also more likely to develop CIP (55). Taken together, the risk factors for CIP may include older age, history of smoking, squamous cell histological type, previous lung disease, prior thoracic irradiation and treatment combinations with other drugs (Table 3).

2.3 Effects of CIP on the Clinical Outcome of Patients With PD-1/PD-L1 Therapy

Several studies have indicated that melanoma patients with irAEs have a survival benefit (56–59), which suggests that the early occurrence of irAEs may predict better outcome of immune checkpoint inhibitor therapy, and appropriate management of these events is needed to maximize the therapeutic effect of these drugs. The mechanisms behind this association are not fully understood. It has been proposed that the shared antigens between melanoma cells and normal melanocytes may account for this association (57, 59, 60). Similarly, several studies have shown favorable treatment efficacy and survival in patients with NSCLC (2, 61, 62). However, whether there is a similar

![FIGURE 1](link-to-image)
association between CIP and tumor response in patients with NSCLC remains controversial. Genova et al (62) have shown that the development of irAEs, including CIP, is a significantly positive predictor of survival outcomes in patients with NSCLC treated with nivolumab. However, in another study, the efficacy of ICI treatment was observably worse in patients with severe grade CIP than in those without severe grade CIP when patients were classified according to CIP severity (63). Thus, several challenges still need to be addressed in the future, and the association between the development of CIP and clinical efficacy in patients with NSCLC treated with ICIs still needs to be evaluated. In addition, although studies have shown that the occurrence of CIP is associated with a better response to ICI therapy, severe CIP can lead to interruption of ICI therapy and even fatality. In conclusion, the effects of CIP on the efficacy and prognosis of ICI therapy in NSCLC patients are still controversial, and more evidence is needed to clarify the relationship.

2.4 Overview of Manifestations

2.4.1 Common Symptoms

The most common clinical symptoms of CIP are dyspnea and cough. Fever and chest pain can also be observed but not often (3). However, it is difficult to distinguish these symptoms from infection or progression of malignancy, especially in patients with NSCLC. For individuals with suspected CIP, laboratory examinations are necessary to exclude infection, including culture of nasopharyngeal, sputum, and urine and sensitivity tests. In addition, some patients with subclinical CIP may experience no respiratory symptoms. Therefore, the diagnosis of CIP also depends on other auxiliary examinations (64).

2.4.2 Radiological Features

Radiological examination, especially chest CT, plays an important role in the diagnosis of CIP. Several radiographic patterns of CIP have been observed, including cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia, hypersensitivity pneumonitis and pneumonitis not otherwise specified (3). The most predominant radiographic pattern is COP (65). Specific findings on chest CT include traction bronchiectasis, consolidation, reticular opacities, ground glass opacities (GGOs), centrilobular nodularity, and honeycombing, of which GGOs are present in the majority of patients (66). In addition, GGO was indicated as a significant predictor of worse overall survival (67). Clinically, the situation will be more complicated, and mixed patterns may be observed. In a case of a 73-year-old woman with NSCLC who received pembrolizumab treatment, organizing pneumonia with “air bronchogram” presented at the upper lung lobes and widespread thickening of the interlobular interstitium at the left lower lobe (68). The use of PET-CT in the diagnosis of immune-related pneumonia in patients with melanoma has been reported, but there were few specificities of the radiological images of pneumonia on PET/CT scans (69, 70). As mentioned above, there are several radiological patterns of CIP, and detailed analysis is needed when facing different patterns of CIP in the clinic.

TABLE 3 | Potential risk factors for checkpoint inhibitor pneumonitis (CIP) in NSCLC.

