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Review Article

Clinical management of checkpoint inhibitor pneumonitis: Focus, challenges, and future directions

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for various malignancies by demonstrating exceptional antitumor effects and significant improvement in patient survival. Despite their overt therapeutic advantages, ICIs also induce immune-related adverse events (irAEs). Of these, checkpoint inhibitor pneumonitis (CIP) represents a prominent manifestation of pulmonary toxicity following ICI therapy, with incidence rates ranging from 2.7 % to 20.0 %. Notably, a substantial proportion of CIP cases show severe manifestations, often leading to life-threatening complications, which emphasizes its clinical significance. Understanding the risk factors and potential pathogenetic mechanisms of CIP, combined with vigilant monitoring during immunotherapy, is pivotal for early detection and management of this condition. Proactive strategies for the timely identification, accurate diagnosis, and effective management of CIP are essential to optimize patient outcomes. However, several challenges persist in CIP management, including management of severe and refractory cases, determining the timing of ICI rechallenge after CIP, management of long-term chronic CIP, and mitigating secondary infections. In order to manage this potentially life-threatening irAE effectively, it is urgent to establish multi-disciplinary treatment (MDT) management, precision CIP management, and practical surveillance systems for CIP monitoring, diagnosis, and management and to call for prospective multi-center clinical trials.

Introduction

Malignant tumors pose significant health challenges, characterized by high mortality and poor prognosis, consequently exerting profound societal and economic impacts.[1,2] Immune checkpoint inhibitors (ICIs), as novel antitumor immunotherapeutics, have emerged as transformative agents, demonstrating exceptional efficacy across a range of malignancies and improving patient survival.[3–7] Presently, China has approved 17 ICIs for clinical use, including ten anti-programmed death-1 (PD-1) monoclonal antibodies (pembrolizumab, nivolumab, tislelizumab, sintilimab, toripalimab, camrelizumab, penpulimab, zimberelimab, serplulimab, and pucotenlimab), five anti-programmed death ligand 1 (PD-L1) monoclonal antibodies (mAbs) (durvalumab, atezolizumab, envafolimab, sugemalimab, and adebrelimab), one anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) mAb (ipilimumab), and one anti-PD-1/CTLA-4 bispecific antibody (candonilimab). While ICIs have been widely applied for cancer treatment due to obvious benefits, their utilization is not devoid of challenges, particularly the emergence of immune-related adverse events (irAEs).[8] The irAEs can involve multiple organ systems, ranging from the skin and endocrine system to the gastrointestinal tract, liver, and lungs. Although most irAEs tend to be mild, a significant subset of patients may suffer from severe, potentially life-threatening complications.[9] Checkpoint inhibitor pneumonitis (CIP) represents the predominant pulmonary toxicity detected post-ICI administration in cancer patients.[10–12] Clinicians should monitor CIP occurrence in patients administered ICIs when they report additional respiratory symptoms or in case of lung infiltrates on chest radiography, especially once pulmonary infections and tumor progression are ruled out.[10–12] CIP has an incidence that fluctuates between 2.7 % and 20.0 %, typically manifesting 2–3 months post-initiation of immunotherapy. Clinical presentations of CIP vary, with symptoms ranging from dry cough, exertional dyspnea, wheezing, to occasional fever and chest pain. Intriguingly, some patients may not have overt respiratory symptoms and only present with newly emerged pulmonary opacities incidentally detected by chest imaging. Conversely, others might face progressive dyspnea, culminating in respiratory failure or even life-threatening conditions.[10–13] Importantly, grade 3–5 CIP cases account for a significant portion of fatal irAEs.[14,15] The diagnos-

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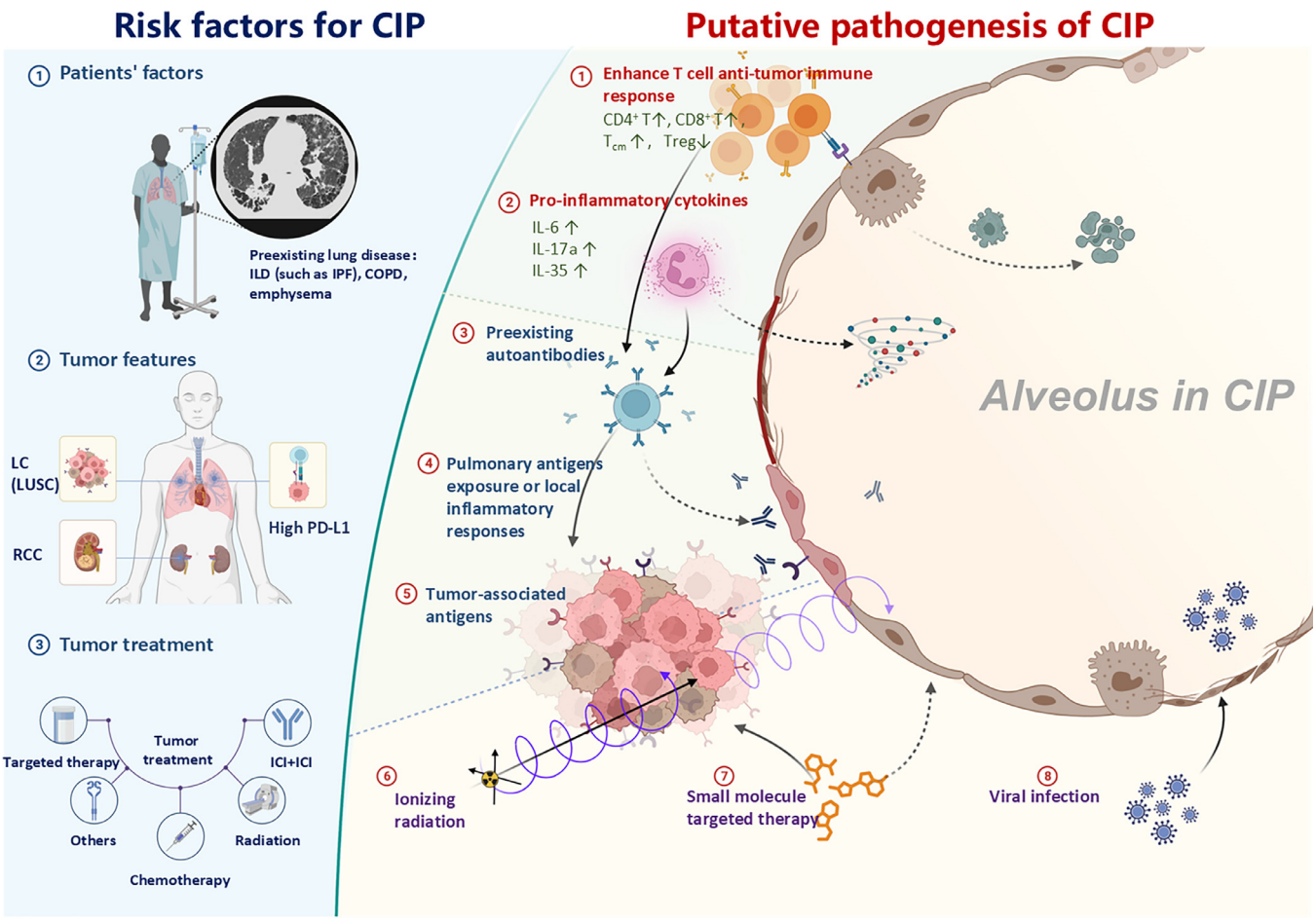

