LITERATURE REVIEW

How to Manage Lung Injury Related to Cancer Therapy?

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ABSTRACT

Modern technology has improved our understanding of cancer biology, especially anti-cancer medicines from cytotoxic chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Nevertheless, these treatments can result in significant pulmonary toxicities, including interstitial lung disease (ILD) and radiation-induced lung injury (RILI), which can result in a high rate of morbidity and mortality despite being less severe than injuries to other organ systems. Lung injury mechanisms occur through various pathways, such as immune-mediated damage and oxidative stress. Through clinical history and examination, imaging techniques such as high-resolution computed tomography (HRCT), and the necessity of eliminating other possibilities of respiratory symptoms, lung injuries due to cancer therapies can be identified. The management strategies are based on the severity of the condition and may include discontinuing the responsible agent, corticosteroid treatment, and supportive care. The challenge is early identification and management of these lung injuries due to the variability in patient responses and the lack of comprehensive guidelines, so there is a need for awareness in monitoring lung health in cancer patients undergoing therapy.

INTRODUCTION

Technological advancements have expanded our understanding of cancer biology, particularly anti-cancer therapies that range from conventional cytotoxic chemotherapy to immunotherapy regimens. Every type of cancer therapy is limited by a range of toxic effects that can specifically affect the pulmonary parenchyma, pleura, and/or pulmonary circulation. These disorders in the lungs can result in high morbidity and mortality, although the adverse effects are relatively less severe than those of other organ systems.[1]

The efficacy of cancer therapy is restricted by lung injuries that are associated with cancer therapy. Various histopathological lesions affecting the pulmonary parenchyma, pleura, airways, and/or blood vessels are associated with radiation to the thoracic region and cancer pharmacotherapies, including conventional chemotherapy, molecular targeted agents, and cancer immunotherapy. Injury patterns can be unpredictable and idiosyncratic, varying significantly from one agent to another. It is also possible for lung injury patterns to vary within specific drug categories. In the majority of cases, early identification of clinical signs can result in a favorable prognosis, as drug-induced toxicity in the thoracic cavity is less prevalent. Failing to identify early clinical signs, however, can be irreversible and fatal.[1,2] It can be challenging to identify and manage lung injuries that are the result of a variety of cancer therapies on account of the patient's condition, comorbidities, the effects of malignancy, and the limited treatment responses. Additionally, the availability of specific guidelines for pulmonary injuries resulting from cancer therapy is restricted. The primary focus of extant therapy guidelines is on managing side effects associated with immunotherapy; however, there are still inconsistencies in current recommendations.[3]

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The underlying mechanisms and management of pulmonary injuries resulting from cancer therapy will be the subject of this literature review. Cancer therapies that will be examined include targeted therapy, chemotherapy, immunotherapy, and radiation therapy.

DEFINITION OF LUNG INJURY DUE TO CANCER THERAPY

Cancer biology developments led to thoracic radiation, chemotherapy, molecular targeted therapy, and cancer immunotherapy. However, lung damage related to the therapy is often a barrier to cancer treatment success. Interstitial lung disease (ILD) is a common cancer-related lung injury[1] and is characterized by particular clinical, radiological, and non-specific pathological patterns resulting from inflammation and lung fibrosis. Many factors can cause ILD, including connective tissue illnesses and environmental and iatrogenic factors. Drug-induced interstitial lung disease (DILD) in cancer patients is mainly induced by cytotoxic chemotherapy, targeted therapy, and immunotherapy.[3,4]

Radiation therapy induces radiation-induced lung injury (RILI), which causes acute radiation pneumonitis and persistent radiation pulmonary fibrosis. Early or progressive radiation toxicity can induce asymptomatic or severe symptoms. The Radiotherapy Oncology Group (RTOG), Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and Southwest Oncology Group (SWOG) classify symptoms by severity. The RILI regulates radiation dosages for lung, breast, and lymphoma patients.[5,6] Immunotherapy may induce pneumonitis, which has many overlapping pulmonary symptoms.[7] Meanwhile, targeted and cytotoxic therapy is also reported to cause noninfectious pulmonary parenchyma, pleura, and vascular issues.[1]

TYPES OF LUNG INJURIES DUE TO CANCER THERAPY

A unique toxicity spectrum limits each type of cancer therapy and can target the pulmonary parenchyma, pleura, and/or pulmonary circulation.[1] The time of lung injury can differ significantly based on the medications used and individual patient characteristics. Symptoms may manifest over weeks to months following the initiation of medication; however, the onset of symptoms varies by particular therapy. It can be categorized as acute (occurring within hours to days of exposure), early (during the first 6 months of exposure), and late (6 months or more after exposure) phases.[8] The following will explain lung injuries caused by some primary cancer therapy modalities.