| Potential risk factors                  | Details |
|----------------------------------------|---------|
| Sex                                    | Males have a higher incidence of CIP |
| Age of patients                        | Patients aged >70 years |
| Tumor histologic type                  | A higher incidence of CIP in patients with squamous NSCLC |
| Smoking status                         | Patients with former or current smoking |
| Prior thoracic radiation therapy       | The incidence of CIP is numerically higher in patients receiving chest-RT compared with non-chest/no RT |
| PD-1 inhibitors                        | The incidence of CIP with PD-1 inhibitors is higher than PD-L1 inhibitors |
| Combination therapy                    | Additional immune-targeted drugs, chemotherapeutic drugs and some specific tyrosine kinase inhibitors (TKIs) |
| EGFR mutation                          | Patients with EGFR mutation are more likely to undergo pneumonitis during the combination therapy of ICIs with osimertinib |
| Sequences of drug administration       | PD-(L)1 blockade followed by osimertinib is related to a higher incidence of pneumonitis |
| Preexisting lung disease               | Pulmonary infection, pulmonary emphysema, COPD, asthma, ILD, pulmonary fibrosis, pneumothorax, and pleural effusion |
| Tumor invasion                         | Tumor invades the central airway was strongly associated with early-onset CIP |
| Tumor invasion                         | Extrathoracic metastasis was related to a lower incidence of CIP |
| Baseline peripheral-blood absolute eosinophil count (AEC) | A high level of baseline AEC(≥0.125×10^9cells/L) correlated with an increasing risk of CIP but a better clinical outcome |
| Baseline level of anti-CD74 autoantibody | A higher level of anti-CD74 autoantibody is also more likely to develop CIP |

NSCLC, non-small-cell lung cancer; CIP, checkpoint inhibitor pneumonitis; RT, radiation therapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand-1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-L2, programmed cell death protein ligand-2; RGMb, repulsive guidance molecule b; TKIs, tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; AEC, absolute eosinophil count.
2.4.3 Auxiliary Examinations
Bronchoalveolar lavage (BAL) is one of the most common invasive examinations of ICI-related pneumonitis. In general, lymphocytes elevated in bronchoalveolar lavage fluid (BALF). Nandoo et al. (37) found that lymphocytes, predominantly CD4+ T cells, were increased in the BALF of CIP patients compared with the BALF from patients who received ICI treatment but had no evidence of CIP (n= 6) or suspected CIP patients (n= 14). Wang et al. found significantly elevated levels of interleukin-17A (IL-17A) and IL-35 in both serum and BALF (71). In addition, they also observed increased numbers of central memory T cells and decreased expression of CTLA-4 and PD-1 in regulatory T cells (Tregs). Enriched IFNγ IL-17-CD8+ T and CXCR3+CCR6+ Th17/Th1 cells were observed in the BALF of CIP compared with infection pneumonia in acute myeloid leukemia and myelodysplastic syndrome (67).

Transbronchial biopsy is seldom used in the auxiliary diagnosis of CIP. In the few cases of transbronchial biopsy, pneumonia tissue after ICI showed inflammation and lymphocyte infiltration (39). Nandoo et al. collected 11 tissue samples by transbronchial biopsy (8/11), core biopsy (2/11) and wedge resection (1/11), and the histopathological results included 4 cellular interstitial pneumonia, 3 organizing pneumonia, 1 diffuse alveolar damage and 3 no abnormalities identified (3).

3 MECHANISMS OF PD-1/PD-L1 INHIBITOR-INDUCED PULMONARY TOXICITY

Due to the lack of effective preclinical studies, the mechanism of PD-1/PD-L1 inhibitor-induced CIP in NSCLC patients is still unclear. Here, we summarize the factors that may be involved in CIP based on existing studies (Figure 2).

3.1 Disordered T Cell Subsets
PD-1/PD-L1 inhibitors can enhance the antitumor function of T cells (72). There is some evidence that T cells may be involved in the development of immune-related pulmonary complications. Increased infiltration of highly proliferative CD8+ T cells was observed in lung biopsy tissue from patients with NSCLC who developed chronic bronchiolitis obliterans organizing pneumonia after nivolumab treatment (37). Suresh et al. found that CD4+ T cells were significantly increased in BAL samples of CIP patients (mainly with NSCLC) after receiving anti-PD-1/ PD-L1 inhibitors (73). Suzuki et al. reported that the proportion of CD8+ T cells with PD-1, Tim-3 and TIGHIT positivity in the BALF of patients with PD-1/PD-L1 inhibitor-induced ILD was significantly higher than that of patients with other types of ILD (74). All of these findings suggest dysregulated alveolar immunity in CIP patients. Kim et al. found significant elevation of Ki-67 (proliferation markers of PD-1+ CD8+ T cell) in metastatic NSCLC patients who received pembrolizumab or nivolumab. Various studies have shown that T cells are activated and infiltrate the lung tissue of CIP patients, which indicates the enhancement of antitumor effects. However, an excessive immune response may lead to damage to normal tissue.

