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Cancer therapy-related interstitial lung disease

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Abstract

With the increasing utilization of cancer therapy, the incidence of lung injury associated with these treatments continues to rise. The recognition of pulmonary toxicity related to cancer therapy has become increasingly critical, for which interstitial lung disease (ILD) is a common cause of mortality. Cancer therapy-related ILD (CT-ILD) can result from a variety of treatments including chemotherapy, targeted therapy, immune checkpoint inhibitors, antibody–drug conjugates, and radiotherapy. CT-ILD may progress rapidly and even be life-threatening; therefore, prompt diagnosis and timely treatment are crucial for effective management. This review aims to provide valuable information on the risk factors associated with CT-ILD; elucidate its underlying mechanisms; discuss its clinical features, imaging, and histological manifestations; and emphasize the clinical-related views of its diagnosis. In addition, this review provides an overview of grading, typing, and staging treatment strategies used for the management of CT-ILD.

Keywords: Cancer therapy; Interstitial lung disease; Lung toxicity

Introduction

The lungs have two distinct blood supply systems, with a large contact surface, making them vulnerable to attacks by different toxic substances. More than 400 drugs have been reported to cause lung injury, with damage to the airways, lung parenchyma, pulmonary vasculature, and pleura. Drug-induced interstitial lung disease (DILD) is the most common form of lung damage. DILD is a very heterogeneous adverse event, ranging from asymptomatic interstitial lung disease (ILD) to respiratory failure and even life-threatening conditions. Among the cases of DILD, cancer drug-related ILD is the most prevalent, accounting for 23–51% of all cases.[1] An analysis of the Japanese Adverse Drug Event Report (JADER) database found methotrexate, gemcitabine, docetaxel, gefitinib, erlotinib, everolimus, and nivolumab to be the top six drugs with the highest ILD reporting rates.[2] Tamura *et al*[3] found that the most common drugs that cause lung toxicity were anticancer drugs (42%), followed by antirheumatic drugs (24%). In addition, radiotherapy (RT) can cause lung toxicity, known as radiation pneumonitis (RP). In clinical practice, RT is often simultaneous or sequential with anticancer drugs, particularly in combination immunotherapy (IO), which makes it difficult to clearly distinguish DILD from RP. Additionally, radiation recall pneumonitis (RRP) is a pulmonary disease that arises as a delayed consequence of RT and is often triggered by systemic agents, such as anticancer drugs.[4] Therefore, ILD caused by cancer therapy is collectively called cancer therapy-related ILD (CT-ILD).

CT-ILD is the most common severe and lethal adverse event associated with tumors. A retrospective study analyzed 770 patients with non-small cell lung cancer (NSCLC), among whom 44 patients (6%) developed pneumonitis during anticancer treatment, resulting in a mortality rate of 36%.[5] A study of the French REISAMIC registry reported a considerably higher frequency of very serious immune-related adverse events (irAEs) in the respiratory system, with ILD being the most common fatal irAEs.[6] Furthermore, another study indicated that pneumonia was predominant in fatal adverse events related to programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors. A

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comprehensive analysis of 53 cohorts also revealed that ILD was the most frequent fatal toxicities associated with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).[7]

CT-ILD has a rapid and potentially life-threatening progression, underscoring the importance of accurate and rapid diagnosis, followed by early treatment. However, the clinical, imaging, and histological features of CT-ILD lack specificity. In addition, a patient may be receiving multiple treatments that can trigger ILD simultaneously. CT-ILD is an exclusive diagnosis that is easily confused with a lung infection, tumor progression, and pulmonary edema. This review aims to provide valuable information on the risk factors associated with CT-ILD, elucidate its underlying mechanisms, discuss its clinical features, imaging, and histological manifestations, and emphasize the clinical-related views of its diagnosis and management methods.

Epidemiology

The precise incidence of CT-ILD is difficult to estimate, as it is influenced by multiple factors, including the specific drug, the RT regimen, the dose, and the combination regimen. A study examining 19,132 cancer patients who received anticancer drugs between 2014 and 2018, reported that 120 (0.62%) patients developed severe DILD.[8] Terbuch *et al*[9] analyzed 2499 patients with advanced cancer participating in phase I clinical trials and found that 60 patients (2.40%) developed DILD. Furthermore, based on a summary of 470 oncology phase I trials, the incidence rates of pulmonary toxicity, total DILD, and grade 3–4 DILD were 2.70%, 0.77%, and 0.31%, respectively.[10]

CT-ILD can be broadly classified into two types: anticancer drug-related lung injury and RT-related lung injury. Various anticancer drugs may cause different degrees of ILD, including chemotherapy (e.g., bleomycin, cyclophosphamide, methotrexate, gemcitabine, and taxanes), small-molecular targeted drugs (e.g., gefitinib, erlotinib, osimertinib, crizotinib, and pralsetinib), mammalian target of rapamycin (mTOR) inhibitors (e.g., sirolimus and everolimus), immune checkpoint inhibitors (ICIs) (e.g., nivolumab, pembrolizumab, durvalumab), and antibody-drug conjugates (ADCs) (e.g., trastuzumab emtansine). Conventional chemotherapy typically carries a low incidence of ILD, while RT is associated with a higher incidence of RP, mainly grades 1–2 in severity. Newer antitumor drugs, especially ADC drugs and ICIs, appear to be more lethal and have a higher incidence of ILD, while TKI-ILD has a lower incidence [Supplementary Figure 1, http://links.lww.com/CM9/C15].