A. LUNG INJURY DUE TO RADIATION

One of the main challenges in providing effective radiation therapy (RT) is the occurrence of side effects, particularly lung injuries caused by radiation (known as RILI). It includes two main conditions: radiation pneumonitis (RP) and radiation fibrosis (RF). The occurrence of RILI is found to be highest in patients with lung cancer (5-25%), followed by mediastinal lymphoma (5-10%) and breast cancer (1-5%). Risk factors for RILI consist of factors contributing to the risk of radiation exposure ($\geq$ 30% of lung volume receives $\geq$ 20 Gy, $\geq$ 65% of lungs receive $\geq$ 5 Gy, average lung dose $\geq$ 20 Gy, absolute lung volume spared < 5 gy < 500 cc or the target location is in the lower lobe), disease risk factors (relapsed or refractory disease, supraclavicle area, bulky disease, chemotherapy, or re radiation), and patients risk factor (> 50 years of age, autoimmune diseases, ILD, smokers or having a history of smoking and chronic obstructive pulmonary disease [COPD]).[5,6]

Pathophysiology of Radiation Lung Injury

Radiation destroys tissues directly or indirectly. Ionizing radiation can cause direct damage to deoxyribonucleic acid (DNA). Before DNA damage occurs, cell water molecules create excess reactive oxygen species (ROS) like superoxides, hydrogen peroxide, hydroxyl radicals, and nitrogen species (NGS) from ionized radiation, indirectly damaging DNA. ROS damage to mitochondrial DNA can cause protein carbonation, lipid peroxidation, increased oxidative metabolism, spontaneous gene changes, and neoplastic transformation. ROS and DNA damage increase intracellular signaling. Various signaling pathways are involved, including TGF-β, PDGF, and IL-1.[9–11] Radiation damages epithelial and endothelial cells, lowering alveolar protection and, within days or weeks, inflammation, vascular permeability, and cytokine release increase. Hypoxia from macrophage accumulation and activation causes ROS, RNS, and proinflammatory, profibrogenic, and proangiogenic cytokines that cause persistent radiation injury. Radiation-induced changes have five phases based on exposure time.[6,12]

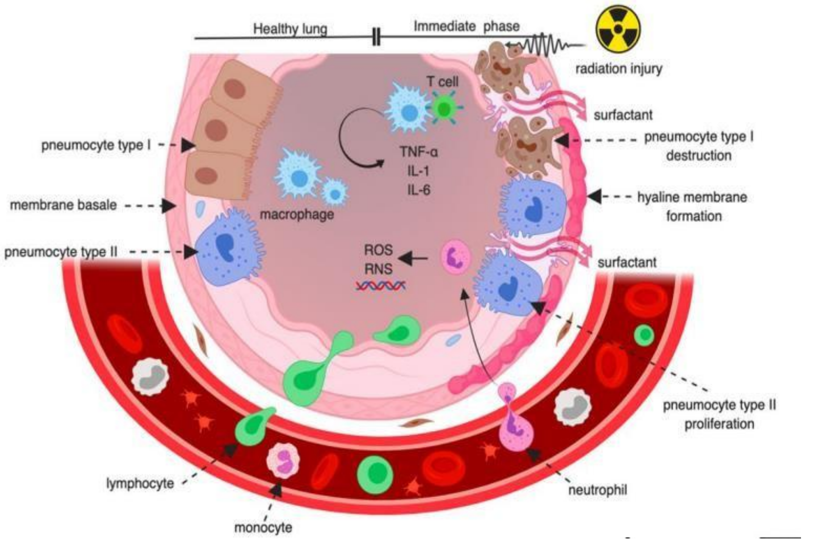

Figure 1. Early phase of radiation lung damage (cytokine release and oxidative damage to the lungs occur)[6]