Fig. 1. An overview of risk factors and potential pathogenic mechanisms of CIP. CD: Cluster of differentiation; CIP: Checkpoint inhibitor pneumonitis; COPD: Chronic obstructive pulmonary disease; ICI: Immune checkpoint inhibitor; IL: Interleukin; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; LC: Lung cancer; LUSC: Lung squamous cell carcinoma; PD-L1: Programmed death ligand 1; RCC: Renal cell carcinoma; T_{cm}: Central memory T-cell; Treg: Regulatory T cell.

tic landscape of CIP is accompanied by complexities, especially when manifestations overlap with certain pulmonary infections or when both conditions coexist. Moreover, a subset of severe CIP cases may be unresponsive to steroids, and the potential for CIP recurrence during steroid tapering further complicates clinical management. Meanwhile, drugs such as glucocorticoids, while being beneficial in CIP, could predispose patients to opportunistic pulmonary infections. Hence, the management of CIP in clinical practice is intricate, underscoring the imperative need for heightened physician awareness.

Risk factors and putative mechanisms of CIP

The risk factors for CIP can be broadly categorized into three main domains: patient-associated, tumor-associated, and treatment-associated factors. While the precise pathogenesis of CIP remains unclear and complex, the prevailing theories suggest mechanisms driven by hyperactivated T cells inflicting damage on the alveolar epithelium, elevated antibody concentrations, and a surge of proinflammatory cytokines post-immunotherapy.[9,16] The putative pathogenic mechanisms of CIP can be classified into ICIs-induced biological and patients' intrinsic and external synergistic mechanisms. There are complex interactions among the three mechanisms. A comprehensive understanding of these risk factors, combined with insights into the potential pathogenetic pathways of CIP, is paramount for formulating targeted preventive and therapeutic approaches (Fig. 1).

Risk factors for CIP

Patient-associated risk factors

Patients with underlying interstitial lung diseases (ILDs), especially idiopathic pulmonary fibrosis (IPF), substantially have elevated risk of CIP *vs*. their non-ILD counterparts.[17–19] Specifically, pre-existing ILD has been associated with elevated incidence of severe (grade 3 or higher) CIP, with rates reaching 15 % as opposed to a mere 4 % in the absence of ILD (odds ratio [OR]: 2.91, 95 % confidence interval [CI]: 1.47–5.74).[20] Concurrently, studies have underscored an enhanced risk of CIP in patients with chronic obstructive pulmonary disease (COPD) or emphysema during ICI intervention.[18,20,21] Considering these findings, it becomes imperative to perform meticulous patient evaluation and judiciously assess the risk–benefit ratio prior to ICI therapy, especially in individuals with pre-existing pulmonary diseases.

Tumor-associated risk factors

Patients diagnosed with lung cancer (LC) or renal cell carcinoma have an enhanced susceptibility to CIP post-ICI therapy compared with those with other malignancies.[22–24] Delving deeper into LC histology, it was found that individuals with squamous cell lung carcinoma have a higher incidence of CIP upon ICI treatment than those diagnosed with lung adenocarcinoma. Additionally, high PD-L1 expression in LC patients further increases CIP risk.[19] In the context of non-lung malignancies, the presence of lung metastasis represents a significant risk factor for CIP.[25] Symptomatic manifestations of CIP in LC cases often go un-

noticed due to their mimicry of the primary LC's symptoms. This emphasizes the paramount importance of vigilant monitoring for potential CIP onset during ICI therapy in LC patients, with particular attention to individuals with squamous cell carcinoma subtypes.

Treatment-associated risk factors

While combining immunotherapy with conventional treatments has improved prognosis in various cancers, these regimens harbor the potential to amplify pulmonary toxicity. Data sourced from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) public dashboard[26] indicate that radiation therapy considerably escalates the risk of CIP. This elevated risk associated with radiation therapy has been confirmed by several studies. For instance, the PACIFIC trial reported a pneumonitis incidence soaring to 33.9%, marking a stark 24.8% increment relative to the control group.[27–29] Furthermore, a condition termed radiation recall pneumonitis (RRP) has been observed, where ICIs induce a resurgence of previous radiation-induced pneumonitis.[30,31] It should be noted that the risk of pneumonitis is accentuated after treatment with a combination of anti-PD-1/PD-L1 mAb and anti-CTLA-4 mAb *vs*. cases administered anti-PD-1/PD-L1 mAb as a monotherapeutic regimen.[22] Emerging evidence suggests that the combined regimen of immunotherapy and small molecule targeted therapy increases CIP incidence.[32,33] A quintessential illustration is the combination of osimertinib with durvalumab, which has been associated with an enhanced rate of CIP.[34,35] Additionally, the extended half-life and persistent therapeutic effect of anti-PD-1/PD-L1 mAbs can increase the CIP risk, especially when epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) are administered post-ICI treatment.[36] The combination of cytotoxic chemotherapy is also considered a risk factor for ICI-related ILD.[37]

Potential pathogenic mechanisms of CIP

ICIs-induced biological mechanisms of CIP

Immune checkpoints play pivotal roles in preserving immune tolerance, modulating T cell responses, and preventing hyper-reactivity.[38,39] By inhibiting the suppressive effects of certain immune regulatory molecules on T cells, ICIs augment the antitumor immunity of T cells. The current pool of ICIs, either approved for clinical use or under active investigation, comprises monoclonal and bispecific antibodies targeting CTLA-4, PD-(L)1, T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), lymphocyte activation gene-3 (LAG3), among others.

The onset of CIP is intricately linked to T cell activation and a subsequent surge in pro-inflammatory cytokines post-ICI treatment. Pathological analysis of CIP patients revealed pronounced T cell infiltration.[40] Moreover, bronchoalveolar lavage fluid (BALF) samples from CIP patients exhibited enhanced lymphocyte amounts, predominantly dominated by CD4+ T cells. These cells exhibited an increase in central memory T cells (T_{cm}) and showed decreased expression of CTLA-4 and PD-1 in BALF Tregs.[41] There was also a notable increase in the subset of CD8+ T cells expressing immune-suppressive proteins, especially CD8+ PD-1+ TIM-3+ and CD8+ TIGIT+ cells.[42] Single-cell transcriptome analysis revealed amplification of both CD4+ and CD8+ T cells in the BALF of patients. Among CD4+ T cells, there was a marked increase in T-helper 17.1 cells, alongside an enrichment of Type 1 regulatory T and naive-like CD4+ T cells. Within the CD8+ T cell population, effector memory T cells predominantly surged, accompanied by a pronounced increase in pro-inflammatory "M1-like" monocytes.[43] The alveolar immune landscape in CIP paints a picture of enhanced activation of inflammatory cell subgroups, juxtaposed with a reduced suppressive phenotype. Likewise, patients with irAEs, particularly severe cases, show elevated pro-inflammatory cytokine levels.[44] Specifically, inflammatory cytokines such as interleukin (IL)−6, IL-17a, and IL-35 were elevated in the BALF of CIP patients.[45,46] While direct antibodies binding to CTLA-4 expressed on regular tissues can trigger organ damage via complement-mediated inflammation,[47] definitive evidence pinpointing such lung damage remains elusive.