TKIs

The incidence of all-grade and high-grade ILD related to EGFR-TKI in a meta-analysis has been reported to be 1.6% (95% confidence interval [CI], 1.0–2.4%) and 0.9% (95% CI, 0.6–1.4%), respectively, with a mortality rate of 13.0% (95% CI, 7.6–21.6%).[11] Another meta-analysis showed that the overall incidence of pneumonitis associated with EGFR-TKI was 1.12% for all grades, 0.61% for high grade, and 0.20% for grade 5.[12] Furthermore, a meta-analysis by Suh *et al*[13] revealed that the overall pooled incidence of anaplastic lymphoma kinase (ALK) TKIs-associated pneumonitis for all grades, high grade, and grade 5 ILD was 2.14%, 1.33%, and 0.22%, respectively.

mTOR inhibitors

An analysis of phases II–III randomized controlled trials involving mTOR inhibitors reported an incidence of all-grade pulmonary toxicity at 10.4%, with high-grade incidence of 2.4%.[14] Another study revealed that the overall incidence of fatal adverse events associated with mTOR inhibitors was 1.8%.[15]

ICIs

A meta-analysis of 19 studies showed that the incidence rate of checkpoint inhibitor-related pneumonitis (CIP) at any grade or high grade is higher in the PD-1 inhibitor group than in the PD-L1 inhibitor group (3.6% *vs*. 1.3%, $P = 0.001$; 1.1% *vs*. 0.4%, $P = 0.02$; respectively).[16] Another meta-analysis revealed that the incidence of CIP in patients receiving PD-1 inhibitor monotherapy was 2.7% for all grades and 0.8% for grade ≥3 CIP.[17] Furthermore, a recent study revealed that the distribution of very severe respiratory toxicity (grades 4–5) associated with ICI was 1.1%.[6]

ADCs

A meta-analysis of drug-associated pneumonitis with ADCs found that the total incidence of all-grade and grade ≥3 pneumonitis was 5.86% and 0.68%, respectively. Specifically, the incidence of all-grade pneumonitis was 13.58%, and for grade ≥3 was 2.19% with trastuzumab deruxtecan (T-DXd), the highest rate observed in ADC therapy.[18] In one meta-analysis focusing specifically on T-DXd monotherapy-associated pneumonitis, a total ILD incidence of 15.4% and a grade 5 incidence of 2.2% were reported.[19]

Pathogenesis

The pathogenesis of CT-ILD has not yet been fully understood. Possible mechanisms may involve cytotoxicity and immune-mediated lung injury. Cancer therapy can directly or after biological transformation damage the alveolar epithelial, airway epithelial cells, or capillary endothelial cells, produce reactive oxygen species (ROS) or induce phospholipid deposition and activate immune cells as a hapten or mimic an antigen, thus causing a cascade of immune reactions [Figure 1].[20,21]

Chemotherapeutic drugs can produce ROS and nitric oxide (NO), triggering oxidative stress mechanisms that result in DNA damage and cell death.[22,23] They can also promote the release of inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α),

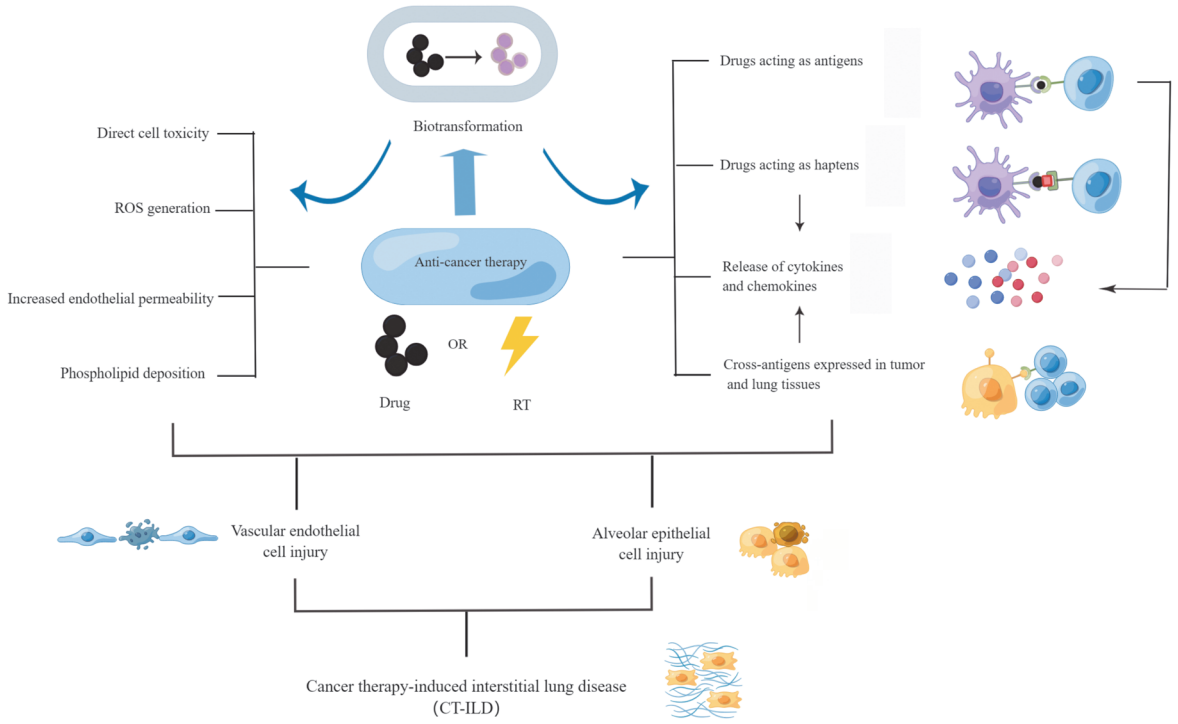

Figure 1: Pathobiology of cancer therapy-related interstitial lung disease. Cancer therapy can directly or after biological transformation damage the alveolar epithelial, airway epithelial cells, or capillary endothelial cells, produce ROS, increase endothelial permeability, or induce phospholipid deposition. The drugs may act as antigens or haptens to activate immune cells or enhance the activity of T cells against cross-antigens expressed in tumors and normal tissues, causing the recruitment of inflammatory cells and the release of inflammatory factors. ROS: Reactive oxygen species; RT: Radiotherapy.

interleukin-1 beta (IL-1β), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-beta (TGF-β).[23,24] These cytokines induce inflammation in lung tissue and may lead to capillary leakage and pulmonary edema (as observed with gemcitabine, for example).[25–27]

EGFR is involved in the repair of lung injury. EGFR-TKIs block EGFR phosphorylation, thus preventing the regeneration and proliferation of damaged epithelial cells, which can lead to the appearance of lung injury.[28,29] EGFR-TKIs exacerbate the progression of lung injury in TNF-overexpressing lung tissues by suppressing TNF-induced EGFR transactivation.[28] TKI-ILD is related to increased expression of interferon-induced protein 10 (IP-10) and heat shock protein 70 (HSP 70).[30,31]