Vascular congestion causes leukocyte infiltration, type I pneumocyte apoptosis, and intra-alveolar edema in the first phase, which begins a few hours to a few days after radiation (Figure 1). Within two weeks of RT, TNF-α, IL-1, IL-6, KL-6, PDGF-β, and bFGF are released as the initial cytokines. The second phase activates 6-8 weeks post-radiation, causing DNA oxidative damage, hypoxia, decreased pulmonary perfusion, and elevated TGF-β1 expression.[6]

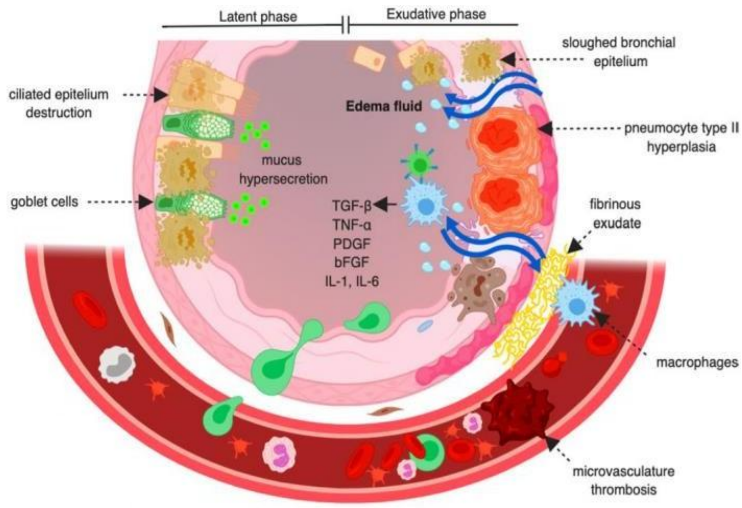

Figure 2. Latent (second phase) and exudative (third phase) of radiation lung injury. The latent phase increases secretion; the exudative phase causes alveolar collapse, pulmonary capillary constriction, and microvascular thrombosis.[6]

Figure 2 displays radiation injury's second and third phases. In the latent phase, respiratory goblet cells grow, and ciliary cells malfunction, increasing secretion. It causes tracheobronchial hypersecretion and alveolar epithelium and endothelium damage. Third, clinical or exudative RP follows RT for 3-12 weeks. Epithelial and endothelial release causes alveolar collapse, pulmonary capillary constriction, and thrombosis; hyaline membranes arise from pneumocyte desquamation and fibrin-rich exudate. Restoration involves type II pneumocyte replication and alveolus basal membrane re-epithelialization. Figure 3 depicts phases four and five. The hyaline membrane dissolves in stage four. Alveolar wall fibroblasts generate collagen. TGF-β1 production is crucial for fibroblast influx and myofibroblast conversion, causing lung fibrosis. Chronic lung illnesses persist due to proatherogenic and proangiogenic substances released by hypoxia.[6] Radiation may cause fibrotic stage 5-6 months later, characterized by pneumocyte hyperplasticity, myofibroblast proliferation, and extensive collagen deposition in the pulmonary interstitium and alveolus. Deposits constrict the alveolar cavity and reduce lung capacity.[6,13]

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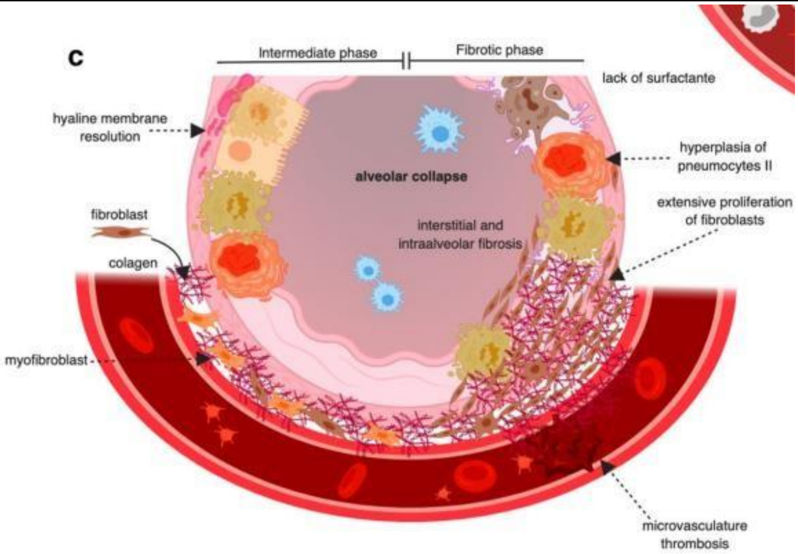