When naïve T cells encounter antigens presented by antigen-presenting cells (APCs) in secondary lymphoid organs, they undergo differentiation/polarization processes according to cell division signals and become Th helper 1 (Th1) cells, Th helper 2 (Th2) cells, Th helper 17 (Th17) cells or Tregs (72). Different T cell subsets may play different roles in irAEs.

3.1.1 Th1/Th2
A Th1/Th2 shift exists in tumor patients, and Th2 cells are often dominant (75). It has been suggested that the shift of Th1/Th2 cells may be related to the immune escape of tumors (76). Anti-PD-1/ PD-L1 therapy can reverse Th1/Th2 in cancer patients by promoting the production of Th1 cells and inhibiting the production of Th2-related cytokines (77). However, Th1 cells may be the dominant response cell in the development of irAEs, as infiltration of Th1 cells has been observed in related tissues. Yoshino et al. reported nivolumab-related colitis in 2 patients with metastatic melanoma, whose pathological examinations of the colon showed infiltration of CD8+ T cells and T-bet-expressing Th1 CD4+ T cells (78). Kim et al. reported enrichment of T-bet + POPGT+ (Th1) and CXCR3 + T-bet + CCR6 + RORGT+ (Th17/Th17) cells in BAL CD4+ T cells of leukemia patients with respiratory symptoms after ICI-based therapy. Interestingly, most Th17/Th1 cells express PD-1 (79). These studies indicated that Th1 cells may be involved in the formation and development of anti-PD-1-associated pneumonitis. In addition, Th1 cells are also associated with some autoimmune diseases (80), which may explain autoimmune symptoms after PD-1/PD-L1 blockade.

3.1.2 Treg
Tregs are an important factor in maintaining immune tolerance. Nedoszytko et al. reported that Tregs with high activity can lead to immunosuppression and decrease the number of Th1 cells (81). Tregs express both PD-1 and PD-L1 (82). Amarnath et al. found that human Th1 cells transform into Tregs through the formation and development of anti-PD-1-associated pneumonitis. In addition, Th1 cells are also associated with some autoimmune diseases (80), which may explain autoimmune symptoms after PD-1/PD-L1 blockade. However, an excessive immune response may lead to damage to normal tissue.
3.1.3 Th17
Th17 cells are a subset of T cells that produce IL-17. Th17 lymphocytes exist in the anatomic barrier, mainly in the digestive system and lungs (85). In previous studies, the antitumor role of Th17 cells seems to be contradictory. On the one hand, Th17 cells can recruit CD8+ cytotoxic T cells and promote their activation and expansion to inhibit the growth of tumors (86, 87). On the other hand, IL-17A produced by Th17 cells has been shown to enhance tumor angiogenesis (88). Jaclyn W. McAlees et al. found that the levels of Th1 and Th17 cells increased in naive PD-1−/− mice, while the production of cytokines in polarized Th1 and Th17 cells in vitro was restricted in WT cells with PD-1 ligation (89). In this way, anti-PD-1 therapy may enhance the antitumor function of Th17 cells. Yun et al. found that under certain conditions, Th17 cells can transform into Th1 cells, lose the secretion of IL-17A, and then secrete interferon γ (IFN-γ), which plays a role in enhancing autoimmunity and antitumor activity (90). As mentioned above, Tregs can suppress the amplification of Th1 cells, but Tregs cannot inhibit the transformation of Th17 cells into Th1 cells (91). After blocking
play a role in the development of immune-related adverse events. That elevated levels of preexisting or emerging autoantibodies expressed on the cell membrane of immune cells, including major histocompatibility complex class II (MHC-II) but is autoantibody active protein, can stimulate the release of cytokines and powerful proinflammatory reactions, which promote the development of irAEs.

Although a large number of cytokines related to the occurrence of irAEs have been found, a considerable lack of data has been reported about CIP in NSCLC patients during anti-PD-1/PD-L1 treatment. At present, there are three main types of cytokines related to the occurrence of CIP: C-reactive protein (CRP), IL-6 and IL-17.