Intrinsic mechanisms of CIP

CIP's onset is intricately associated with inherent predisposing factors in cancer patients. Firstly, the presence of pre-existing autoantibodies is associated with irAEs onset. Post-ICI therapy, there is a potential activation of the humoral immune response. This could subsequently lead to either the formation or proliferation of pre-existing antibodies, which are thought to be associated with the onset of irAEs.[48–50] Notably, the presence of anti-CD74 autoantibodies has a moderate association with CIP development.[51] Secondly, high CIP incidence in LC patients might be attributable to tumor-associated antigens and autoantibodies. This phenomenon could arise from antigenic cross-reactivity between tumor-associated antigens and pulmonary tissues. Such cross-reactivity induces T cell activation targeting both the tumor and lung tissue, culminating in CIP. Prior to ICI treatment, identifying peripheral blood autoantibodies against tumor-associated antigens in cancer patients might represent predictive biomarkers of irAEs. This could also hint at potential mechanisms whereby antibodies formed due to tumor-associated antigens become irAE pathogenic contributors.[52] Specifically, a positive response in an autoantibody panel targeting tumor-associated antigens (p53, breast cancer 2 [BRCA2], Hu antigen D [HuD], tripartite motif-containing protein 21 [TRIM21], and New York esophageal squamous cell carcinoma 1 [NY-ESO-1]) has been associated with elevated incidence of CIP (hazard ratio [HR] = 3.504, $P = 0.032$).[53] Lastly, the intrinsic mechanisms driving CIP might be attributed to potential exposure to pulmonary antigens or localized inflammatory responses, especially in individuals with pre-existing pulmonary conditions, e.g., COPD and pulmonary fibrosis.[54,55] The inflammatory response in airways due to smoking-induced elastin-specific T cell reactions was reported, with enhanced levels of anti-elastin antibodies and elastin-specific T cells in COPD patients.[56] Enhanced T cell antitumor immune response by ICIs might inadvertently induce immune reactions against pre-existing antigen exposures, thus intensifying localized inflammatory reactions, which in turn could pave the way for CIP.

External synergistic mechanisms of CIP

The ionizing radiation emitted during radiotherapy can break robust chemical bonds, producing highly reactive free radicals, which either directly or indirectly, cause DNA damage. Such radiation directly exerts cytotoxic effects on normal lung tissues, predominantly impacting vascular endothelial cells and alveolar epithelial cells. Subsequently, injured cells may release inflammatory cytokines, regulating immune cells. This cascade causes acute pneumonitis, leading to secondary pulmonary fibrosis and culminating in radiation pneumonitis.[57,58] Meanwhile, ICI therapy stimulates T-cell-mediated inflammatory reactions and cytokine cascades, enhancing lymphocyte response associated with radiation pneumonitis, marked by a surge in inflammatory mediators such as tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and various interleukins (e.g., IL-4, IL-6, IL-10, IL-13, IL-17, and IL-18).[58] This suggests a potential interplay between two therapeutic approaches, amplifying lung immune-related damage and subsequent fibrotic transformation in lung tissue.

The exact mechanisms of the elevated lung toxicity when small molecule targeted therapy is combined with immunotherapy remain enigmatic.[32,35] However, it was postulated that *EGFR*-TKIs might enhance major histocompatibility complex-1 (MHC-1) antigen presentation, thereby intensifying antigen-specific CD8(+) cytotoxic T lymphocyte activities.[59]

Moreover, infections are considered potential triggers of CIP post-ICI therapy. Notably, instances of CIP secondary to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection have been documented.[60,61] Viral infections can damage the alveolar epithelium, inducing antigen release and stimulating local immune reactions. This

includes the mobilization of cytotoxic T cells and a surge in pro-inflammatory cytokines, e.g., IL-6. The ensuing interaction between the virus and the host's immune system may induce immune hyperactivation, causing further damage to the alveolar epithelium. This process is similar to lung injury caused by ICIs. The analogous aberrant inflammation and suppressed lymphocyte functions observed in both CIP and viral infections point toward a plausible synergistic mechanism that could induce CIP post-SARS-CoV-2 infection.[62–64] However, due to the distinct immunological dysfunctions and alveolar cell damage caused by various pathogens, as well as heterogeneous immune responses following ICI treatment, alongside the complex coexistence of infection and CIP, elucidating the precise synergistic mechanisms remains challenging.

Prophylaxis and surveillance of CIP

Prophylaxis of CIP

As of now, the medical community lacks robust clinical strategies to both predict and avert CIP in cancer patients administered ICIs. Nevertheless, rigorous monitoring of those patients deemed high-risk, pinpointing and circumventing potential CIP risk factors, and timely intervention during ICI administration can curtail the deleterious effects associated with CIP. A holistic surveillance protocol spanning the duration of ICI therapy may be invaluable in bolstering the early detection and treatment efficacy in CIP [Fig. 2].

Baseline assessment of CIP risk in cancer patients administered ICIs

In patients with risk factors for CIP, a meticulous baseline evaluation is paramount. This entails capturing a comprehensive medical history, especially regarding potential risk factors, and performing a thorough physical examination. Emphasis should be placed on comprehensive respiratory function evaluations at baseline, including physical examinations, symptomatic assessments, chest computed tomography (CT) (with a preference for high-resolution computed tomography [HRCT]) and pulmonary function tests (PFTs).[65] PFTs should evaluate ventilation function, total lung capacity, and diffusing capacity. If feasible, incorporating the six-minute walk test would further improve the assessment.