Figure 3. Phase 4 and 5 radiation-induced lung injury (in phase 4, there is a solution of the hyaline membrane; in the fibrotic or phase 5, there is a collapse of the alveolar cavity and a decrease in lung volume)[6]

Assessment of Lung Injury Due to Radiation

Clinical and radiological features define RP. Before diagnosing, other conditions should be ruled out, especially deterioration of disease or infections. The most common symptoms are found to be dry cough and mild–severe dyspnea. Patients may also experience low-grade or severe fever (<10%). The pulmonary physical examination can include normal, consolidated, pleural rub, or adventitious lung sounds.[5,6] Dyspnea increases months after radiation-induced pulmonary fibrosis (PF) lung scarring. Tachypnea and cyanosis indicate illness progression while cor pulmonale and pulmonary hypertension can result from RP and PF.[5]

There are no specific laboratories or imaging of RILI. To rule out other causes a complete blood count and differential count is required. Thoracic CT detects RILI better than conventional imaging due to early ground-glass attenuation, advanced patchy consolidation, linear scarring with consolidation, and loss of lung volume during fibrosis.[5] Several researchers stage RILI by clinical symptoms and imaging for treatment. The most common adverse event classification is Common Terminology Criteria for Adverse Events (CTCAE) 5.0. At stage 1 RILI, asymptomatic patients with pulmonary fibrosis have <25% lung volume. Stage 2 RILI is a symptomatic patient presence of pulmonary hypertension, with 25-50% PF related to hypoxia. Significant symptoms, such as hypoxia, right heart failure, and pulmonary fibrosis >50-75%, characterize stage 3 RILI. Life-threatening respiratory disorders, hemodynamic/pulmonary complications requiring intubation and ventilation, and >75% pulmonary fibrosis and severe honeycombing characterize stage 4 RILI. Stage 5 is death of the patient.[9]

Management of Lung Injuries Due to Radiation

The management of RILI is carried out according to the condition state. Stage 1 RILI patients rarely need treatment, but symptom monitoring can detect worsening. These patients temporarily stop RT and are monitored every 2-3 days. Patients with stage ≥ 2 RILI should postpone cancer treatment. Comprehensive treatment includes anti-inflammatory and symptomatic medications. They may receive antibiotics and prophylaxis for gastrointestinal stress ulcers. Stage ≥ 3 RILI requires immediate hospitalization and discontinuation of RT.[9,14]

Stage RILI ≥ two needs glucocorticoids, which inhibit proinflammatory receptors such as cytokines and chemokines. Oral prednisone, 0.5-1 mg/kg/day, treats mild symptoms, while intravenous methylprednisolone 2-4 mg/kg/day is given in severe symptoms for over six weeks. After symptoms and imaging improve, the drug dose should be lowered to avoid rebounding.[9] The American Society of Clinical Oncology and the Society for Immunotherapy of Cancer recommend a dose of 1–2mg/kg/day prednisone for grade 2 RILI and 1–2mg/kg/day intravenous methylprednisolone for grade ≥3 RILI, tapered off over 4–6 weeks. Meanwhile, The European Society for Medical Oncology considers 2-4mg/kg/day methylprednisolone (or equivalent) for RILI class ≥3, tapering off over six weeks.[15]