### 3.2 Increased Preexisting and Emerging Autoantibodies

An increasing series of studies have shown that the occurrence of irAEs may be associated with increased preexisting and emerging autoantibodies in human immunity. PD-1-targeted therapy leads to the dysfunction of Tregs and mediates the production of pathological autoantibodies in both PD-1-knockout mice and patients (95, 96). A multivariate analysis indicated that the presence of preexisting antibodies, such as rheumatoid factor (RF), antinuclear antibody, antithyroglobulin, and antithyroid peroxidase, was independently associated with the development of irAEs in different organs. It can be concluded that increased preexisting and emerging autoantibodies are probably involved in the mechanism of CIP. Salahaldin A. Tahir et al. found a median 1.34-fold significant increase in autoantibodies against CD74 after immune checkpoint therapy in patients with immune-related pneumonia, which suggested that CD74 autoantibodies play a role in pneumonitis (55). CD74, an autoantibody active protein, can stimulate the release of inflammatory mediators (97) as an intracellular chaperone of major histocompatibility complex class II (MHC-II) but is expressed on the cell membrane of immune cells, including macrophages (55). Taken together, the above results suggest that elevated levels of preexisting or emerging autoantibodies play a role in the development of immune-related adverse events.

### 3.3 Unbalanced Inflammatory Cytokines

Cytokines, a class of small molecular proteins with a wide range of biological activities, are mainly synthesized and secreted by immune cells. Cytokines have multiple biological functions, such as regulating innate immunity and adaptive immunity, influencing tumor growth and participating in inflammation (98). The pathophysiological mechanisms of immune-related adverse events are also thought to be mediated via cytokines. Lim and colleagues analyzed the expression of 65 cytokines in longitudinal plasma samples collected prior to therapy and during treatment in melanoma patients treated with ICIs alone or in combination. Eleven elevating cytokines (G-CSF, GM-CSF, Fractalkine, FGF-2, IFNα2, IL-12p70, IL-1α, IL1, IL-1RA, IL-2 and IL-13) were significantly upregulated at baseline and early during treatment and were associated with the development of high-grade irAEs (99). In a similar study, 40 cytokines were assessed in plasma. Shaheen Khan et al. found that the upregulation of various cytokines, especially induced C-X-C motif chemokine ligand (CXCL) 9, 10, 11 and 13 after ICI treatment, was closely associated with the development of irAEs (100). CXCL9, CXCL10 and CXCL11 can activate T cells by binding to C-X-C motif chemokine receptor (CXCR) 3 and have been implicated in a variety of autoimmune diseases, including thyroiditis, systemic sclerosis, and inflammatory bowel disease (IBD) (101). ICIs can activate T cells, leading to excessive release of cytokines and powerful proinflammatory reactions, which promote the development of irAEs.

Although a large number of cytokines related to the occurrence of irAEs have been found, a considerable lack of data has been reported about CIP in NSCLC patients during anti-PD-1/PD-L1 treatment. At present, there are three main types of cytokines related to the occurrence of CIP: C-reactive protein (CRP), IL-6 and IL-17.

#### 3.3.1 CRP and IL-6

CRP is an acute phase protein that is secreted by liver cells in response to inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α) (102). A retrospective study reported that serum CRP levels were significantly elevated in patients with irAEs, such as pituitary inflammation, hepatitis, thyroiditis and autoimmune colitis (103). IL-6 has a proinflammatory effect in the TME (104) and plays an active role in innate and adaptive immunity, such as the activation of Th cells, inhibition of Tregs, and differentiation of B cells (105). Several studies have shown that elevated levels of IL-6 after ICI treatment are closely related to irAEs, such as psoriasiform (89) and Crohn’s disease (106). Wussler, Kozuharov et al. (107) have shown that IL-6 and CRP were significantly higher in patients with pneumonia. CRP and IL-6 levels are elevated in NSCLC patients who developed CIP after atezolizumab treatment compared with baseline levels (108). Therefore, the development of CIP may be attributed to the excessive activation of the immune system induced by CRP and IL-6 as well as its powerful pro-inflammatory properties. Taken together, the above results suggest that dysregulated immune activation and supraphysiological levels of CRP and IL-6 are involved in the mechanism of CIP in NSCLC patients.