ICI-induced pneumonia may be associated with the following five aspects: (1) Imbalance of T cell subsets. Treatment with ICI can activate immune function, leading to an imbalance of T cell subsets. The alveolar lavage fluid from patients with CIP showed an increase in $CD8^+$ T and $CD4^+$ T cells and a decrease in cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and PD-L1 positive Treg cells.[32] Another analysis of biopsy pathology in patients with CIP found elevated $CD8^+$ T cells and activated memory $CD4^+$ T cells, and decreased resting memory $CD4^+$ T cells.[33] (2) Activation and increase of pre-existing autoantibodies.[34,35] Anti-CD74 autoantibody levels increase significantly in CIP patients during pneumonia compared to those before ICI treatment.[36] (3) The production and release of cytokines/chemokines. Studies have found an association between the appearance of CIP and various inflammatory cytokines, and chemokines, including C-reactive protein (CRP), interleukin-6 (IL-6), IL-10, IL-17A, IL-35, interferon-gamma (IFN-γ), and C-X-C motif chemokine ligand (CXCL)9/CXCL10/CXCL11.[37–39] (4) Cross-antigen reactivity: Tumor cells possess antigens on their surface that are identical to those found in normal lung tissue. Overactivated T cells mistakenly recognize antigens on the surface of normal tissue cells and initiate an attack.[40–42] Furthermore, the dissolution of tumor cells and disintegration of tumor tissues during anticancer therapy can lead to the diffusion of antigenic epitopes.[43] (5) Microbial modulation of host immunity may be related to the toxicity of IO.[44]

ADC-ILD can potentially be linked to multiple mechanisms, including (1) target-dependent uptake of the ADC, (2) target-independent uptake of the ADC in healthy cells, (3) bystander killing caused by the release of free payload from cancer cells, and (4) the presence of circulating free payload due to deconjugation of the ADC.[45]

Ionizing radiation induces free radicals and DNA damage, promoting oxidative stress, vascular injury, and inflammation. Persistent inflammation sustains injury to alveolar epithelial and endothelial cells, recruiting a large number of immune cells and releasing cytokines. Alveolar epithelial injury leads to reduced release of pulmonary surfactant, resulting in decreased alveolar tension. Endothelial cell damage causes changes in vascular permeability, leading to pulmonary edema. Prolonged damage to the alveoli and vascular systems results in

excessive proliferation of fibroblasts and eventually leads to fibrotic changes.[46,47]

Risk Factors

The development of CT-ILD is largely unpredictable and idiosyncratic, although it may be associated with the cumulative dose and renal insufficiency. Risk factors for different types of CT-ILD may vary [Supplementary Table 1, http://links.lww.com/CM9/C15].

Age

Older patients have shown a higher susceptibility to developing CT-ILD, with a higher incidence of severe cases. A retrospective study found that patients with fatal bleomycin pulmonary toxicity were older than other patients in the study sample. For patients aged over 40 years old, especially those with renal insufficiency, the risk of fatal pulmonary toxicity was reported to exceed 10%.[48] Similarly, studies have shown that advanced age was a risk factor for the ILD associated with gemcitabine,[49] nab-paclitaxel,[50] gefitinib,[51] ALK-TKI,[52] and RT.[53] However, a study evaluating T-DXd, found the opposite result: age <65 years was associated with the occurrence of CT-ILD.[19]

Ethnicity and gene

According to a meta-analysis, the frequency of ILD among EGFR-TKI-treated patients was higher in Asian patients compared to non-Asian patients, although this difference did not reach statistical significance (2.5% *vs.* 0.9%, odds ratio [OR] = 2.79, 95% CI = 0.82–9.40, $P = 0.11$). Among Asian patients, the incidence of ILD was found to be higher in Japanese patients compared to that of other Asian countries (3.8% *vs.* 0.3%; OR = 12.7, 95% CI, 1.69–95.1; $P = 0.0009$).[54] Additionally, the incidence of all- and severe-grade EGFR-TKI-related ILDs in Japanese studies was found to be higher than in non-Japanese studies.[12] Xie *et al*[7] also identified that the frequency of fatal toxicity related to EGFR-TKIs in Japanese patients was higher, compared to non-Eastern Asian patients. Similarly, the incidence of ALK-TKI-related pneumonitis was significantly higher in studies from Japan compared to non-Japanese studies, both for all grade (6.25% *vs.* 1.14%, $P <0.001$) and high-grade pneumonitis (3.31% *vs.* 0.39%, $P <0.001$).[13] These findings were similarly observed in the study of T-DXd.[19]

A study investigating the association between DILD and human leukocyte antigen (HLA) alleles showed that the higher frequency of HLA-DRB1*04:05 was in the Japanese population, compared to other populations, which may partly explain the high incidence rate of CT-ILD in the Japanese population.[54] Schwaiblmair *et al*[55] found that in patients with advanced pancreatic cancer treated with gemcitabine and erlotinib, the combination of HLA-B*15:01 and DRB1*15:01 was associated with ILD. Previous studies have shown that gene polymorphism may also be related to DILD.[56–58]

Previous lung diseases

Several studies have shown that previous lung disease was a risk factor for the development of lung toxicity in patients treated with gemcitabine.[59,60] Pre-existing ILD is related to the increased incidence of docetaxel and paclitaxel-related ILD.[50,61,62] Additionally, Sakurada *et al*[63] found pre-existing ILD was a risk factor for chemotherapy-induced ILD. Smoking, decreased lung function, and pre-existing chronic ILD have also been identified as being associated with the occurrence of ILD during gefitinib treatment or chemotherapy.[51] Hotta *et al*[64] found that poor performance status (PS) scores and previous pulmonary fibrosis increased the risk of ILD associated with gefitinib and erlotinib. Poor PS score, smoking history, previous or concomitant ILD, and pleural effusion also increased the risk of crizotinib-related ILD. A recent analysis of nine phase I and II studies of T-DXd found that low oxygen saturation levels and coexisting lung comorbidities were associated with increased CT-ILD.[19] Preexisting ILD, chronic obstructive pulmonary disease (COPD), emphysema, asthma, and obstructive pneumonia are related to the appearance of CIP. Both COPD and ILD have been confirmed to be risk factors for the development of RP.[65,66]

