



Cancer Treatment-Related Lung Injury 36

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Abstract

Lung injury associated with cancer therapeutics is often the limiting factor that trumps otherwise successful cancer therapy. Thoracic radiation as well as cancer pharmacotherapeutics, including conventional chemotherapy, molecular targeted agents, and cancer immunotherapies, have been associated with

a unique spectrum of histopathologic injury patterns that may involve the lung parenchyma, pleura, airways, and/or pulmonary vasculature. Injury patterns may be idiosyncratic, unpredictable, and highly variable from one agent class to the next. Variability in lung injury patterns within a specific therapeutic class of drugs also occurs, adding to the conundrum. Drug-induced toxicities to the thoracic cavity are infrequent, and early recognition of clinical clues portends a good outcome in most cases. Failure to recognize early clinical signs, however, may result in irreversible and potentially lethal consequences.

This chapter provides an overview of our current knowledge of thoracic complications associated with cancer pharmacotherapies.

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The review is not intended to be a treatise of all cancer agents that adversely affect the lungs, but rather a discussion of established risk factors and histopathologic patterns of lung injury associated with broad classes of cancer agents. Optimal management strategies, based on existing clinical experience, will also be discussed. Complications associated with thoracic radiation are also reviewed. It is hoped that these discussions will facilitate early recognition and management of treatment-related thoracic complications and, ultimately, better patient outcomes.

Keywords

Drug-induced lung disease · Lung injury · Toxicity · Chemotherapy · Immunotherapy · Targeted therapy · Radiation · Pneumonitis · Malignancy · Pulmonary · Interstitial pneumonitis · Pleural effusions · Respiratory · Cancer treatment

Introduction

Recent advancements in the understanding of cancer biology have fueled a new era in anticancer therapeutics that extends beyond the class of conventional cytotoxic chemotherapy and radiation therapy regimens. Strategies that exploit the cancer genome in the development of molecular-targeted therapies and schemes that harness the immune system to tilt immune equilibrium in favor of enhanced tumor killing have rapidly emerged as standard of care for patients with a variety of malignancies and have joined the ranks of cytotoxic drugs in the medical management of some cancers. Each class of cancer therapeutics has been limited by a unique spectrum of toxicities that may target the lung parenchyma, pleura, and/or pulmonary circulation. Although drug-related adverse events within the thoracic cavity are infrequent relative to other organ systems, they are an important source of severe and life-threatening toxicity. Therefore, failure to recognize early clinical clues may have catastrophic consequences. Respiratory distress is a frequent reason for ICU transfer in cancer patients and is attributable to infectious

causes associated with cytotoxin-related immune suppression in most cases. In addition, cytotoxic therapies as well as the molecular-targeted and immune therapies are reported to cause a unique spectrum of noninfectious complications that affect the lung parenchyma, pleura, and vascular structures. For example, interstitial pneumonitis is an important sequela of cancer therapy and frequent reason for drug withdrawal [1–9]. Inhibitors of antiangiogenic pathways are a source of severe vascular side effects within the lungs, including thromboembolic events and pulmonary hemorrhage. The cardiotoxic effects of these agents as well as the Bcr-Abl inhibitors may result in pulmonary edema associated with congestive heart failure [10, 11]. The emergence of pleural and pericardial effusions owing to Bcr-Abl inhibition has also been described [12–16].

Familiarity with established common adverse lung events and management of potentially life-threatening complications relating to conventional and new anticancer agents are essential for treating clinicians, including the ICU staff, oncologists, and organ specialists. This chapter provides an update and review of the clinical and pathophysiologic findings associated with specific notorious cancer pharmacotherapies and presents evidence-based algorithms, where available, in the management of thoracic complications associated with chemotherapeutic agents and radiation therapy.

Chemotherapy-Induced Lung Injury**General Principals****Incidence and Risk Factors**

Pneumotoxicity may be predictable and dose dependent with some agents (busulfan, bleomycin, nitrosoureas). Other reactions are idiosyncratic and dose independent, occurring as a result of immune-mediated processes, bioactivation, or toxic drug metabolites. The frequent use of complex multi-drug and multimodality regimens and overlapping clinical and radiographic manifestations of lung injury caused by drug toxicity, infection, and cancer relapse render precise estimates difficult. Predisposing factors, including patient age, tobacco