#### 3.3.2 IL-17

IL-17 is an important cytokine with diverse functions, playing an important role in autoimmune diseases and inflammation. IL-17 is expressed in CD8+ T cells, natural immune γδ T cells, NK cells and ILC3s in the lungs. The abnormal expression of IL-17 is associated with the pathology of many lung diseases, including asthma, pneumonia and pulmonary fibrosis (109). In addition, IL-17 has been found to be associated with the development of some irAEs, such as colitis (110) and psoriasiform dermatologic toxicity (111). Lou et al. showed that the levels of IL-17 in serum significantly increased in NSCLC patients with CIP following ICI treatment (112). The underlying mechanism may be that blocking PD-1 and PD-L1 could destroy immune tolerance and increase the activation of T cells (113), including the increase in Th17 cells in peripheral blood (114). An increase in the percentages of Th1 and Th17 cells can induce higher levels of IL-17A in plasma and BALF (71). It is worth noting that the levels of IL-17A and IL-35 increased when CIP was diagnosed.
and decreased during clinical recovery, indicating that IL-17A is related to the occurrence and development of CIP. Therefore, IL-17 may mediate off-target lung destruction in CIP.

3.4 Different Treatment Modes
A higher incidence and severity of CIP have been observed with anti-PD-1 therapy than PD-L1 inhibitors in patients with NSCLC, suggesting that the mechanisms of CIP induced by the two agents are not completely the same (28). The incidence and severity difference of CIP may be related to PD-1 ligands, including PD-L1 and PD-L2. It has been confirmed in animal models that the expression of programmed death ligand 2 (PD-L2) in tumor cells may inhibit antitumor immunity and may be involved in the resistance to monoanti-PD-L1 therapy (115). It is conceivable that the blockade of PD-L1 and PD-L2 with PD-1 inhibitors can reverse such resistance and enhance antitumor immunity. However, at the same time, the blockade of PD-1 triggers stronger T cell expansion and cytokine production without strongly T cell expansion and cytokine production without.

However, PD-1 inhibitors can not only block the interaction between PD-1 and its receptor PD-1, which is associated with immune tolerance in lung tissue. However, PD-1 inhibitors can not only block the interaction between PD-1 and its ligands PD-L1 and PD-L2 but also increase the binding of PD-L2 to repulsive guidance molecule b (RGMb). RGMb has been observed to be expressed in lung interstitial macrophages, alveolar epithelial cells and other cells of the immune system, such as CD4+ and CD8+ T cells (118). Blockade of PD-1-PD-L2 signaling has been observed to increase cytokine production and/or CD4+ T cell proliferation (119). Moreover, the increased interaction of RGMb–PD-L2 mediated by PD-1 inhibitors might disrupt the immune tolerance of lung tissue by increasing the vigorous clonal expansion of T cells that reside in the lung and then lead to the occurrence of pneumonitis (118) (Figure 3). Recently, the combination of radiotherapy and immunotherapy has attracted increasing attention. This combination therapy model has shown improved efficacy in patients with NSCLC (120). However, a history of previous radiotherapy may increase the incidence of CIP (42, 121). Myers and Lu found significantly elevated T cells in pulmonary tissues of C57BL/6 mice after combination therapy with anti-PD-1 and thoracic irradiation. They suggested that healthy tissue damaged by thoracic irradiation is more easily destroyed by T cells activated during ICI treatment, which may be the underlying mechanism of the increased incidence of CIP after radiotherapy (122).

Further research is still needed to determine whether and how miR-146a affects the development of irAEs, especially CIP. In addition, B cells, natural killer (NK) cells, and dendritic cells may also be involved in the development of CIP after PD-1 blockade (136–138). The expression of PD-1 on NK cells has been observed in cancer patients (138). Hsu et al. (139) found that NK cells expressing PD-1 may mediate immunosuppression in tumors by interacting with PD-L1+ tumor cells. PD-1/PD-L1 blockade can activate the cytotoxicity of NK cells to tumors by releasing PD-1–imposed immune inhibition. When ICI treatment induces inflammation in nonmalignant lung tissue through various non-NK cell-mediated mechanisms, activated NK cells can directly kill infected cells and produce proinflammatory cytokines. Thus, NK cell activation mediated by PD-1/PD-L1 blockade may promote inflammation and aggravate damage to normal lung tissues.