Histological type

A meta-analysis summarizing studies related to docetaxel plus gemcitabine found that patients with lung cancer had a higher incidence of serious CT-ILD than patients with breast cancer.[67] Similarly, a retrospective analysis of patients receiving gemcitabine-based chemotherapy in the Japanese nationwide administrative database showed that lung cancer was associated with a high incidence of CT-ILD.[68] Another meta-analysis by Ma *et al*[69] showed that patients with NSCLC have a higher incidence of ILD related to ICI compared to other cancers. Furthermore, a retrospective study reported that the frequency of ICI-related ILD was higher in squamous cell carcinoma than in adenocarcinoma.[70] A recent study on T-DXd-induced ILD revealed that uterine carcinomatosis (26.47%) and NSCLC (24.77%) were the most common types.[71]

Combination therapy

Drug combinations can have varying effects on lung toxicity. The combination of the same type of drugs may cause similar pulmonary patterns of toxicity, while the combination of different types of drugs may worsen or alleviate it. For example, gemcitabine combined with docetaxel has been shown to increase the incidence rate of CT-ILD.[67] The proportion of ILD induced by ICIs combined with EGFR-TKI is significantly higher than that of either drug alone.[72] Combining PD-1/PD-L1 inhibitors with CTLA-4 inhibitors has been associated with the risk of CT-ILD.[73] However, a meta-analysis showed that compared to single or dual ICI treatments, ICIs plus chemotherapy reduced both all grades and high grades of CT-ILD.[74] A recent meta-analysis of randomized clinical trials showed that TKI combined with bevacizumab reduced the incidence of CT-ILD, while the combination of chemotherapy and bevacizumab did not.[75]

RT subsequent to or in combination with chemotherapy, especially with paclitaxel, can increase the risk of lung toxicity.[76] A retrospective study showed that the incidence rate of RP was 81.7% in patients receiving concurrent chemoradiotherapy, and V20 greater than V30 was identified as a risk factor.[77] Sequential chemoradiotherapy appears to have a higher risk of pulmonary toxicity compared to concurrent chemoradiotherapy.[53] Several studies have confirmed that RT combined with ICIs increased severe lung toxicity.[78] In addition, there is an increased risk of pneumonitis when TKI is combined with RT compared to TKI or RT alone.[79,80] However, other studies have reported no significant increase in pneumonitis incidence in the combination groups.[81,82] It has been suggested that the occurrence of pneumonitis may be influenced by factors such as the timing and sequence of TKI and RT overlap, as well as the specific type of TKI administered.[83–85]

Clinical Features

The onset time of CT-ILD can vary greatly, ranging from hours to years after initiating treatment. The clinical presentation of CT-ILD is often non-specific and CT-ILD may have an insidious onset without any clinical symptoms or may develop acutely with symptoms such as dyspnea, cough, fever, fatigue, chest pain, or hemoptysis.[86] Some cases can progress slowly or rapidly to respiratory failure and can even be life-threatening. Lung auscultation may reveal normal sounds or wet rales or "velcro-like" crackles.[25] Later stages of the disease can be accompanied by signs of right ventricular dysfunction and pulmonary hypertension, such as lower limb edema and jugular vein dilation.[87] There are no distinctive clinical characteristics specifically attributed to the causation of the drug.

Radiographic Features

CT-ILD imaging also shows no specificity, which is usually found in tumor patients during routine imaging examinations. Cleverley *et al*[88] revealed that only 45% of patients with DILD have consistent imaging and histology. However, imaging examination still plays a central role in the diagnosis of CT-ILD. Even in the absence of symptoms, the presence of CT-ILD patients can be detected by imaging examinations, which can also be used to assess the severity of the condition. High-resolution computed tomography (HRCT) is more accurate than conventional chest radiographs in evaluating abnormalities of the lung parenchyma and airway, pattern characteristics, and distribution of lesions, and is more sensitive in the early diagnosis of CT-ILD. For example, one study showed that 23 cases of DILD were abnormal in HRCT, but only 17 cases in chest radiographs.[89] Another study showed that HRCT showed good sensitivity and specificity in diagnosing DILD, especially in organizing pneumonia (OP) and diffuse alveolar damage (DAD).[90] Therefore, in cases of suspected CT-ILD, if the patient's condition allows, it is recommended to undergo HRCT evaluation. HRCT is also essential in the differential diagnosis and follow-up after treatment.

There are many patterns of CT-ILD imaging, and different patterns can be caused by a single drug, or present in the same patient. Some common patterns include non-specific interstitial pneumonia (NSIP), OP, DAD, hypersensitivity pneumonitis (HP), and simple pulmonary eosinophilia (PEo) [Table 1].

Imaging findings of ILD induced by different treatments share similarities, but also present variations. The imaging characteristics of gefitinib-induced ILD can be classified into four patterns: (1) non-specific areas of ground glass attenuation, corresponding to NSIP; (2) multifocal areas of airspace consolidation, corresponding to OP; (3) patchy distribution of ground glass attenuation with thickened interlobular septa, corresponding to PEo; and (4) extensive bilateral ground-glass attenuation or airspace consolidation accompanied by traction bronchiectasis, corresponding to DAD. Among these, pattern 1 is the most frequently observed pattern. Pattern 4 exhibits a higher mortality rate compared to the other patterns.[28,91,92] A newly discovered drug-related lung disease called transient asymptomatic pulmonary opacity was observed in patients receiving EGFR-TKI treatment. This condition resolves spontaneously without the need for specific treatment while patients continue their TKI therapy.

In a retrospective study of 66 patients treated with the mTOR inhibitor everolimus, 14 patients (21%) developed drug-related pneumonitis (OP pattern in eight, NSIP pattern in five, and HP pattern in one).[93] In another study, the classification of mTOR inhibitor-associated pneumonia revealed 16 cases (70%) of OP and seven cases (30%) of NSIP.[94]

Naidoo *et al*[95] proposed five imaging classifications for CIP: OP, ground-glass opacities (GGOs), interstitial pneumonitis, hypersensitivity pneumonitis, and pneumonitis not otherwise specified. GGO is the most common type and is associated with a poor prognosis.[95,96] Among the 20 patients with CIP, the OP pattern was the most

Table 1: Radiologic patterns of cancer therapy-related interstitial lung disease at HRCT.