use history, cumulative dose, renal dysfunction, oxygen therapy, and preexisting lung disease, may influence the incidence, severity, and latency period of lung toxicity following drug exposure. The significance of these risk factors varies with individual agents within a particular drug class and across drug classes. For example, preexisting fibrosis is a significant independent risk factor in the development of severe and accelerated pulmonary toxicity following therapies with conventional cytotoxic therapies such as gemcitabine, oxaliplatin, amrubicin, bleomycin, methotrexate, and the molecular targeted therapies everolimus, temsirolimus, erlotinib, gefitinib [17–21]. Whether prior lung fibrosis potentiates toxicities associated with the class of drugs known as immune checkpoint inhibitors has not been established. Cancer agents within one therapeutic class may produce histopathologic patterns of lung injury with widely varying frequencies. For instance, pulmonary hypertension is a well-established adverse event following the Bcr-Abl inhibitor, dasatinib, but extremely rare among other agents within this class of drugs. Thus, estimates of the incidence of lung injury caused by individual chemotherapeutic agents vary broadly. Reported estimates are included in discussions of individual agents.

Diagnosis

Pneumotoxicity associated with chemotherapeutic agents represents a diagnostic conundrum. Toxicity is typically assessed through clinical, radiographic, and histopathologic studies, although no single abnormality is pathognomonic. Biomarkers and laboratory studies are not sufficiently sensitive to distinguish drug-related lung injury from competing diagnoses. Histopathologic features of chemotherapy-induced lung injury are not specific for DILD and can be seen in a wide variety of clinical contexts and competing diagnoses, including pneumonia, congestive heart failure, and cancer progression. High-resolution CT (HRCT) scans may detect early abnormalities; however, imaging findings are nonspecific. Interstitial and mixed alveolar-interstitial abnormalities are frequent findings on computed tomography (CT). These abnormalities appear as bilateral (may be

asymmetrical) reticular markings, septal thickening, and ground-glass opacities that typically localize to the subpleural and lower lung zones. Radiographic manifestations of pulmonary fibrosis, including traction bronchiectasis and honeycombing, herald the onset of end-stage lung disease. Other findings, including nodular lesions, pleural effusions, and lymphadenopathy, may be confused with cancer progression.

Bronchoalveolar lavage (BAL) with or without lung biopsies may be helpful in excluding competing diagnoses of infection or background disease. BAL findings of increased numbers of lymphocytes, eosinophils, fibroblasts, and dysplastic type II pneumocytes may aid in the diagnosis of chemotherapy-induced lung injury; however, none of these findings are diagnostic. Decreased CD4/CD8 ratios on BAL fluid are also supportive findings; however, ratios vary widely and cannot distinguish sufficiently between drug-induced and other causes of ILD [22–24]. The diagnosis of DAH is supported by findings of progressively bloody BAL samples on sequential aliquots and/or cytologic evidence of increased numbers of hemosiderin-laden macrophages on BAL fluid. Serum elevations of the WBC count, erythrocyte sedimentation rate, and C-reactive protein are also common but non-specific findings. Toxicity to the lung parenchyma is usually signaled by a reduction in the diffusing capacity (DLCO). With disease progression, a restrictive ventilatory defect is seen [25–28]. Alteration in DLCO is generally accepted as the most sensitive parameter in assessing drug-related injury, although its predictive potential for the detection of early change has been variable. Irreversible changes in lung function are seen with end-stage lung disease. In earlier stages, normalization of pulmonary function may occur, typically within 2 years of toxin exposure [25, 27, 29, 30].

The diagnosis of DILD is, therefore, based on the exclusion of competing causes in the context of a compatible clinical presentation and temporal relationship between the administration of the suspected drug and onset of symptoms. Measureable improvements in clinical signs and symptoms following drug withdrawal and/or

recrudescence of disease with drug rechallenge are supportive of the diagnosis. Delayed toxicities, occurring months to years after drug withdrawal (gentamycin, bleomycin, busulfan) and disease progression despite discontinuation of the offending agent (immune checkpoint inhibitors), are diagnostically challenging features of some agents. Drug rechallenge is justified only in a minority of patients, and its use as a diagnostic tool is discouraged.

Clinical Presentation

Manifestations of pneumotoxicity are nonspecific and protean. Most commonly, symptoms of cough (typically nonproductive), dyspnea, hypoxia, and low-grade fever develop insidiously over weeks to months after drug exposure. Fulminant disease, which may rapidly progress to respiratory failure and acute respiratory distress syndrome (ARDS), is also seen. Symptom onset varies with individual drugs and may be classified into acute (within hours to days of drug exposure), early (within the first 6 months of drug exposure), and late (6 months or more after exposure) time periods. Delayed pulmonary fibrosis, occurring months to years after exposure to bleomycin, busulfan, cyclophosphamide, gemcitabine, and the nitrosoureas as a late manifestation of DILD, has also been described [31–33].