Management of CIP risk factors

Proactive management of risk factors for CIP is essential in its prevention. In patients with COPD or emphysema, adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for holistic treatment and standardized management is imperative. In cases with IPF and other ILDs, continuation of previous anti-fibrotic regimen or other ILD treatments is recommended. Moreover, measures to prevent respiratory infections and associated complications are critical steps in mitigating the onset or exacerbation of CIP.[66]

Surveillance of CIP

Patient education and home self-monitoring

Currently, CIP detection and monitoring are primarily anchored in patient-reported symptoms. When patients show emergent respiratory symptoms such as dyspnea, chest discomfort, or cough, chest imaging examinations are typically prescribed to detect CIP.[67–70] However, given the often-debilitated overall health and reduced physical activity inherent in cancer patients, their capacity to discern and relay respiratory symptoms may be hindered. Tragically, by the time some patients seek medical care based on experienced symptoms, they may already be grappling with an advanced stage of CIP, leading to suboptimal therapeutic outcomes. For effective management of irAEs, including CIP, early detection, accurate diagnosis, and timely treatment are paramount. Achieving these goals requires a collaborative approach involving patients, caregivers, and an MDT of healthcare professionals. Enhanced patient education is also pivotal. Both patients and their families should be familiar with the risks associated with CIP and should be equipped with the knowledge about the clinical manifestations of CIP. They must be proactive in monitoring for indicative clinical signs, reporting them without delay, and seeking prompt medical help to facilitate the early detection of CIP. An informed patient is more likely to seek medical attention promptly when symptoms arise.

Nursing proactive monitoring

Nursing staff, especially in respiratory or oncology departments, play pivotal roles in the proactive monitoring of CIP,[66] as follows: (1) Patient education: Nurses should provide thorough education on CIP to patients administered ICIs, their families, and caregivers. (2) Medication adherence: In cases with pre-existing pulmonary conditions, adherence to respiratory medications should be ensured. (3) Active monitoring plan: A comprehensive plan should be devised for patients, detailing how they can self-monitor symptoms and oxygen saturation levels. Nurses can further guide families in creating a proactive monitoring system, emphasizing early detection.

Medical staff monitoring

High emphasis on education for oncologists, emergency physicians, primary care doctors, and other frontline medical staff is essential.

Oncologists, in particular, bear significant responsibilities in the holistic care of cancer patients,[66–70] including the following aspects: (1) Ongoing monitoring: Regular respiratory assessments during follow-up visits are crucial, e.g., symptom assessment, physical examination, oxygen saturation assessment, blood gas analyses if necessary, and PFTs to detect early-stage CIP. Any changes in pulmonary imaging should be meticulously examined. New lung infiltrates should trigger a differential diagnosis, with CIP at the forefront of considerations. (2) Multidisciplinary approach: A dedicated team of specialists should be formed for CIP diagnosis and management. This team should consist of experts from oncology, pulmonology, radiology, and other relevant disciplines. (3) Referral system: A systematic referral process should be designed and implemented to ensure standardized diagnosis and treatment of patients with suspected CIP.

Given that primary care and emergency physicians often serve as the first line of detection in CIP, equipping them with specialized training is essential to sharpen their clinical understanding and diagnostic abilities concerning CIP. Recommended steps include the following: (1) Medical history: routinely inquire about recent immunotherapy sessions in cancer patients, particularly within the past 3 months. (2) Differential diagnosis: in patients actively undergoing antitumor treatment, consider a comprehensive differential diagnosis of CIP in case of symptoms such as fever, fatigue, dyspnea, and other respiratory abnormalities or in case of evident hypoxemia or new pulmonary infiltrates. (3) Referrals: in case of suspected CIP, promptly refer patients to experienced oncologists or pulmonologists specializing in CIP diagnosis and treatment.

Diagnosis and grading of CIP

When new or exacerbated respiratory symptoms arise, or when chest CT reveals novel lung infiltrates, CIP should be suspected. CIP diagnosis remains a challenge, as no gold standard currently exists. For a probable diagnosis of CIP, the following criteria were proposed[67–70]: (1) a documented history of ICI administration in cancer patients; (2) onset of new respiratory symptoms or novel shadows or abnormalities on chest images; and (3) a rigorous exclusion of other potential causes of pulmonary pathologies. It is very necessary to combine clinical manifestations, laboratory findings, radiological manifestations, and tissue biopsy and BALF findings to identify CIP clinically. An MDT facilitates the diagnosis of CIP (Fig. 2).