Patterns	Imaging manifestations at HRCT
NSIP	GGO or patchy consolidation, often with reticular opacities, with or without tractive bronchiectasis; bilateral and symmetric, mainly involving the lower lungs and subpleural areas.
OP	Multifocal patchy consolidation shadow, showing peribronchovascular and/or peripheral distribution, may present with "reversed halo sign".
DAD	The exudation phase showed extensive bilateral GGO and gas cavity consolidation, tractive bronchiectasis, and decreased lung volumes in the fibrotic phase.
HP	Bilateral diffuse GGO and/or poorly defined lobular central nodules, and mosaic attenuation.
PEo	Unilateral or bilateral, non-segmental consolidation or GGO, transient, and migratory.

DAD: Diffuse alveolar damage; GGO: Ground-glass opacity; HP: Hypersensitivity pneumonitis; HRCT: High resolution computed tomography; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; PEo: Pulmonary eosinophilia.

common (n = 13), followed by the NSIP pattern (n = 3), the HP pattern (n = 2), and the DAD pattern (n = 2).[97] The DAD pattern had the highest severity grade, followed by OP, while NSIP and HP had lower severity grades.[97] Although different types of CT-ILD present variations, one common aspect among them is that the DAD pattern has a poor prognosis. The most common types of CT-ILD among different subtypes are OP or NSIP.

Histopathology

The pathologic features of CT-ILD are also non-specific, and diagnosis requires the integration of clinical, laboratory, and imaging information. Cancer therapy may impact multiple compartments and, as a result, can cause overlapping histological patterns of lung toxicity. Several common histopathological patterns were observed including HP, OP, DAD, NSIP, eosinophilic pneumonia, pulmonary hemorrhage, and granulomatous pneumonitis.[87,98]

HP is characterized by cellular bronchiolitis and cellulate-rich inflammation in the surrounding lung tissue, along with scattered non-caseous granulomas.[87,99] OP is identified by the proliferation of fibroblasts in the alveolar cavity producing immature collagen, as well as infiltration of lymphocytes, plasma cells and histiocyte.[87,100] DAD is characterized histologically by the presence of an alveolar cavity lined with hyaluronic membrane, type II alveolar epithelial cells, and fibroblast proliferation, but it is difficult to observe abundant hyaluronic membrane in the acute or exudative phase.[98,100] NSIP histologically shows evenly distributed fibroblastic foci, which may not be obvious or absent; with infiltrations of lymphocytes and plasma cells within the alveolar septum and peribronchial spaces.[87,100,101] Eosinophilic pneumonia is characterized by a large number of eosinophils that fill the alveolar cavity, together with fibrin and some erythrocytes.[99,100]

Diagnostic Criteria and Procedure

The diagnosis of CT-ILD is particularly complicated due to the diverse range of cancer therapies and the varying occurrence time, cumulative dose, and clinical manifestations of lung injury between different patients and treatments. CT-ILD is an exclusive diagnosis, and commonly considered differential diagnoses include lung tumor progression, pulmonary edema, infectious pneumonia, and pulmonary embolism. The diagnostic criteria have been proposed in a previous study[87] and include (1) a history of exposure to drugs that can cause lung injury; (2) clinical, imaging, and histopathological patterns that are consistent with earlier observations of the same drug; (3) exclusion of other possible causes; (4) symptoms improved after withdrawal of the causative drug; and (5) symptoms worsen on rechallenge. Recently, Johkoh *et al*[102] proposed new diagnostic criteria: (1) new parenchymal opacities found on computed tomography (CT) or chest radiography; (2) a temporal association between the presentation and the initiation of a therapeutic agent; and (3) exclusion of other causes of ILD. However, it can sometimes be challenging to completely exclude other causes or potential co-existing factors. Furthermore, since early treatment is crucial for improved outcomes in CT-ILD, a definitive diagnosis, excluding all alternative etiologies, may not always be mandatory prior to initiating steroid treatment, particularly in severe cases.[103] Therefore, patients can be categorized as either definite, probable, or possible according to determinants.

Based on the consensus of DILD published by Kubo *et al*,[86] we summarize the diagnostic procedure for CT-ILD in Figure 2. It is important that patients be thoroughly evaluated before receiving cancer therapy, which has been reported to induce severe ILD, especially for baseline chest imaging findings. Additionally, high-risk patients should be more closely screened and monitored. For new-onset cough, dyspnea, fever, chest tightness, or aggravation of existing respiratory symptoms, CT-ILD should be considered and chest CT (HRCT is recommended) should be performed as soon as possible. CT may facilitate early detection of CT-ILD when it is still in the reversible stage or may help identify other potential causes that could explain the symptoms of the patient.[104]

Bronchoscopy combined with bronchoalveolar lavage (BAL) has no definite value in the diagnosis of CT-ILD, but it can help rule out an infection, alveolar hemorrhage, or tumor progression.[105,106] Solazzo *et al*[107] found that among 26 ILD cases, 12 were from infection and 14 were from DILD. The total number and classification count of BAL cells in different CT-ILD patterns varied but without specificity.[108] However, the American Thoracic Society states that when combined with clinical information and chest imaging, BAL cell patterns and other characteristics provide useful information for the diagnosis of patients with suspected DILD,[109] especially for lymphocytosis in HP.[110] Therefore, BAL combined with bronchoscopy is recommended if the patient's condition allows.

Whether a patient with suspected CT-ILD should perform a lung biopsy depends on the clinical context: If the patient cannot be definitively diagnosed after multidisciplinary team (MDT) discussions on clinical, radiological, and bronchoscopic information, or if a vastly different treatment strategy is required according to the differential diagnosis, a lung biopsy may be necessary.[100] However, this decision requires full consideration of benefit-risk analysis, expected outcomes, and consultation with the patient. Evidence for the use of biopsy to diagnose CT-ILD is limited, with only small sample studies reported.[90,111] A study of 418 surgical lung biopsies (SLBs) diagnosing ILD revealed that a specific diagnosis was made in 88.0% of cases with a low incidence of postoperative complications and mortality,[112] with similar results reported in another study.[113] However, SLB should be approached with caution in patients with immunocompromise, mechanical ventilation dependence, or severe respiratory dysfunction, as such patients may have an increased mortality rate.[114] In a recent meta-analysis that included 43 studies, it was found that transbronchial lung cryobiopsy (TBLC) and SLB had diagnostic rates of 76.8% and 93.5%, respectively, for ILD. Additionally, TBLC demonstrated a lower mortality rate compared to SLB.[115] TBLC may be considered an acceptable alternative to SLB in diagnosing