Histopathologic Features of DILD

The response of the lungs to drug-related adverse events results in stereotyped histopathologic patterns of lung injury. Drug-induced interstitial lung diseases (DILD) (nonspecific interstitial lung disease, NSIP; pulmonary fibrosis, PF; hypersensitivity reactions, HP; sarcoid reactions) and alveolar processes (diffuse alveolar damage, DAD; diffuse alveolar hemorrhage, DAH; eosinophilic pneumonias, EP; noncardiogenic pulmonary edema, NCPE; alveolar proteinosis) are the most frequent histopathologic patterns of response to standard chemotherapeutic agents as well as molecular-targeted therapies and immunomodulating agents. Pleural diseases (pleural effusions, fibrosis), drug-induced vascular disorders (thrombosis, pulmonary hypertension, pulmonary veno-occlusive disease, PVOD),

airway disorders (bronchospasm, infusion reactions), and mediastinal diseases (lymphadenopathy, fibrosis) have also been described, particularly following molecular-targeted and immunomodulating therapies. Finally, immune suppression following conventional and targeted therapies as well as immune activation triggered by immunomodulating agents may incite a variety of opportunistic pneumonias. The often life-threatening pneumonias that may emerge in the setting of immune suppression are discussed elsewhere.

Specific Clinical and Histopathologic Patterns of DILD

Interstitial Lung Disease. Interstitial pneumonitis is one of the major patterns of lung injury following systemic cancer therapies. This pattern of lung injury may arise from direct cytotoxicity, oxidative stress, and immune-mediated mechanisms. Pneumonitis may be stratified into six major categories according to clinicoradiographic and histopathologic findings: (1) nonspecific interstitial pneumonitis, (2) organizing pneumonia, (3) hypersensitivity pneumonitis, (4) diffuse alveolar damage/acute respiratory distress syndrome, (5) diffuse alveolar hemorrhage, and (6) eosinophilic pneumonia. Characteristic imaging features and the cancer agents that have been implicated in the development of category of lung injury are listed in Tables 1 and 2. The diagnosis of drug-induced ILD requires a high index of suspicion. Individual agents may elicit multiple patterns of lung injury. Lung injury patterns within a single class of drugs may vary widely. Furthermore, there are pathognomonic imaging findings or histopathologic markers that distinguish drug-induced ILD from other causes. Drug interruption with or without the addition of systemic corticosteroids is the mainstay of treatment of drug-related IP. Optimal dose, timing, and duration of steroids in this setting have not been well established; however, 0.5–1 mg/kg/day of prednisone or its equivalent is generally given for 8–12 weeks. Although most patients present with mild disease, any of the ILD injury patterns may progress to pulmonary fibrosis, particularly with acute and fulminant presentations of ILD, such as that seen in the setting of ARDS/DAD.

Table 1 Drug-induced lung injury: Conventional chemotherapy

		Responsible agents: conventional chemotherapy									
Radiographic pattern	Clinical findings	Imaging findings	Alkylating agents	Antimetabolites	Cytotoxic antibiotics	Topoisomerase inhibitors	Podophyllotoxins	Taxanes/microtubule inhibitors	Others		
Interstitial lung disease											
NSIP	Subacute onset of dry cough, dyspnea, low-grade fevers, evolving over weeks	GGOs, reticular opacities with predominant peripheral lung and lower lung distribution with subpleural sparing; traction bronchiectasis; volume loss over the lower lobes with advanced disease	Busulfan BCNU CCNU Cyclophosphamide Ifosfamide Temozolomide Oxaliplatin Melphalan	Methotrexate Cytarabine Fludarabine Azacitidine Gemcitabine Azathioprine 6-Mercaptopurine	Bleomycin Mitomycin C	Topotecan Irinotecan Amrubicin Daunorubicin Liposomal Doxorubicin	Etoposide Teniposide	Paclitaxel Docetaxel	ATRA Arsenic trioxide Procabazine		
OP	Subacute onset of dry cough, dyspnea, low-grade fevers, weight loss, evolving over weeks	Bilateral migratory, patchy areas of lung consolidation or GGOs in a predominant peripheral and lower lobe distribution; opacities tend to wax and wane (hallmark) nodular opacities; reverse halo sign	Busulfan Cyclophosphamide Ifosfamide Oxaliplatin	Methotrexate Azathioprine 6-Mercaptopurine	Bleomycin	Topotecan			L-asparaginase		