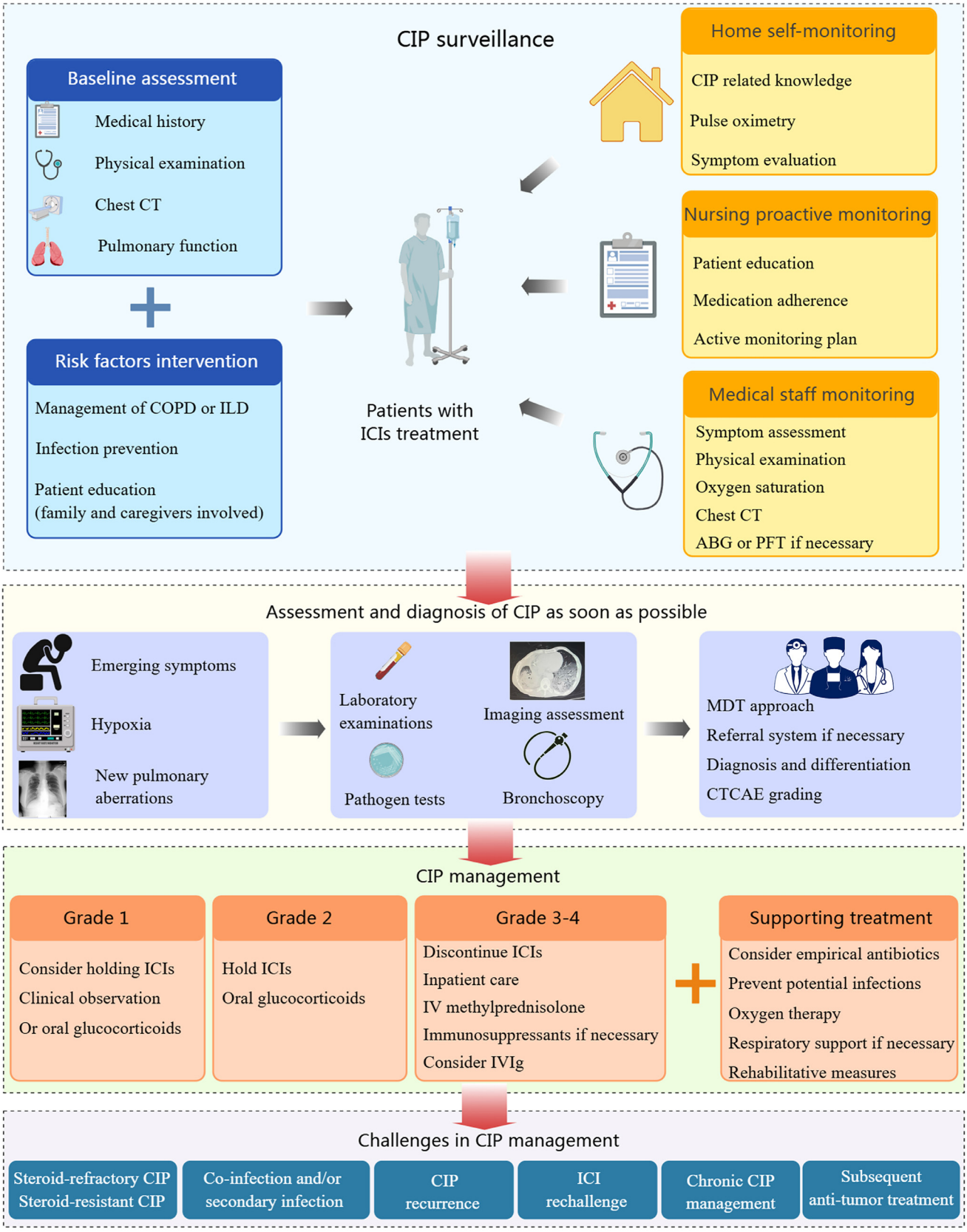

Fig. 2. Flowchart of clinical management for CIP. ABG: Arterial blood gas analysis; CIP: Checkpoint inhibitor pneumonitis; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; ICI: Immune checkpoint inhibitor; ILD: Interstitial lung disease; IV: Intravenously; IVIg: Intravenous immunoglobulin; MDT: Multi-disciplinary treatment; PFT: Pulmonary function test.

Table 1
Common differential diagnoses of CIP.

Diseases	Relevant findings
CIP	ICI administration history; new respiratory symptoms or novel shadows or abnormalities on chest images; exclusion of other potential causes of pulmonary pathologies.
Infectious diseases	
Bacterial pneumonia	Productive cough; consolidation on CT relatively common; possible elevated procalcitonin; positive sputum culture for bacteria
Viral pneumonia	Positive nucleic acid/antigen test in throat swab or other respiratory samples; positive blood test for nucleic acid or specific antibodies; common viruses include influenza, SARS-CoV-2, and cytomegalovirus
Pneumocystis jirovecii pneumonia	Positive serum β-D-glucan and lactate dehydrogenase tests; positive nucleic acid test in respiratory samples
Aspergillus pneumonia	Positive serum β-D-glucan and galactomannan tests; positive galactomannan test in BALF samples; halo sign or cavity on CT images
Radiation pneumonitis	Occurs in weeks to months after radiation therapy; pulmonary opacities typically align closely with the irradiated area
Pulmonary hemorrhage	Hemoptysis; decreased hemoglobin; bloody BALF
Pulmonary edema	Signs of heart failure and fluid overload; more abnormalities in the gravity-dependent area on CT images
Pulmonary embolism	Elevated D-dimer; overt deep vein thrombosis; subpleural wedge-shaped consolidation on CT images (pulmonary infarcts)
Tumor progression	Progression of the underlying LC could manifest as nodules or consolidation, resembling organizing pneumonia; cancerous lymphangitis could manifest as interstitial thickening

BALF: Bronchoalveolar lavage fluid; CIP: Checkpoint inhibitor pneumonitis; CT: Computed tomography; LC: Lung cancer; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

Diagnostic appraisal for CIP

Clinical manifestations

The median time to the onset of immune-related pneumonitis is 2.1–2.8 months after the first dose of anti-PD-1/PD-L1, with a wide range from several days to 2 years.[22,71]

The clinical manifestations of CIP are non-specific. Dry cough and exertional dyspnea are the major manifestations. Fever, hemoptysis, and chest pain are less common. In severe cases, patients have cyanosis and tachypnea. Manifestations of irAEs in other organs might occur concurrently, e.g., rashes.

Laboratory findings

Routine laboratory examinations are essential for evaluating individuals with suspected CIP, including complete blood count, liver and kidney function tests, and assessment of inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In cases exhibiting hypoxemia, arterial blood gas analysis should be conducted with reference to baseline values. To rule out infections, pathogen tests are imperative. These tests detect a broad range of potential culprits, including viruses (e.g., influenza, SARS-CoV-2, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus, adenovirus), bacteria, atypical pathogens (e.g., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, mycobacteria), and fungi (e.g., pulmonary aspergillosis, *Pneumocystis jirovecii*). Comprehensive pathogen evaluations often involve analyzing sputum specimens, nasopharyngeal swabs, and BALF samples. Collaborating with infectious disease specialists is invaluable in such scenarios.

Radiological manifestations

Immediate chest CT, with a particular emphasis on HRCT, is indispensable for CIP diagnosis. HRCT images may reveal CIP presentations such as organizing pneumonia, non-specific interstitial pneumonia, hypersensitivity pneumonitis, and acute interstitial pneumonia/acute respiratory distress syndrome (ARDS).[22,72] While imaging can reveal new pulmonary aberrations, a comprehensive differential diagnosis should integrate imaging findings, patient medical history, and additional diagnostic evaluations.

Bronchoscopy and lung biopsy

While bronchoscopy is considered a diagnostic tool for CIP, its definitive role remains under scrutiny. BALF samples from CIP patients typically reveal an elevated lymphocyte count and an inverted CD4/CD8 ratio.[71] Crucially, BALF analysis may help rule out infections, especially in patients with no response to steroid therapy. Additionally, bronchoscopy facilitates the differential diagnosis of CIP, helping exclude other conditions such as pulmonary hemorrhage and tumor metastasis. However, given its invasive nature, not all patients, especially advanced stage cancer cases, can tolerate bronchoscopy. As such, it is not routinely administered in suspected CIP cases. Yet, in situations where differential diagnosis is challenging or in cases of failed initial CIP treatment, bronchoscopy should be considered.

Transbronchial and CT-guided percutaneous lung biopsies provide histological insights by procuring pathological specimens. The obtained specimens may show various histological patterns, including organizing pneumonia, diffuse alveolar damage, cellular interstitial pneumonitis, and eosinophilic pneumonia.[10,22] However, given the potential risks associated with biopsy procedures, especially in critically ill patients, a lung biopsy is not always crucial for diagnosing CIP.

Differential diagnosis of CIP

CIP's clinical presentations and chest CT manifestations can strikingly resemble those of several other pulmonary conditions.[73–75] It is therefore essential to rule out other conditions, e.g., various pulmonary infections (bacterial pneumonia, influenza pneumonia, coronavirus disease 2019 (COVID-19) pneumonia, and opportunistic infections like *Pneumocystis jirovecii* pneumonia, cytomegalovirus pneumonia, and aspergillus pneumonia), radiation pneumonitis, pulmonary embolism, pulmonary hemorrhage, tumor progression, and pulmonary edema (Table 1). The ability to distinguish CIP from these conditions is critical, not only at the initial diagnosis but also when encountering poor treatment response or the recurrence of symptoms or pulmonary infiltrates after initial improvement. In patients with pre-existing ILD at baseline, ILD exacerbation is commonly associated with ICIs.