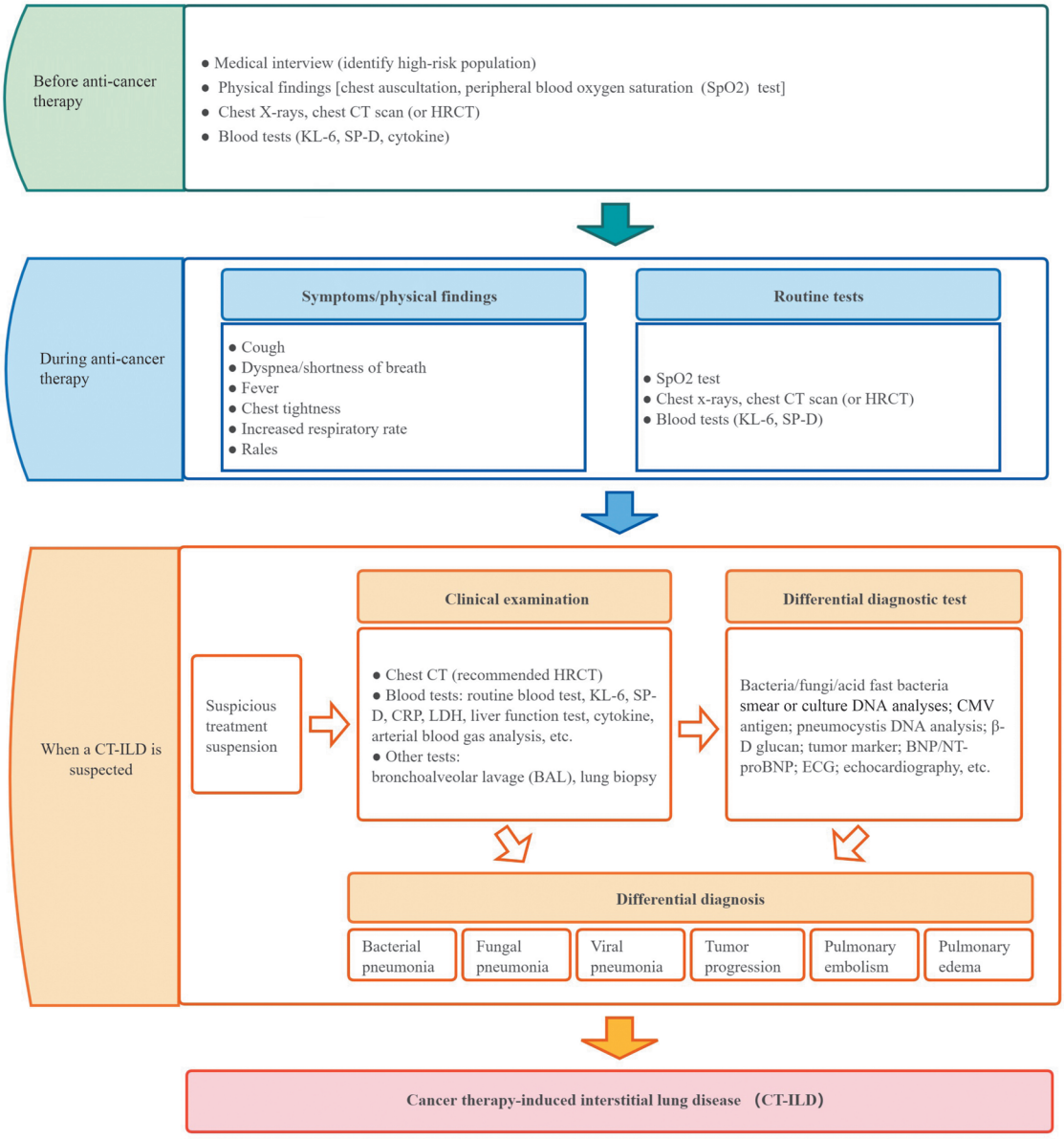

Figure 2: Flow chart of diagnosing CT-ILD. BAL: Bronchoalveolar lavage; BNP: Brain natriuretic peptide; CMV: Cytomegalovirus; CRP: C-reactive protein; CT: Computed tomography; CT-ILD: Cancer therapy-related interstitial lung disease; ECG: Electrocardiogram; HRCT: High resolution computed tomography; KL-6: Krebs von den Lungen-6; LDH: Lactate dehydrogenase; NT-proBNP: N-terminal pro b-type natriuretic peptide; SpO2: Oxygen saturation; SP-D: Surfactant protein-D.

undetermined ILD.[116] Compared to conventional transbronchial lung biopsy (TBLB), TBLC offers a larger tissue yield but carries a higher risk of complications.[117] TBLB combined with HRCT can improve the diagnostic accuracy of ILD.[118] A retrospective study of 245 cases of ILD found that bronchoscopy caused a change in the diagnosis of 58 patients (23.7%). Compared to BAL alone, combining BAL with TBLB increased the diagnostic rate from 21.8% to 34.1% ($P = 0.027$).[119] In clinical practice, the combination of TBLB and BAL is more commonly used for the diagnosis and differential diagnosis of CT-ILD. For patients with peripheral lesions, ultrasound or CT-guided lung biopsy can be considered. While not essential for the diagnosis of CT-ILD, a pathological biopsy can provide valuable guidance for differential diagnosis and pathological classification. Additionally, it is also crucial in evaluating tumor progression and subsequent efficacy. However, biopsy alone is not the definitive diagnostic gold standard, but rather it should be considered within the context of MDT discussions for diagnosis.

MDT discussions involving the integration of clinical, radiological, and pathological information are recommended to enhance confidence in the diagnosis of CT-ILD. One study has shown that MDTs changed the original histological diagnosis by 30% and improved the diagnosis from probable to confident by a further 17%.[120] MDTs have higher reliability in the diagnosis of ILD than radiologists or clinicians alone. A joint statement from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) states that the diagnosis of ILD recommends a dynamic diagnosis by a respiratory

physician, a radiologist, and a pathologist.[121] Therefore, we recommend that the diagnosis, treatment, and management of CT-ILD require the joint participation of respiratory physicians, oncologists, radiologists, pathologists, and pharmacists to form the MDT. This approach can improve the accuracy of the diagnosis of CT-ILD and jointly develop rational treatment strategies.