(continued)

Table 1 (continued)

		Responsible agents: conventional chemotherapy									
Radiographic pattern	Clinical findings	Imaging findings	Alkylating agents	Antimetabolites	Cytotoxic antibiotics	Topoisomerase inhibitors	Podophylotoxins	Taxanes/ microtubule inhibitors	Others		
HP	Acute, subacute and chronic forms of disease; dry cough, dyspnea,	Mosaic attenuation caused by air trapping; diffuse ground-glass opacification without interstitial thickening; poorly defined centrilobular ground-glass nodules		Methotrexate				Paclitaxel Docetaxel			
Eosinophilic pneumonia	Acute onset of dyspnea and dry cough, low-grade fever evolving over 1-3 weeks after initiation of the offending agent	Patchy, diffuse, ground-glass or reticular opacities randomly distributed throughout the bilateral lungs	Busulfan Cyclophosphamide Oxaliplatin BCNU Oxaliplatin	Methotrexate Cytarabine Fludarabine Gemcitabine Pentostatin	Bleomycin			Paclitaxel Docetaxel	Interleukin-2		
AIP/ARDS/DAD	Dry cough and dyspnea, hypoxia may develop more rapidly (days – weeks) versus other forms of ILD	Diffuse bilateral septal thickening, GGOs and consolidations in the dependent areas of the lungs; volume loss	Busulfan, Cyclophosphamide, Ifosfamide, Temozolomide, Oxaliplatin Melphalan	Methotrexate Azathioprine Cytarabine Fludarabine Azacitidine Gemcitabine Pentostatin Pemetrexed Zincostatin	Bleomycin Mitomycin C	Topotecan	Etoposide Teniposide	Paclitaxel Docetaxel Vincristine Vinblastine Vindesine Vinorelbine Ixabepilone	ATRA Arsenic trioxide		

Vascular disease		Thromboembolism		Dyspnea often accompanied by pleuritic chest pain or tightness. May be acute, subacute, or chronic; hemodynamic instability with right heart strain, shock if massive	Acute: complete or partial intraluminal filling defects on CTA Chronic: complete occlusive disease in vessels that are smaller than adjacent patent vessels; recanalization, webs, flaps, partial filling defects form obtuse angles with the vessel wall	Cisplatin Oxaliplatin	5-Fluorouracil				Thalidomide Lenalidomide L-asparaginase GM-CSF GCSF
		Pulmonary hypertension	Progressive dyspnea, fatigue, chest pain, palpitations, LE edema, cyanosis	Abrupt narrowing/ tapering of peripheral pulmonary vessels Right atrial/ventricular enlargement Dilatation of central pulmonary artery Mosaic attenuation due to variable lung perfusion	Cyclophosphamide Procarbazine BCNU	Gemcitabine	Bleomycin Mitomycin	Interferon- α Interferon- β			
Pleural disease		Pleural effusions	Progressive dyspnea, pleuritic chest pain	CXR: Blunting of costophrenic angle, fluid within horizontal or oblique fissures, mediastinal shift as fluid progresses Echo-free space on ultrasound evaluation	Cyclophosphamide	Methotrexate Gemcitabine	Mitomycin	Docetaxel Paclitaxel	ATRA Arsenic trioxide Procarbazine	(continued)	

Table 1 (continued)

		Responsible agents: conventional chemotherapy							
Radiographic pattern	Clinical findings	Imaging findings	Alkylating agents	Antimetabolites	Cytotoxic antibiotics	Topoisomerase inhibitors	Podophylotoxins	Taxanes/microtubule inhibitors	Others
Pleural fibrosis	Progressive dyspnea	Pleural thickening with/without calcification Associated volume loss of affected hemithorax	BCNU Bleomycin Cyclophosphamide						
Airway disease									
Infusion reaction/bronchospasm	Acute wheezing/bronchospasm; may be accompanied by hemodynamic instability, chest pain	Imaging studies of the chest may be normal	Cyclophosphamide Ifosfamide Carboplatin Cisplatin Oxaliplatin	Methotrexate Gemcitabine Pemetrexed	Bleomycin Mitomycin C	Amrubicin Daunorubicin Liposomal Doxorubicin	Etoposide Teniposide	Paclitaxel Docetaxel Vincristine Vinblastine Vindesine Vinorelbine	L-asparaginase
Other									
Methemoglobinemia	Shortness of breath, hypoxia headache, fatigue, exercise intolerance, cyanosis seizures, coma with higher levels of methemoglobin	CXR may be normal; discordant oxygen saturation via pulse oximetry versus arterial blood gas Chocolate-brown color of blood	Cyclophosphamide Ifosfamide						
Acute chest pain syndrome	Acute chest pain, typically occurs during infusion	Chest imaging may be normal			Bleomycin				