CIP grading

Once CIP is diagnosed, its severity should be graded to guide treatment. The classification is based on clinical manifestations and chest imaging findings. It is advisable to use the Common Terminology Criteria for Adverse Events (CTCAE) as a standardized metric for grading the severity of CIP.[67,69,70,76]

Therapeutic strategies for CIP

After confirming a diagnosis of CIP, it is imperative to devise a treatment strategy that aligns with pneumonitis severity, the patient's current health conditions, and the overall health status.[77] A proactive stance that encompasses prevention, timely identification, accurate diagnosis, and effective management of CIP across the entire treatment

Table 2
Active ongoing prospective clinical studies of management strategies in CIP and unspecified irAEs.

NCT number	Patients	Design	Treatments	Primary end point
NCT 05899725	CTCAE Grade 3–4 CIP	Randomized, open-label, Multicenter	Corticosteroids ± ruxolitinib	Proportion of patients with steroid dose ≤10 mg daily at improvement to CTCAE grade 1 at week 8
NCT 05280873	CTCAE Grade 3–4 CIP	Randomized, open-label	Methylprednisolone ± pirfenidone	Time to reduction by one grade
NCT 04375228	Steroid-dependent irAE	Non-randomized, open-label, multicenter	Rituximab or tocilizumab	Percentage of participants able to discontinue steroid treatment within 4 weeks after the last dose of rituximab/tocilizumab
NCT 05660421	Steroid-refractory CTCAE Grade 2–4 irAE	Single arm	Corticosteroid and itacitinib	Rate of improvement at day 28

CIP: Checkpoint inhibitor pneumonitis; CTCAE: Common Terminology Criteria for Adverse Events; irAE: Immune-related adverse event; NCT: National Clinical Trial.

process is crucial to optimize patient outcomes.[78] The treatment approach for CIP hinges on the relevant clinical grade (Fig. 2).[67,69,70,76] In grade 1 CIP, patients might either undergo clinical observation or be administered monotherapy with oral glucocorticoids, and should be considered for continued ICIs. In grade 2 CIP, treatment typically involves oral glucocorticoids and continued ICIs. In grades 3–4 CIP, patients should undergo inpatient care and discontinue ICIs, and prompt initiation of high-dose steroids is recommended after excluding concurrent infections. Donkor *et al*[79] compared management strategies across various guidelines. Up to now, these CIP management strategies in different available guidelines were mainly based on lower-level evidence, e.g., retrospective studies and expert opinions/consensuses. Several ongoing prospective studies are evaluating management strategies for CIP and unspecified irAEs (Table 2).

Despite rigorous treatment, some individuals might show symptom aggravation or recurrence upon steroid tapering.[80] In such scenarios, or in cases with rapidly progressing CIP or recurrent manifestations, a combination therapy comprising alternate immunosuppressants and/or immunoglobulins may be useful.[81] In addition, plasma exchange can also be considered for life-threatening cases.[82] Moreover, introducing anti-fibrotic agents should be contemplated for cases progressing to pulmonary fibrosis. More details about the management of severe and refractory CIP are discussed later.

In cases where an infection remains a differential diagnostic possibility, empirical treatment with antibiotics is advisable. Furthermore, when extended steroid therapy is anticipated, prophylactic antibiotics should be considered to prevent potential infections. Respiratory support becomes a cornerstone in the management of grade ≥3 CIP. During drug administration, incorporating rehabilitative measures may further enhance patient recovery. It is pivotal to recognize that despite comprehensive treatment, some patients may still have exacerbations. Other cases might evolve to pulmonary fibrosis. A smaller subset of patients could even face fatal outcomes either due to rapidly advancing CIP or secondary severe infections.

Challenges and future directions in CIP management

Management of severe and refractory CIP

Managing severe and life-threatening irAEs presents significant challenges. Notably, irAEs involving the respiratory system have the highest prevalence and constitute the predominant cause of irAE-related fatalities.[83] Even with intensive therapeutic intervention, the 90-day mortality rate/hospice referral of these patients remains alarmingly high, i.e., approximately 50 %, with CIP and secondary infections considered the primary causes of death.[84] In a study including 26 refractory or recurrent CIP cases,[84] 12 individuals (46 %) were steroid-refractory, while the remaining 14 were steroid-resistant. In terms of immunosuppressant use, 21 cases (80.8 %) were administered TNF inhibitors, 9 cases (34.6 %) were treated with mycophenolate mofetil (MMF), and 1 had cyclophosphamide. The results indicated improved CIP in 38 % of the cases, temporary amelioration in 50 %, and unchanged condition in 12 %. Another study analyzed 65 CIP cases of whom 12 were steroid-refractory.[85] Within this subgroup, 50 % had diffuse alveolar damage (DAD), 75 % had bilateral multifocal lung involvement, 11 required intensive care, and 8 died. Meanwhile, five of these patients were managed with infliximab or a combination of infliximab and intravenous immunoglobulin (IVIg), but unfortunately died due to pneumonia or subsequent infections, underscoring the grim prognosis of these patients.

While glucocorticoids stand as the cornerstone treatment option for CIP, a subset of patients are steroid-refractory, with no alleviation of irAEs after treatment. Others might display initial responsiveness but fail to achieve symptom resolution, which can be defined as steroid-resistance. These steroid-refractory or steroid-resistance cases are referred to as steroid-unresponsive irAEs.[86] The clinical management of such patients remains a great challenge.

In steroid-unresponsive CIP, addition of other immunomodulatory agents, e.g., infliximab, MMF, and cyclophosphamide, is the standard treatment approach.[87,88] However, the actual application of these agents in clinical settings remains low,[24] potentially due to a limited understanding or a lack of robust clinical evidence. Currently, a TNF-α mAb, infliximab, is recommended as a first-line therapeutic for severe CIP,[89] although its efficacy rate leaves room for improvement. Other agents, e.g., cyclophosphamide, MMF, and tacrolimus, have been used in the management of refractory CIP.[90] While MMF is a second-line option, its action is somewhat delayed, making it less suitable for acute CIP management. However, MMF can facilitate the tapering of glucocorticoids.

IVIg is increasingly recommended for severe and refractory CIP cases. Its ability to neutralize antibodies and bolster resistance to infections, combined with a favorable safety profile, has earned it considerable support in the medical community.[91,92] Nevertheless, robust evidence supporting its widespread use is not available.

Plasma exchange offers a mechanism to purge the plasma of various pathogenic elements, including autoantibodies, immune complexes, cryoglobulins, toxins, and therapeutic monoclonal antibodies. For substantially life-threatening irAEs, early initiation of plasma exchange may be advantageous. By clearing pro-inflammatory cytokines, chemokines, pathogenic antibodies, and ICIs, such an intervention holds the promise of halting irAE progression and possibly reversing its effects. While plasma exchange has been recommended for severe ICI-related conditions like myasthenia gravis and Guillain-Barré syndrome, its application for CIP is not universally accepted.[82,93]

Given the suboptimal outcomes associated with current treatment modalities for severe and refractory CIP, multiple novel immunosuppressive agents are being explored, e.g., monoclonal antibodies and kinase inhibitors targeting specific pro-inflammatory cytokines or pathways.[94–96] For instance, anti-IL-6 receptor monoclonal antibodies, including tocilizumab, have demonstrated promising outcomes in certain patient cohorts,[97,98] with a reduced risk of infection. In a cohort of 87 irAE patients,[97] 34 (12 CIP cases included) were administered tocilizumab (39.1 %), of whom 27 (79.4 %) had clinical improvement.