Management

Grading management

CT-ILD was graded according to clinical symptoms and imaging results [Table 2].[122,123] Severity grading facilitates hierarchical management. Treatment for suspected CT-ILD should, in principle, be discontinued. Treatment of CT-ILD is primarily based on glucocorticoids [Figure 3].

In grade 1 patients, it is advisable to suspend the causative treatment until there is evidence of radiographic improvement, and closely monitor the patient's condition [Figure 3]. In general, it is usually appropriate to continue the original treatment dosage. For the challenges of ADCs, it is necessary to consider the duration of resolution (same dose if ≤28 days, dosage reduction if >28 days) and the specific medication (permanent discontinuation of trastuzumab emtansine).[45,124] If there is no improvement, patients should be treated as grade 2.

In grade 2 patients, cancer therapy should be temporarily suspended, and a treatment regimen of 0.5–1 $mg \cdot kg^{-1} \cdot d^{-1}$ of prednisone (or equivalent) should be started [Figure 3]. In patients who have been receiving ICI, it is recommended to immediately administer 1–2 $mg \cdot kg^{-1} \cdot d^{-1}$ of prednisolone (or equivalent).[125] For patients who have previously received ADCs, prompt administration of prednisolone at a dose of ≥1 $mg \cdot kg^{-1} \cdot d^{-1}$ is recommended.[124] In most cases, cancer treatment is suspended until resolution to grade 1 or lower, but for patients with ADC-ILD, it is recommended to permanently discontinue ADC.[45,124] If there is no improvement after 48–72 h of prednisone, treat it as grade 3.

In severe cases (≥grade 3), it is recommended to permanently discontinue cancer therapy and receive prednisone (or equivalent) at a dose of 1–2 $mg \cdot kg^{-1} \cdot d^{-1}$ [Figure 3]. Patients who have been receiving ADCs should be promptly treated with initial pulse therapy with methylprednisolone at a dose of 0.5–1 g/day for at least 3 days, followed by prednisone treatment at a dose of 1.0 $mg \cdot kg^{-1} \cdot d^{-1}$.[45] Oxygen supplementation is recommended in the presence of signs or symptoms of hypoxemia. In cases where an underlying infection cannot be definitively ruled out or to prevent secondary infections, the consideration of empirical anti-infection is warranted. In corticosteroid-refractory cases who have been receiving ICI and ADCs, treatment with additional immunosuppressive agents such as infliximab, mycophenolate mofetil, cyclophosphamide, or intravenous immunoglobulin can be considered.[45,125] It should be noted that the evidence for the use of these medications in CT-ILD is limited.

Typing management

A prospective study from the French REISAMIC registry reported that CIP has the highest death rate, higher than myocarditis.[6] The lung is a unique organ directly exposed to the external environment, serving as both the site of gas exchange and a portal for microorganisms to invade. Consequently, most patients will be infected with various pathogenic microorganisms simultaneously or exhibit a secondary infection after lung injury caused by various physicochemical factors related to cancer therapy. Treatment of lung injuries may be more complex than that of other organs. There have been reported cases of multiple TKI or chemotherapy-related ILD and RP complicated with a secondary infection.[126–129] A recent study[130] has proposed the clinical types of CIP, including the mixed type, which refers to CIP complicated with infectious pneumonia, tumor progression, or RP. The authors also proposed the induced type (with different etiologies, such as RT induction, cytomegalovirus, or Epstein-Barr virus reactivation), and pure type (idiopathic, with or without autoimmune disease). We suggest that other CT-ILD may also have a mixed type, for which additional treatment should also be provided to treat comorbidities in addition to CT-ILD, such as anti-infective and anticancer therapy [Figure 3]. Regarding anticancer treatment, patients with CT-ILD may have a compromised health status and limited options for therapy. In such cases, the use of less toxic antiangiogenic agents, such as anlotinib and bevacizumab, can be considered. These medications effectively suppress vascular endothelial growth factor (VEGF), reducing vascular permeability and alleviating pulmonary exudation. In an interleukin-induced pneumonitis model, the anti-VEGF antibody demonstrated protection against vascular-to-alveolar leakage of protein

Table 2: Grading systems of CT-ILD.

Grades	Symptoms	Imaging
Grade 1	Asymptomatic; only clinical or diagnostic observations, no treatment required; no intervention needed.	Confined to one lobe of the lung or <25% of lung parenchyma.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	Involves more than one lobe of the lung or 25–50% of lung parenchyma.
Grade 3	Severe symptoms; hospitalization required; limiting self-care ADL; oxygen indicated	Involves all lung lobes or >50% of lung parenchyma.
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., intubation and ventilation)	

ADL: Activities of daily living; CT-ILD: Cancer therapy-related interstitial lung disease.

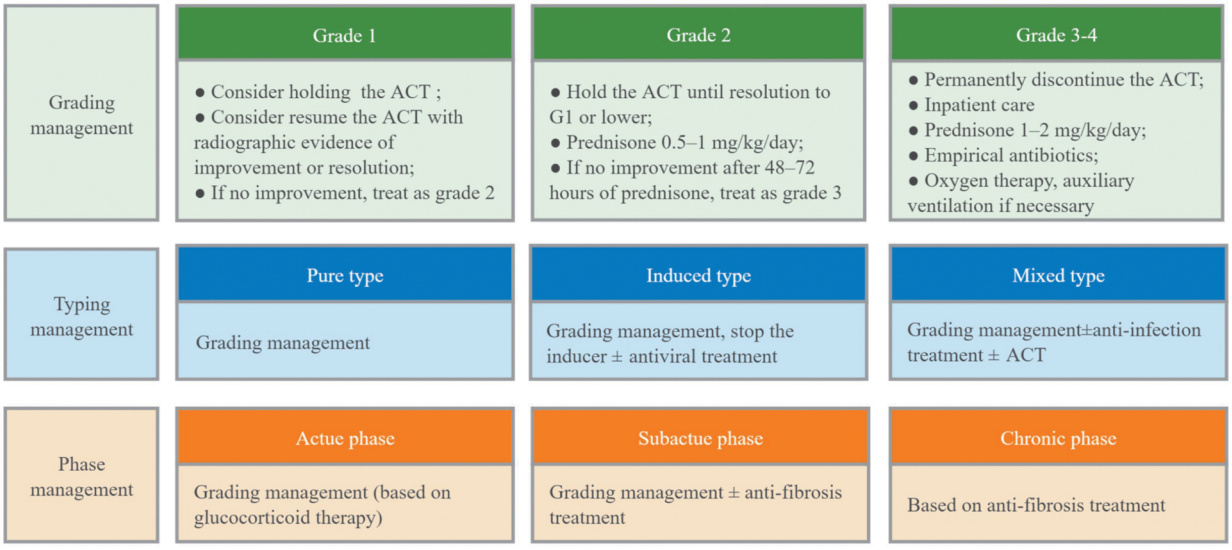

Figure 3: The grading, typing, and phase management of cancer therapy-related ILD. ACT: Anti-cancer treatment; ILD: Interstitial lung disease.