Table 2 Drug-induced lung injury: Targeted agents and immunotherapies

Radiographic pattern	Clinical findings	CT findings	Molecular-targeted therapies		Rapamycin inhibitors	Proteasome inhibitors	ICIs	
			MoAB	TKIs			Ipilimumab	Other
NSIP	Subacute onset of dry cough, dyspnea, low-grade fevers, evolving over weeks	GGOs, reticular opacities with predominant peripheral lung and lower lung distribution with subpleural sparing; traction bronchiectasis; volume loss over the lower lobes with advanced disease	Cetuximab	Gefitinib	Everolimus Temsirolimus	Bortezomib Carfilzomib	Ipilimumab	Thalidomide
			Panitumumab	Erlotinib			Nivolumab	IL-2
			Alemtuzumab	Imatinib			Pembrolizumab	
			Rituximab	Osimertinib			Atezolizumab	
			Brentuximab	A fatinib			Durvalumab	
				Dasatinib			Avelumab	
				Sorafenib				
				Sunitinib				
				Vandetanib				
				Idelalisib				
				Trametinib				
				Crizotinib				
				Ceritinib				
				Alectinib				
				Brigatinib				
				Ibrutinib				
OP	Subacute onset of dry cough, dyspnea, low-grade fevers, weight loss, evolving over weeks	Bilateral migratory, patchy areas of lung consolidation or GGOs in a predominant peripheral and lower lobe distribution; opacities tend to wax and wane (hallmark) nodular opacities; reverse halo sign (nonspecific)	Rituximab	Imatinib	Everolimus Temsirolimus Sirolimus (rare)	Bortezomib Carfilzomib	Ipilimumab	
			Panitumumab				Nivolumab	
							Pembrolizumab	
HP	Acute, subacute and chronic forms of disease; dry cough, dyspnea	Mosaic attenuation caused by air trapping; diffuse ground-glass opacification without interstitial thickening; poorly defined					Ipilimumab	
							Nivolumab	
							Pembrolizumab	
							Atezolizumab	
							Durvalumab	

(continued)

Table 2 (continued)

Radiographic pattern	Clinical findings	CT findings	Molecular-targeted therapies		Rapamycin inhibitors	Proteasome inhibitors	ICIs	Other
			MoAB	TKIs				
AIP/ARDS/ DAD	Dry cough and dyspnea, hypoxia may develop more rapidly (days – weeks) versus other forms of ILD	centrilobular ground-glass nodules Diffuse bilateral septal thickening, GGOs and consolidations in the dependent areas of the lungs; volume loss	Cetuximab Panitumumab Alemtuzumab Rituximab Brentuximab Ofatumumab Ibritumomab Trastuzumab Pertuzumab Ado-trastuzumab Gemtuzumab	Gefitinib Erlotinib Imatinib Sorafenib Vandetanib Crizotinib Ruxolitinib	Everolimus Temsirolimus	Bortezomib	Ipilimumab Nivolumab Pembrolizumab Atezolizumab Durvalumab Avelumab	Thalidomide Lenalidomide CAR-T inhibitors Blinatumomab
Eosinophilic pneumonia	Homogeneous opacities, peripheral, and upper-lobe distribution (reverse batwing sign, also known as reverse pulmonary edema sign)	Peripheral opacities with upper-lobe predominant distribution					Ipilimumab Nivolumab Pembrolizumab	

Nonspecific Interstitial Pneumonitis (NSIP). Nonspecific interstitial pneumonitis and organizing pneumonia (OP) are the most common morphologic patterns of interstitial lung disease following systemic chemotherapy, including the molecular-targeted and immune checkpoint inhibitor therapies. Dry cough and progressive dyspnea, developing insidiously, over weeks to months following drug exposure are notable clinical features of both syndromes. Diffuse ground-glass and reticular opacities with peribronchovascular predominant fibrosis and sparing of the subpleural space help to distinguish NSIP from other forms of pulmonary fibrosis (Fig. 1). However ground-glass

consolidations localizing to the lung periphery and bibasilar areas are also frequently seen, particularly in late forms of disease, rendering these diagnostic clues imperfect [34]. An extensive list of conventional cytotoxic chemotherapies has been linked to the development of NSIP. These most commonly include the cytotoxic antibiotics (bleomycin, mitomycin), the nitrosoureas (BCNU, CCNU), other alkylating agents (busulfan, cyclophosphamide), antimetabolites (methotrexate, gemcitabine, procarbazine, cytosine, arabinoside), the podophyllotoxins (etoposide), taxanes (paclitaxel), and the anti-angiogenesis inhibitors (thalidomide, pomalidomide, lenalidomide). Among the molecular-targeted