4 MANAGEMENT OF CIP
The treatment of CIP varies among the clinical grades of CIP. Current treatment options mainly include interruption of ICI therapy, glucocorticoid administration, and immunosuppressive medications such as intravenous immunoglobulins (IVIG), infliximab, cyclophosphamide, and mycophenolate mofetil (7,
There are several published guidelines that are involved in the management of CIP (14, 140, 143). These guidelines have issued different recommendations for patients with CIP according to their toxicity severity from grade 1 (mildest) to grade 5 (death associated with toxicity). For grade 1 CIP (asymptomatic), ICI might be considered holding while closely monitoring the symptoms of patients every 2–3 days with repeated chest CT scans and pulmonary function testing at least every 3 weeks. If any of the symptoms, radiographic testing or pulmonary function deteriorates, ICI therapy can be withdrawn, and systemic corticosteroid therapy should be initiated. Patients with grade 2 CIP need to withhold ICI therapy immediately and recommend systemic methylprednisolone treatment (0.5–1.0 mg/kg daily). Steroids can be administered orally or intravenously and taper over 4–6 weeks if symptoms improve after 48–72 h. Empiric treatment with antibiotics should start if infection is suspected. When no clinical improvement can be observed 48–72 hours after the beginning of steroid treatment, patients with CIP should be treated as grade 3–4. For grade 3–4 CIP, these patients should permanently discontinue ICI treatment and be hospitalized. Current guidelines recommend that methylprednisolone should be administered orally or intravenously at a dose of 2–4 mg/kg/day, along with empirical antibiotic therapy. If symptoms improve after 48–72 h, steroids should be tapered over 8 weeks. In contrast, if symptoms do not improve or deteriorate, additional immunosuppressive therapy should be considered. Currently, immunosuppressive agents mainly include IVIG, infliximab, cyclophosphamide, and
mycophenolate mofetil (MMF) (14, 140, 143). In addition, IL-6 blockade (tocilizumab) may be a potential second-line treatment for CIP without affecting the efficacy of immunotherapy (144, 145). However, the agent still lacks clear evidence of efficacy and safety, which needs further investigation.

5 POTENTIAL PREDICTIVE BIOMARKERS OF CIP

CIP is a life-threatening adverse event in some instances and possesses a higher rate in NSCLC than other tumor types. Thus, potential predictive biomarkers for CIP are necessary. The potential biomarkers reported to date mainly involve cell-based biomarkers, chemokines/cytokines, autoantibodies and genetics. In addition, there are some other emerging novel biomarkers on the rise, such as tumor genomics, microbiome and radiographic features (146). Recently, Lin et al. (147) conducted a real-world retrospective study to explore blood biomarkers related to the occurrence and prognosis of CIP in lung cancer patients. They found that increased levels of IL-6 and IL-10, neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lactate dehydrogenase (LDH) or reduced absolute lymphocyte count (ALC) and albumin (ALB) levels during ICI treatment may act as biomarkers for the early diagnosis of CIP. Furthermore, squamous carcinoma may be related to an increased risk of CIP, and an increase in IL-6 levels along with a reduction in ALB levels at the onset of CIP were predictive of severe grade and poor prognosis of CIP. A case report has shown increased levels of several cytokines, including IL-1 receptor antagonist (IL-1 RA), IL2 RA and CXCL2, during radiation followed by ICI therapy, which indicates that these cytokines may be promising biomarkers for predicting the development of pneumonitis induced by combined therapy with radiation and ICIs (148). An increased level of anti-CD74 autoantibody pre- and posttreatment is considered a potential predictive biomarker for the development and timely treatment of CIP (55). Moreover, a high baseline eosinophil count (≥0.125 × 10⁹ cells/L) can serve as a biomarker for predicting an increased risk of CIP (54). Hoefsmit et al. extensively explored the susceptible genetic loci likely to be related to irAEs. They found that several immune-related genes, including surfactant protein C (SP-C), autoimmune regulator (AIRE), telomerase reverse transcriptase (TERT) and mucin 5B oligomeric mucus/gel forming (MUC5B), might contribute to predicting the development of CIP (149).