Several drugs for RILI have been introduced, and some research suggests mesenchymal stem cells (MSC) block myofibroblasts and inhibit lung fibrosis. Pentoxifylline (Ptx) derivate ethyl xanthine reduces platelet aggregation, increases microvascular blood flow, and may reduce RILI. In randomized clinical studies by Yan Y et al., 1,200 mg/day Ptx was found to reduce RILI side effects. Vitamin E and Ptx combination also helped post-radiation pulmonary fibrosis. Macrolide antibiotic azithromycin is an immunomodulator and anti-inflammation: azithromycin decreases inflammation by reducing LPS-induced MDC via JNK, NF-κB p65, and IP-10/CXCL10 pathways. Azithromycin also enhances macrophage polarization, diminishes neutrophil effect, prevents autophagosome clearance, and lowers pro-fibroblast and proinflammatory cytokines (IL-1β, IL-6, TNF-α, TGF-β1, but the dosage is unknown. Other drugs are angiotensin-converting enzyme inhibitors (ACEI) and amifostin: ACEI reduces lung collagen deposition and fibrosis while, amifostin reduces radiation-induced DNA damage and tissue oxygen.[9]

B. LUNG INJURY DUE TO CHEMOTHERAPY

Chemotherapy improves survival and quality of life but has adverse effects. Chemotherapy problems mainly affect the lungs, and can be caused by ,medication toxicity, immunosuppressive infections, and immune system-mediated tissue damage. The impact of chemotherapy on the lungs might be immediate or chronic. Bleomycin, methotrexate, taxanes, cyclophosphamide, gemcitabine, and bevacizumab cause pulmonary toxicity. Other than clinical evaluation in respiratory-symptomatic patients and radiological monitoring, chemotherapy-induced lung harm cannot be prevented.[16,17]

Mechanism of Lung Injury Due to Chemotherapy

In the 1960s, the toxicity of bleomycin was investigated. Bleomycin was found to cause 40-45% lung damage and 1-3% fatal outcome. Risk factors include age, cumulative dosage, decline in glomerular filtration rate (GFR), and increased creatinine. ROS-induced bleomycin hydrolase inactivation may cause inflammatory cytokines release and lung fibrosis. DNA strand breaks damaged chromosomes, causing bleomycin-sensitive lung injury. A similar mechanism of proinflammatory lung injury is also seen in patients who receive methotrexate (MTX) and cyclophosphamide. Methotrexate boosts free radicals, activating p38 mitogen-activated protein kinases (MAPK), mediators of inflammation and lung fibrosis to augment interleukin responses, while, cyclophosphamide increases the inflammation cascade by activating the TGFβ, fibronectin, and procollagen in response to DNA damage and oxidative stress.[2]

For nearly 40 years, DNA-targeting mycomycin C has killed bacteria and cancer cells. The drug also forms ROS and other highly reactive species in tissue and causes apoptosis and tissue injury. Mitomycin C can cause interstitial pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease in cancer patients. GCN2 and SMAD signaling pathway suppression by mitomycin C may damage the lungs. Actinixin D, an anti-cancer drug, also damages the lungs by inhibiting DNA replication and RNA chain elongation. Lung injuries have also been reported in patients taking platinum-based chemotherapy. Cisplatin can increase free radicals and cause eosinophilic pneumonia. Pulmonary fibrosis is also found in carboplatin. Oxaliplatin also can cause interstitial pneumonitis and lung fibrosis while gemcitabine is associated with complications in the lung, like dyspnea, pulmonary edema, PVOD, pleural effusion, diffuse alveolar damage, interstitial pneumonitis, pulmonary fibrosis, pulmonary vascular damage, and inflammation and induces the release of cytokines and interleukins. TNF-α is directly linked to lung toxicity severity in research. Chemotherapeutic taxanes also cause lung injury. Paclitaxel and docetaxel are common taxane drugs. Paclitaxel causes interstitial pneumonitis and lung fibrosis as well as immunological (type IV hypersensitivity reactions) and non-immunological lung damage while docetaxel causes interstitial pneumonitis, bilateral and widespread opacity, and respiratory failure. The mechanism is unknown; however, patients' steroid reactions reflect immunological causes.[18]