Moreover, emerging agents, including IL-17 inhibitors, IL-1 inhibitors, and Janus kinase (JAK) pathway inhibitors,[94–96] are under investigation for various irAEs. However, their efficacies in CIP remain unknown, underscoring the need for robust clinical trials.

As some CIP cases transition to a fibrotic state during disease progression, anti-fibrotic medications, including pirfenidone and nintedanib, have been assessed, providing clinical benefits in select cases.[99,100]

Interplay between CIP and radiation pneumonitis

Radiotherapy remains a major therapeutic modality for cancer. A notable side effect, radiation pneumonitis, can occur 1–6 months post-radiotherapy in patients administered thoracic cancer treatment. Particularly in LC patients administered concurrent chemoradiotherapy, the incidence of grade ≥2 pneumonitis ranges from 10 % to 40 %.[101] In the era of immunotherapy, the synergistic effects of immunotherapy and radiotherapy used in combination are under exploration in many malignancies. This combination, however, appears to increase the risk of pneumonitis, evidenced by the PACIFIC study, which examined the usefulness of durvalumab maintenance therapy *vs*. placebo in patients with stage III unresectable non-small cell lung cancer (NSCLC) post-concurrent chemoradiotherapy. The latter study revealed that durvalumab significantly increased both progression-free survival (PFS) and overall survival (OS) rates. However, a notable finding was the elevated incidence of pneumonitis or radiation pneumonitis or pneumonia in the durvalumab cohort compared with the placebo group. Yet, the escalation in grade ≥3 pneumonia rate was not statistically significant between the two groups.[27] In patients administered concurrent chemoradiotherapy followed by ICI treatment, a mean lung dose (MLD) of ≥16 Gy and V40 were identified as independent predictors of the onset of grade ≥2 adverse events (AEs). However, ICI treatment did not amplify the risk of grade ≥3 AEs.[102]

Following immunotherapy, the previously irradiated lung segment might show characteristics reminiscent of radiation pneumonitis, commonly referred to as RRP.[58,103] Specifically, in the KEYNOTE-001 study, patients with a history of radiation therapy exhibited elevated odds of developing pulmonary toxicity relative to the non-radiotherapy group (63 % *vs*. 40 %).[104] Fortunately, these patients typically had milder respiratory symptoms, which demonstrated commendable responsiveness to steroid therapy. It is pertinent to mention that post-lung radiation, some patients on immunotherapy might develop pneumonitis beyond the irradiated site, aligning more with the hallmark features of CIP. This phenomenon might be underpinned by enhanced immune-mediated damage to the lung tissue, consequent to antigen exposure post-radiation-induced lung insult. Furthermore, patients might concurrently develop radiation pneumonitis and CIP, which requires meticulous differentiation. Moreover, even in individuals with non-lung metastatic malignancies administered radiation therapy, a tangible risk of CIP was reported. Intriguingly, a study revealed that integrating localized lung radiotherapy in patients with previous irAEs significantly increases the risk of radiation pneumonitis, with 61 % showing grade ≥2 radiation pneumonitis. This susceptibility might result from immune dysregulation caused by irAEs, culminating in enhanced susceptibility to radiation pneumonitis.[105]

When differentiating between radiation pneumonitis and pulmonary inflammation attributable to immunotherapy, evidence indicates distinct patterns in their presentations. CIP tends to show bilateral involvement spanning multiple lung lobes. In contrast, radiation pneumonitis often has a clear demarcation, aligning with the radiation field. Notably, radiographic manifestations in individuals administered both radiation therapy and ICIs reveal a broad spectrum of presentations.[106] The therapeutic approach for radiation pneumonitis is similar to that used in CIP. For grade 1–2 radiation pneumonitis, the primary treatment modality remains symptomatic treatment and/or anti-infective therapy if necessary. However, when managing grade 3–4 pneumonitis, administration of glucocorticoids becomes imperative. In patients administered both immunotherapy and radiation therapy, whether sequentially or concurrently, newly onset pneumonitis requires a meticulous differential diagnosis. It is vital to differentiate between radiation pneumonitis and CIP, or their simultaneous occurrence. Such differentiation paves the way for aggressive glucocorticoid intervention in severe CIP cases and the prompt initiation of requisite immunosuppressive treatments.

CIP and infectious diseases

Cancer patients inherently face high infection risk, a vulnerability that escalates further for cases under ICIs. This increased susceptibility largely results from the administration of glucocorticoids and other immunosuppressive agents, e.g., infliximab, to manage irAEs.[107] Recognizing and efficiently addressing infections is paramount throughout the entire CIP treatment process.

Initial presentation of new respiratory symptoms, combined with pulmonary imaging findings, requires the exclusion of infections before confirming a CIP diagnosis. The spectrum of lung infections in cancer patients is large, encompassing bacterial (including tuberculosis and non-tuberculous mycobacterial infections), viral, and fungal infections.[108] Notably, instances of *Mycobacterium avium* complex infections were reported in patients administered ICIs.[109] Some infections, including those associated with COVID-19, might act as catalysts for CIP. For instance, coronavirus HKU1 infections were reported to cause diffuse ILD.[61] Administering treatments for irAEs demands vigilant monitoring for subsequent infections. A study involving 758 cancer cases on ICIs[110] reported that of the 156 patients administered glucocorticoids and immunosuppressive agents for irAE management, 20 % had infections within 90 days (7 % and 13 % of opportunistic and non-opportunistic infections, respectively). Given that CIP management often involves high-dose glucocorticoid and immunosuppressive treatments, there is an enhanced predisposition to infections. This risk is especially pronounced in refractory CIP cases, where severe secondary infections may lead to death.[84,85] Therefore, clinicians must be attuned to the potential of simultaneous infections in CIP cases treated with glucocorticoids and immunosuppressive agents, involving both opportunistic and non-opportunistic pathogens. Consistently, the National Comprehensive Cancer Network (NCCN) guidelines advocate for prophylactic anti-infective therapy.