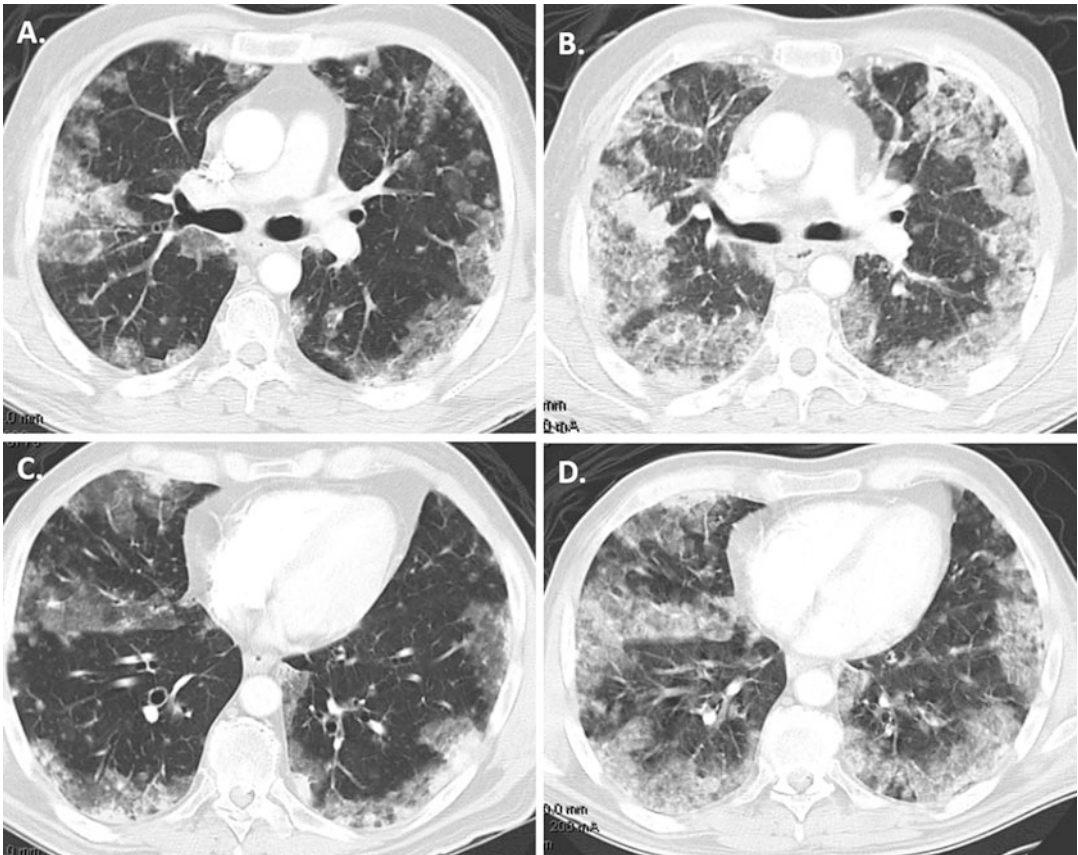


Fig. 1 Gemcitabine-induced lung injury. A 54-year-old man was hospitalized for progressive dyspnea, dry cough, and severe hypoxia 3 weeks after initiation of gemcitabine therapy for pancreatic cancer. The extensive nodular infiltrates with subpleural predominance seen on CT at baseline (a, c) were biopsy-proven to represent metastatic disease. The admitting CT of the chest (b, d) demonstrated

relatively stable nodules with marked increase in the peripheral ground-glass and consolidative opacities bilaterally. Pathologic analysis of lung tissue obtained by transbronchial biopsies confirmed nonspecific interstitial pneumonitis (NSIP) superimposed on known metastatic disease, likely due to gemcitabine therapy

therapies, cetuximab, erlotinib, gefitinib, brentuximab, panitumumab, obinutuzumab, dasatinib, brigatinib, and m-tor inhibitors, everolimus and temsirolimus, are most frequently implicated. NSIP is also triggered by the programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibition and, to a lesser extent, the anti-cytotoxic T lymphocyte antigen (anti-CTLA-4) immune checkpoint inhibitors.