and fluid caused by PD-1 signal blockade.[131] A clinical case provides evidence for the favorable therapeutic effect of combining bevacizumab with corticosteroid treatment in ALK-ILD.[132] In the IMpower150 trial, patients with pneumonitis who did not receive bevacizumab had a reported "Not recovered/Not resolved" outcome rate of 29.4%, while those who received bevacizumab had a significantly lower rate of 9.1%.[131]

RRP is a rare and special CT-ILD mainly found in patients' previously irradiated lungs after treatment with inciting agents. Extensive research has shown that a range of cancer therapies, including chemotherapy,[133] targeted therapy,[84] and IO[4] can cause RRP. Recent studies have also suggested a possible association between RRP and vaccination[134,135] as well as coronavirus disease 2019 (COVID-19) infection.[136] Based on these findings, we propose that other CT-ILDs may also have an induced type, which is characterized by alterations in the immune microenvironment induced by drugs, viruses, or RT, and the addition of other cancer therapies, which may contribute to the development of ILD. Taken together, we recommend discontinuing potential inducers along with the culprit cancer therapy in cases of the induced type. Furthermore, antiviral therapy should be considered if virus induction is suspected [Figure 3].

Phase management

The dynamic process of lung tissue injury and repair in CT-ILD shows phased characteristics in imaging and pathology over time, owing to differences in treatment time, the severity of CT-ILD, and therapeutic effect. Previous studies have identified three stages of RP: early stage, intermediate stage (acute pneumonitis), and late stage (pulmonary fibrosis).[46,137,138] Min *et al*[139] proposed that TKI-LID undergoes an acute and chronic process, with an acute phase characterized by DAD. With the help of T lymphocytes and macrophages, the acute injury appears to progress to the chronic phase. A recent study has revealed that patients treated with ICI develop chronic pneumonitis in addition to acute pulmonary toxicity.[140] Recently, Zhou *et al*[141] proposed a clinical phase of CIP: acute, subacute, and chronic phases. Another study also demonstrated that a proportion of patients will develop chronic ICI pneumonitis.[142] Wijsenbeek *et al*[143] have classified ILD into acute, subacute, and chronic phases. Therefore, we suggest that other CT-ILDs may also have acute, subacute, and chronic phases, although not all patients experience all three phases. Some patients who receive timely treatment in the acute phase and recover quickly may not enter the chronic phase.

Treatment for CT-ILD in the acute phase should be dominated by glucocorticoid-based anti-inflammatories. From the mechanisms discussed earlier, it is evident that various forms of CT-ILD involve the release of cytokines, particularly during the acute phase. In patients refractory to corticosteroids during this stage, the utilization of cytokine-targeting drugs, including IL-1, IL-6, and TGF inhibitors, may represent a potential treatment approach. A study demonstrated clinical improvement in 27 out of 34 cases (79.4%) of irAEs treated with IL-6 receptor antagonist tocilizumab.[144] ROS plays a crucial role in the occurrence and progression of CT-ILD, and antioxidants and certain natural adjuvants may have a protective effect.[23]

In the chronic phase, corticosteroid treatment shows limited effectiveness for patients, and prolonged use of glucocorticoids may lead to increased adverse reactions. Fibrosis is a prominent feature during this phase, and patients in this stage may benefit from antifibrotic therapies. A small-sample prospective study indicated that pirfenidone may improve exercise capacity in patients with radiation-induced lung fibrosis.[145] There have also been case reports describing the use of pirfenidone or nintedanib used to treat ILD caused by TKIs or ICIs.[146] Table 3 summarizes the potential personalized treatments for CT-ILD patients.

Table 3: Personalized treatment regimens for the management of CT-ILD.

Targets	Proposed drugs	Applicable phase and types
VEGF(R)	Bevacizumab; anlotinib	Acute/subacute; TKI-ILD,[132] CIP[131]
ROS	Amifostine	Acute; RP[148]
TNF	Infliximab	Acute; CIP,[149] ADC-ILD[124]
TGF-β	Metformin	Acute; TKI-ILD[150]
IL-6	Tocilizumab	Acute; CIP[144]
Anti-fibrotic drugs	Pirfenidone; nintedanib	Subacute/chronic; RP,[151] TKI-ILD,[146] and CIP[147]
Immuno-suppresive agents	Mycophenolate mofetil; cyclophosphamide; intravenous immunoglobulin	Acute/subacute; CIP,[149] ADC-ILD[124]

ADC: Antibody-drug conjugates; CIP: Checkpoint inhibitor-related pneumonitis; CT-ILD: Cancer therapy-related interstitial lung disease; IL-6: Interleukin-6; ILD: Interstitial lung disease; ROS: Reactive oxygen species; RP: Radiation pneumonitis; TGF-β: Transforming growth factor-beta; TKI: Tyrosine kinase inhibitor; TNF: Tumor necrosis factor; VEGF(R): Vascular endothelial growth factor receptor.

Conclusions

The prevalence of CT-ILD has increased with the increasing use of cancer therapies. Accurate identification and diagnosis of CT-ILD pose challenges, and the treatment options are limited. The implementation of grading management has proven insufficient to address the current concerns, prompting the proposal of a more personalized approach utilizing typing and phase. Future research on improving diagnostic methods may help in the timely detection of CT-ILD, such as radiomics-based diagnosis and home monitoring. More effective treatment may involve exploring and understanding the mechanisms of CT-ILD.

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Conflicts of interest

None.

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