Lung Injury Assessment Due to Chemotherapy

Toxicity is diagnosed through clinical, radiographic, and histopathological examination, although no pathognomonic abnormality exists. The symptoms are frequently non-specific and changeable. Non-productive cough, dyspnea, hypoxia, and low-grade fever are the most prevalent drug-related symptoms weeks to months later. Clinical findings include a pulmonary infiltrate, and fulminant illness can lead to ARDS or respiratory failure.[1,19] The medication determines whether effects appear acutely (within hours), early (within six months), or late. High-resolution computed tomography (HRCT) can show abnormalities; however, the results are not specific. The most prevalent CT findings are alveolus-interstitial mixture abnormalities, such as reticular marking, septal thickness, and bilateral ground glass abnormalities (typically asymmetrical). During hematological exams, leukocytes, blood sedimentation rate, and C-reactive protein (CRP) can increase. Bronchoalveolar lavage can be performed to rule out other causes.[1]

Management of Lung Injury Due to Chemotherapy

Like other medication-induced lung injury, chemotherapy-induced lung injury is treated by discontinuation of the causative drugs. Steroids and broad-spectrum antibiotics are recommended for most individuals. The ideal dose, period, and duration of steroid treatment under these conditions are unknown.

However, 0.5-1 mg/kg/day prednisone or similar is usually administered for 8-12 weeks. In chemotherapy patients with respiratory problems, serology, culture, and bronchoscopic investigations are needed to rule out infection. Therapy for chemotherapy-induced lung injury varies greatly. Some individuals recover after stopping chemotherapy and high-dose steroids while others require intubation and mechanical ventilation due to increasing respiratory failure despite steroid treatment.[19–21]

Several studies have examined antioxidants in cancer treatment. Because it protects normal cells, antioxidant supplementation is said to be used as prevention and therapy, even in small doses. High-dose antioxidants can limit cancer cell growth without affecting normal cells. Numerous studies have shown that antioxidants do not interfere with chemotherapy, enhance its cytotoxic effects, protect normal tissues, and improve patient survival and therapeutic response. However, the impact of antioxidants on chemotherapy-induced lung injury needs further study.[22]

C. LUNG INJURY DUE TO IMMUNOTHERAPY

Immunotherapy is one of the standard treatments for metastasized cancers. However, significant side effects include interstitial pulmonary toxicity. PD-1, its ligand, and CTLA4 are immunological checkpoint molecules because they suppress host immunity. Antibodies that suppress PD-1, PD-L1, or CTLA-4 activate the immunological response. Immunotherapy medications have immune-related adverse events (irAEs) and differ from cytotoxic drugs. Interstitial pneumonia caused by immune cells is rare yet severe. The incidence of toxicity in lung cancer immunotherapy is found to be higher than in other cancers.[2,23] Approximately 13% of anti-PD-1 drugs cause respiratory irAEs. Immune-associated pneumonitis is the most frequent respiratory irAE and is noninfectious lung inflammation characterized by interstitium and alveolar infiltrates.[24]

Mechanism of Pneumonitis Due to Immunotherapy

Three processes proposed by Postow et al. may cause IrAEs. First, the activity of T-cells against cross-antigens expressed in tumor and normal tissue increased. IR-pneumonitis patients' BAL samples exhibited increased lymphocytosis, primarily CD4+ T cells and central memory T cells, and lower Treg CTLA-4 and PD-1 expression, according to Suresh et al. PD-1+ and CTLA-4+ Tregs inhibit CD8+, conventional T, and macrophage inflammation. Increased alveolar T cells and decreased Treg phenotypic anti-inflammatory characteristics can dysregulate T cell activity. The second mechanism is an increase in autoantibodies, which can cause irAEs. Studies show autoantibodies in autoimmune illnesses can produce irAEs. However, the relationship of these autoantibodies is still being studied.[25,26] Third, irAEs increase inflammatory cytokines. Atezolizumab-treated ir-pneumonitis patients have high CRP and IL-6. Severe ICI toxicity is associated with increased cytokine expression.[26,27]

Lung Injury Assessment Due to Immunotherapy

Non-specific immunotherapy-associated pneumonitis symptoms range widely. Therefore, patient care team members must be suspicious and vigilant. Dyspnea and cough predominate, while fever and chest pain are rare. One-third of patients start asymptomatic. Hypoxia can worsen quickly and, although rare, symptoms may resemble asthma or allergic bronchopulmonary aspergillosis. Potential pneumonitis patients should undergo a physical assessment and examination.[28,29]