Organizing Pneumonia. The histologic hallmark of organizing pneumonia (OP) is fibrin plugs within the lumens of distal airways with associated chronic inflammation. This finding, coupled with patchy unilateral or bilateral areas of consolidation that migrate from one area of the lung to another on sequential chest imaging studies, should heighten the suspicion for OP. Other findings include tree-in-bud branching linear opacities, areas of nodular consolidation, and centrilobular nodules. A lymphocyte-predominant fluid is seen on bronchoscopically obtained sample analysis [35]. PFT abnormalities typically include a mixed obstructive-restrictive pattern in secondary OP. Chemotherapeutic agents that are most commonly implicated in the development of OP include conventional agents (cyclophosphamide, oxaliplatin, methotrexate, bleomycin, busulfan), targeted therapies (rituximab, cetuximab, adalimumab, alemtuzumab, everolimus), and immunomodulating agents (ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab). The prognosis of OP is generally favorable. Systemic steroids represent standard therapy, although the precise dose and duration of treatment have not been established. Most reports favor a slow steroid taper (4–6 weeks), to avoid disease relapse. Due to their anti-inflammatory properties, macrolides have also been used with occasional benefit [36].

Hypersensitivity Pneumonitis (HP). This immune-mediated ILD typically develops following repeated exposure to an offending agent. Imaging findings suggestive of HP include mosaic attenuation, reflective of air trapping and diffuse ground-glass opacification. A predilection for the upper lobes may be seen in chronic forms of the disease. Associated symptoms of fever, dyspnea, dry cough, and rash typically occur over the first 3–4 weeks following drug exposure and may wax and wane

without adjustments in therapy. Poorly formed granulomas and BAL lymphocytic alveolitis are common histopathologic findings. Chemotherapeutic agents that most commonly provoke this type of reaction include bleomycin, busulfan, carmustine (BCNU), methotrexate, procarbazine, the taxanes (paclitaxel, docetaxel), and interferon- α . Methotrexate is the prototype agent associated with HP, which may develop regardless of route of methotrexate administration (oral, intrathecal, intramuscular, or intravenous). Hypersensitivity reactions have been reported following both Taxol and Taxotere administration, which may arise as a result of the drug or its diluent. Taxol is formulated in a highly allergenic polyoxyethylated castor oil (Cremophor EL) solvent. Up to 10% of patients develop HP following paclitaxel administration, which is marked by urticaria, bronchospasm, angioedema, and, in extreme cases, hypotension. Paclitaxel-induced HP has been attributed to its Cremophor EL suspension vehicle rather than the agent itself. A hypersensitivity reaction reported following interferon- α has been attributed to the immune-stimulating properties of interferon- α , rather than a reaction to the agent itself. Drug withdrawal and steroid therapy typically produce favorable outcomes, with complete resolution of clinical signs and symptoms in early-stage disease. Chronic HP may progress to pulmonary fibrosis with fatal outcomes.

Noncardiogenic Pulmonary Edema (NCPE), Diffuse Alveolar Damage (DAD), and Acute Respiratory Distress Syndrome (ARDS). Drug-induced injury to the alveolar-capillary membranes may result in capillary leak and a permeability (noncardiogenic) pulmonary edema. ARDS and its histologic hallmark, DAD, may ensue as the disease progresses. Early histopathologic findings include the accumulation of proteinaceous inflammatory debris, capillary congestion, atelectasis, alveolar edema, and intra-alveolar hemorrhage. This is followed days later by edema of the alveolar septa, thickened alveolar membranes, epithelial cell hyperplasia, and hyaline membrane deposition [37]. Corresponding imaging findings of DAD include septal thickening, atelectasis, and diffuse ground-glass and consolidative opacities, which are most pronounced in the dependent portions of the lungs. DAD may progress to irreversible

pulmonary fibrosis. Drug-induced DAD/ARDS may be idiosyncratic, without any relationship to drug dosage or duration of therapy.