6 DISCUSSION

CIP is rare but can be life threatening and accounts for 35% of PD-1 and PD-L1 inhibitor-related deaths. The incidence and onset time of CIP can vary due to different PD-1/PD-L1 agents. The excessive immune response caused by the extra blockade of PD-L2 with a PD-1 inhibitor may be involved in the onset of CIP. Combination therapy has a higher incidence of CIP than monotherapy, with a shorter median onset time. The possible mechanism is the overlap of pulmonary toxicity of different treatments.

In this article, we pay close attention to the clinical features of pulmonary irAEs during PD-1/PD-L1 blockade, implying that clinicians should monitor patients receiving anti-PD-1/PD-L1 therapy to optimize clinical safety and efficacy. The clinical symptoms of pulmonary toxicity, radiological examination, especially chest CT and BALF, play an important role in the diagnosis of CIP. Clinicians should be fully aware of the association between the presence of CIP and cancer outcomes in NSCLC, balancing the benefits and risks of immunotherapy and thereby identifying patients who would gain most from treatment.

There is growing evidence that several possible mechanisms are involved in the development of CIP, and it is clear that there are multiple factors at play, such as disordered T cell subsets, increased preexisting and emerging autoantibodies, unbalanced inflammatory cytokines, previous chest radiotherapy, previous lung disease and combined immunotherapy. Further prospective studies on the mechanisms of CIP are needed to provide a more comprehensive and robust management of CIP. Deep studies on the mechanism of CIP in NSCLC are still limited. Preclinical studies on the molecular and histopathology of irAEs are in progress. To better understand the mechanism, the establishment of animal models is necessary. At present, some models have been established (150, 151). However, there is still a lack of empirical evidence regarding whether the existing models can truly reproduce the complex tumor microenvironment in the human body and whether the models are repeatable. Furthermore, research on biomarkers is also underway (152–154), which will be instrumental in the prediction, diagnosis and monitoring of CIP. Further research should aim to explore a series of biomarkers that can efficiently and timely predict the development, diagnosis, treatment and prognosis of CIP to achieve early detection and diagnosis of CIP.

Immunotherapy has crossed the gap of cancer treatment. As the main immune checkpoint inhibitors for the treatment of NSCLC, the combined treatment of PD-1/PD-L1 and CTLA-4 inhibitors has a better response and long-term cancer control, but it increases the incidence of CIP (155, 156). The emergence of novel checkpoint inhibitors, such as LAG-3, TIM-3, TIGIT, VISTA inhibitors and dual immunomodulators (targeting PD-1 and LAG-3), may change the existing immunotherapy strategies (157, 158). However, when it brings possible synergy, it may also bring potential irAEs. More clinical trials on the efficacy and safety of novel immune checkpoint inhibitors and combination therapies are needed. As a new therapeutic method, chimeric antigen receptor T cell (CAR-T) immunotherapy has played an increasingly important role in cancer treatment. A recent study reported that the recruitment and infiltration of CAR-T cells in NSCLC tumors can be enhanced when combined with a PD-1 inhibitor and immunogenic chemotherapy (159). Whether the combination of immunotherapies will affect the incidence and severity of irAEs needs more clinical data. For the treatment of NSCLC, various new immunotherapy modes, such as new immune checkpoint inhibitors, CAR-T therapy, ICIs combined chemoradiotherapy and targeted therapy, still need to balance efficacy and safety to optimize the optimal treatment regimen.

Understanding the mechanism of CIP will help to better manage patients with adverse events. At present, glucocorticoids are the main...
treatment, but some irAEs are insensitive to glucocorticoid. Mechanism-based therapy can improve symptoms, avoid treatment interruption or dose reduction due to irAEs, and finally prolong overall survival.

**AUTHOR CONTRIBUTIONS**

JY and YW collected information and wrote the manuscript. XY reviewed clinical studies and helped process the tables. LG provided language editing. JX conceived the idea for this review. XY, JY, and YW collected information and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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