Table 1. Classification of pneumonitis severity based on CTCAE version 5 and ASCO 2018 guidelines.[2]

Guideline	G1	G2	G3	G4
CTCAE version 5	Asymptomatic, clinical, or diagnostic observations solely; intervention not warranted.	Symptomatic, medical intervention is necessary, as it restricts instrumental ADL.	Severe symptoms, limiting self-care ADL, oxygen indicated	Critical respiratory distress, necessitates immediate intervention, such as tracheotomy or intubation.
ASCO Guideline	Asymptomatic, localized to a single lung lobe or <25% of the lung parenchyma, requires only clinical or diagnostic observations.	Symptoms affect multiple lobes of the lung or 25–50% of the lung parenchyma, necessitating medical intervention and restricting instrumental ADL.	Critical manifestations need hospitalization, affecting all lung lobes or > 50% of the lung parenchyma, restricting ADL, oxygen therapy indicated.	Critical respiratory failure needs immediate intervention, specifically intubation.

CTCAE: Common Terminology Criteria for Adverse Events; ASCO: American Society of Clinical Oncology; G: grade; ADL: activity of daily life; Instrumental ADL: activities of daily life such as shopping, preparing food, using the telephone, managing money, and others.

The Society of Immunotherapy of Cancer (SITC) and ASCO have developed a guideline for cancer treatment based on the severity of pneumonitis. Grade 2 pneumonitis requires nasopharyngeal, sputum, urine culture, and sensitivity testing to rule out infection. Bronchoscopy and biopsy are unnecessary in lower grades. If clinical evidence suggests pneumonitis, but the supporting exam is negative, the tissue sample can separate pneumonitis from other clinical and radiological diagnoses, such as infection and tumor spread. HRCT is the preferred imaging. A pulmonary function test can also help. Meanwhile, histological findings for immunotherapy-related pneumonitis are non-specific.[28,29]

Pneumonitis Therapy Due to Immunotherapy

There are no established ICI pneumonitis management guidelines. In grade 1 toxicity patients, doctors should consider withholding ICI therapy and re-examine CT imaging in 3-4 weeks. If follow-up imaging demonstrates improved pneumonitis, ICI therapy will continue. In contrast, if the imaging showed pneumonitis worsens, the patient should be treated according to grade 2 toxicity criteria. Asymptomatic grade 1 patients should be observed or given 0.5-1 mg/kg steroids. In grade 2 lung injury, the patient should discontinue ICI medication and start oral prednisone 1-2 mg/kg/day or another similar steroid. After 48-72 hours, the therapy response should be evaluated, and if there is an improvement, the steroid dose tapered for 4-6 weeks.

Re-administration of immunotherapy may be considered if toxicity is resolved without complication. Unimproved patients should be handled according to grade 3 toxicity criteria.[20,30] Hospitalization is needed for grade 3 or 4, severe symptoms, and hypoxia. Patients should discontinue ICI medication, receive empirical broad-spectrum antibiotics, and have BAL bronchoscopy. Patients should receive intravenous methylprednisolone 1-2mg/kg/day or similar steroids promptly. Some guidelines recommend 4 mg/kg/day methylprednisolone. In severe conditions, intravenous bolus steroids may be given. Infliximab, cyclophosphamide, immunoglobulin IV (IVIG), or mycophenolate mofetil may be given to patients who do not improve after 48 hours, but limited data exist on these medicines' efficacy for ICI pneumonitis. If the patient shows improvement after 48 hours, the steroid dose can be gradually reduced for 4-8 weeks.[19,27]

Steroid reduction should be done slowly and carefully for ≥6 weeks to avoid pneumonitis relapses. In severe pneumonitis (> grade 3), early relapse in shorter therapy duration is common (<5 weeks).[28] Immunocompromised patients need prophylactic antibiotics. In patients on long-term steroid therapy (>12 weeks), trimethoprim/sulfamethoxazole for Pneumocystis jirovecii may be recommended. Other pharmaceutical and non-pharmacological therapies include oxygen, symptomatic, and pulmonary rehabilitation.[2]