Cancer patients are at a significantly higher risk of SARS-CoV-2, which often results in adverse prognostic outcomes.[111] While extended evidence suggests no marked increase in the incidence of serious adverse events (SAEs) in patients on ICI therapy relative to those on chemotherapy in the context of SARS-CoV-2 infection,[112] the concurrent rise of COVID-19 presents significant diagnostic and therapeutic challenges for CIP management. Distinguishing between COVID-19 and CIP is particularly difficult because of overlapping clinical and pulmonary imaging manifestations. Key differentiation methods include epidemiological tracing and definitive pathogen detection. Moreover, during the COVID-19 pandemic, clinicians encountered intriguing scenarios such as SARS-CoV-2 infection following ICI treatment, concomitant presentation of COVID-19 and CIP, COVID-19-induced CIP,[60] and CIP recurrence due to a subsequent COVID-19 infection after initial CIP resolution.[64,113] To address such complex clinical scenarios, a well-calibrated therapeutic approach is crucial. Administering appropriate doses of glucocorticoids is a primary consideration, supplemented, if needed, by agents like tocilizumab and JAK inhibitors.[114]

CIP recurrence and ICI rechallenge

Continuous vigilance is paramount for patients with improvement post-CIP treatment. A significant concern is the potential recurrence of CIP during steroid tapering, as well as when reconsidering ICI rechallenge.[80,115] In patients with CIP recurrence during steroid tapering, it might be imperative to reintroduce glucocorticoids or even combine them with other immunosuppressive agents.

Given the notable survival advantages conferred by ICIs in cancer patients, the decision to rechallenge with ICIs remains a topic of keen interest. Rechallenge may represent a viable option in cases with previous grade 1–2 CIP. However, the inclination toward rechallenge appears markedly decreased in patients with grade ≥3 CIP.[116] In a study assessing irAEs in 452 patients, 101 developed CIP of whom 34 % experienced CIP recurrence upon ICI rechallenge.[117] The latter study emphasized that the odds of CIP recurrence are significantly elevated post-rechallenge (OR: 2.26, 95 % CI: 1.18–4.32; $P = 0.01$). Another study of 180 patients with at least one grade ≥2 irAE and subsequent rechallenge reported that 24 cases developed pneumonitis. Remarkably, following rechallenge, 10 of these patients experienced pneumonitis recurrence, with two patients developing grade 3 or 4 CIP.[118] In yet another study including 93 irAE cases, out of the 40 who underwent rechallenge, 5 had previously detected CIP. Notably, only a single patient experienced CIP recurrence post-rechallenge.[119] It is pivotal to note that while CIP recurrence rates post-rechallenge are considerable, the incidence of severe irAEs after ICI rechallenge remains relatively consistent.[120]

Chronic and prolonged manifestations of irAEs

IrAEs persisting for >12 weeks post-treatment are termed "chronic irAEs".[86,121] While studies comprehensively assessing chronic pulmonary irAEs remain somewhat scant, a subset of CIP cases progress to lung fibrosis after the acute phase. This progression manifests clinically as reduced exercise capacity, persistent cough, and episodes of respiratory distress. Such lingering effects not only impede subsequent cancer treatments, e.g., ICI administration and radiotherapy, but also significantly compromise pulmonary function and the overall quality of life. Given these repercussions, it is imperative for clinicians to maintain high vigilance, ensuring robust monitoring, management, and therapeutic interventions for affected individuals.

Development of an MDT management system for CIP

The complexity of CIP makes multidisciplinary collaboration essential for accurate diagnosis and adequate management. The CIP MDT team should be part of the irAE MDT board and comprise specialists with expertise in irAE management, including pulmonologists, oncologists, rheumatologists, infectiologists, critical care specialists, radiologists, pathologists, pharmacologists, etc. The CIP MDT could provide timely consultations for patients with suspected CIP. In case of differences in diagnosis, the MDT approach should be used to improve diagnostic accuracy in CIP patients. The MDT team can design a comprehensive treatment strategy for severe and refractory CIP. Moreover, The CIP MDT team also carries out regular training for CIP management in multiple hospitals.

Establishment of a precision CIP management system

As previously mentioned, CIP diagnosis and management in clinical practice are highly complex and variable. Currently, diagnosis of CIP primarily relies on exclusionary criteria. It is imperative to identify effective diagnostic biomarkers (e.g., specific inflammatory factors, cytokines or immune cells), particularly those reported in lung tissue biopsy and/or alveolar lavage.[122] The establishment of effective diagnostic criteria, such as the integration of various clinical findings and diagnostic biomarkers, is imperative for proper clinical diagnosis of CIP, to design more precise and personalized treatments. Moreover, CIP grading relying solely on symptoms and imaging data is insufficient. Therefore, precise risk stratification and predictive models for CIP are urgently needed to identify high-risk patients, such as those with steroid-refractory CIP, steroid-resistant CIP, or life-threatening CIP. Such models would provide guidance for intensive treatment strategies in high-risk patients. Furthermore, multiple immunosuppressive agents targeting different specific pro-inflammatory cytokines or pathways are being explored.[122] Further studies and clinical validation are required to determine the potential values of pro-inflammatory cytokines or pathways-related biomarkers in the precise treatment of CIP.

Development of a CIP pharmacovigilance system

Currently, research on CIP largely relies on case series studies, and a dedicated pharmacovigilance system for CIP is notably absent. Medical institutions can harness the capabilities of drug monitoring information systems and leverage artificial intelligence for real-time medical record surveillance. It is advisable to develop a CIP-centric pharmacovigilance system rooted in the hospital's existing pharmacovigilance framework. The national oncology pharmacovigilance initiative[123] provides continuous monitoring of approved drugs, enabling the selective screening of pharmaceutical side effects, the detection of adverse event signals, and the execution of thorough clinical assessments. Regulatory recommendations can then be made based on these findings. In the future, a specialized CIP pharmacovigilance system might be developed, drawing from the vast reservoir of data in the pharmacovigilance database. This would pave the way for more in-depth CIP studies, subsequently enhancing clinical guidelines and practice.

Conclusions

CIP is a significant irAE that arises after the administration of ICIs in cancer patients. Although its occurrence is relatively low, the severe manifestations of CIP are noteworthy, often resulting in unfavorable prognoses, placing them among predominant life-threatening irAEs. Swift identification, precise diagnosis, and timely intervention may potentially improve CIP outcomes. The design of a comprehensive, end-to-end surveillance management system for CIP throughout the duration of ICI treatment and integrating the concerted efforts of healthcare professionals, patients, and caregivers may considerably increase early diagnostic and therapeutic potentials, thereby serving as a pivotal strategy to improve patient outcomes.

While the current understanding of CIP provides a basis, research gaps and clinical challenges persist.[10] Key questions include the following. How can we proactively intervene to mitigate the risk of CIP in susceptible patients? What strategies could be used to enhance precision in distinguishing and diagnosing CIP? How can we promptly identify cases unresponsive to steroids? What are the optimal approaches to treat steroid-unresponsive cases? Could early introduction of immunomodulators confer therapeutic benefits for CIP? Which immunomodulator classes or novel targeted therapies hold promise for these patients? To shed light on these crucial areas of uncertainty, there is an imperative need for methodologically rigorous, standardized, and prospective studies.

CRediT authorship contribution statement

Yan Xu: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Ruxuan Chen:** Writing – original draft, Writing – review & editing. **Ruili Pan:** Writing – original draft. **Xiaoxing Gao:** Writing – original draft. **Hui Huang:** Writing – review & editing. **Mengzhao Wang:** Conceptualization, Supervision, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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