D. LUNG INJURY DUE TO TARGETED THERAPY

Advances in cancer molecular biology have ushered in a new era of molecular-targeted therapies. Targeted antineoplastic agents include monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKI), which are often used to manage various malignancies and are effective anti-cancers. However, using these agents has caused different side reaction reactions than other anti-cancer agents. In recent years, pulmonary toxicity due to targeted therapy has been reported.[28] Tyrosine kinase inhibitors (TKIs) are tiny compounds that block the activation of protein kinases implicated in the cellular growth mechanism. These proteins are frequently overexpressed or hyperactivated in certain cancer types, making these medications important therapeutic agents for managing solid tumors.[2]

Mechanism of Pulmonary Toxicity Due to Targeted Therapy

The mechanism of lung injury can differ between targeted therapies. Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, is reported to reduce alveolar regeneration, which EGFR regulates typically. By lowering the PI3K pathway, targeted therapy with EGFR inhibitors is claimed to disrupt lung tissue repair pathways by causing inflammation. EGFR inhibition in airway epithelial cell repair prolongs inflammation and acute lung injury in preclinical models by modulating airway microenvironment gene expression.[2,29]
Anaplastic Kinase Lymphoma (ALK) inhibitors, including first-generation until third-generation, can produce pulmonary interstitial toxicity.[30,31] Crequit et al. hypothesized that crizotinib-associated ILD may cause pneumonitis drug hypersensitivity due to its slow onset, necessitated sensitization of the substance, resolution after discontinuation, and reappearance after re-administration. Multi-kinase inhibitors inhibiting platelet-derived growth factor receptors (PDGFR) more often increased ILD, such as imatinib. Patients having a history of pneumonia are more susceptible to imatinib-induced ILD.[2,31]

Assessment of Pulmonary Toxicity Due to Targeted Therapy

Patients with new or worsening respiratory symptoms after molecular-targeted therapy agents may be considered to have pulmonary toxicity. Dyspnea on effort, cough, and fever are the main symptoms. The severity of lung injury depends on the disease and drug used. ILD is challenging to distinguish from other respiratory disorders due to non-specific clinical manifestation findings. As such, imaging must be done immediately by clinicians. Initial tests like a thoracic x-ray are non-specific and sometimes normal in early-stage illness. CT scan or HRCT is the second step in diagnosing ILD and can reveal lung parenchymal tissue's distribution and aberrant patterns that may be connected to ILD histology. Other supportive tests include culture, serological tests, and bronchoscopy with bronchoalveolar lavage in at-risk patients.[3,28]

Pulmonary Toxicity Therapy Due to Targeted Therapy

While pulmonary toxicity may respond to treatment, fatality has been documented. Discontinuing the targeted medication when symptoms develop and administering systemic glucocorticoids with supportive care can improve symptoms and radiographs. The patient's comorbidity and infection must be considered before administering glucocorticoids. Based on severity, high-dose methylprednisolone (500–1,000 mg/day for three days) is advised. A study found that 53.3% of patients who stopped treatment and were given systemic glucocorticoids had symptom resolution and radiological improvement.[28] As mentioned, lung injuries can be classified in grades 1–4. It requires stopping medication treatment in suspicious patients, and systemic glucocorticoids are also advised; however, clinical trials are lacking. In grade 1 and 2 lung injury patients, the targeted agent may be readministered to patients after symptoms and radiological improvement. However, not for grade 3 and 4 patients.[27,30] When treated again at a similar dose, most patients with the same medication combination and low-dose glucocorticoids did not develop pulmonary toxicity recurrence. However, another study reported 36.4% recurrence.[28]

SUMMARY

Some cancer therapy modalities can cause injury to the lungs. Lung injuries due to cancer therapy can generally be established based on anamnesis related to signs and symptoms as well as a history of drug use, physical examination, and radiological examination. Before a diagnosis of lung injury related to cancer therapy is made, the clinician needs to first rule out other possible causes. The management provided is generally symptomatic, prophylactic, and temporary discontinuation or stopping of cancer therapy.

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Conflict of Interest

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Authors' Contributions

Concepting and preparation, manuscript writing, revising, and corresponding: HH. Concepting and preparation, manuscript writing, revising: MHS. Manuscript writing: FF. All authors contributed and approved the final version of the manuscript.

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