Compelling causal drug-related associations arise from nearly all classes of antineoplastic therapies, including cytotoxic antibiotics (bleomycin, mitomycin C); alkylating agents (busulfan, bis-chloroethyl nitrosourea (BCNU), chloroethyl cyclohexyl nitrosourea (CCNU), high-dose cyclophosphamide); antimetabolites (methotrexate, gemcitabine, azathioprine, cytosine-arabioside, fludarabine); molecularly target agents (gefitinib, erlotinib, cetuximab); antilymphocyte monoclonal antibodies (rituximab, alemtuzumab, ofatumumab); and the rapamycin inhibitors (everolimus, temsirolimus) and the immunomodulating agents (immune checkpoint inhibitors, chimeric antigen receptor T cells [CAR-T], bispecific T cell engagers [BiTE], methotrexate). Chemotherapeutic agents such as bleomycin, mitomycin C, busulfan, gentamycin, everolimus, and the nitrosoureas may promote DAD by disrupting the alveolus via apoptosis. Others interfere with repair of the alveolar epithelial barrier (gefitinib, erlotinib, cetuximab) or immune mechanisms (immune checkpoint inhibitors, chimeric antigen receptor T cells [CAR-T], bispecific T cell engagers [BiTE], methotrexate). In many cases, specific mechanism of drug-induced DAD is unknown. Prompt discontinuation of the offending agent is vital, although disease progression may occur despite drug withdrawal.

NCPE leading to ARDS has been described following ruxolitinib, a novel Jakafi one-half inhibitor, as a result of a cytokine rebound reaction. This reaction is mitigated with the preemptive use of corticosteroids and supportive therapy [38, 39]. Cytokine storm has also been described following all-trans retinoic acid (ATRA) and arsenic trioxide therapies in the treatment of acute promyelocytic leukemia (APL). The differentiation syndrome is characterized by potentially fatal NCPE and ARDS and occurs in up to 25% of APL patients undergoing induction therapy. Unlike many of the lung injury processes, in patients with ATRA and arsenic-related differentiation syndrome, de-escalation of drug dose rather than drug withdrawal, along with systemic steroid

therapy, has been associated with successful resolution of toxicity in patients with mild to moderate forms of this syndrome [40, 41].

The onset of ARDS is heralded by acute dyspnea, hypoxia, and bilateral alveolar infiltrates. Reactions may be mild and self-limited, although progression to ARDS with fatal outcomes occasionally occurs. Drug withdrawal, supplemental oxygen, and the judicious use of diuretics usually effect a rapid recovery. With the exception of ATRA- and arsenic-induced NCPE (see above), drug rechallenge with the offending drug often results in recrudescence of symptoms and is not recommended. Aggravating factors that potentiate disease progression to ARDS include multi-agent protocols and the concomitant or sequential use of radiation or oxygen therapy, particularly following therapy with bleomycin or busulfan [42, 43]. Once established, the response of ARDS to drug withdrawal and corticosteroid therapy is variable. Progressive respiratory impairment, leading to respiratory failure and death, has been reported with some agents (busulfan, cyclophosphamide, bleomycin) despite drug withdrawal. Among molecular-targeted therapies, ARDS has been best described following agents that inhibit EGFR (gefitinib, erlotinib, cetuximab), the antilymphocyte monoclonal antibodies (rituximab, alemtuzumab, ofatumumab), and the rapamycin inhibitors (everolimus, temsirolimus). Acute withdrawal of the JAK1/2 inhibitor, ruxolitinib, has been associated with the development of ARDS as a result of a cytokine rebound reaction. Preemptive use of corticosteroids, along with supportive therapy and a slow taper off this agent, is recommended to mitigate this potential problem [38, 39].

Diffuse Alveolar Hemorrhage and Hemoptysis. DAH is typically seen as sequelae of alveolar-capillary membrane injury. Disruption of the alveolar and capillary basement membranes facilitates the entry of red blood cells into the alveoli and represents the histologic change that underlies DAD. Thus, any chemotherapeutic agent that prompts the development of DAD may cause DAH. However, DAH is an uncommon sequela of chemotherapeutic agents, with only a handful of drugs being implicated. Agents such as high-dose

cyclophosphamide, cytarabine, gemcitabine, mitomycin, erlotinib, alemtuzumab, and rituximab are most frequently cited as causes of DAH, probably because of the propensity of these agents to trigger DAD. Occasionally, bland alveolar hemorrhage has been described in the absence of DAD following rituximab and alemtuzumab therapy [38, 44]. Affected patients may present with acute hypoxemic respiratory distress. Patients often present with abrupt dyspnea and cough which may progress to acute hypoxemic respiratory failure. Hemoptysis may be minimal or absent in approximately 25–30% of patients, despite massive bleeds [45, 46]. The diagnosis of DAH is confirmed by progressively bloody aliquots of bronchoalveolar lavage (BAL) fluid. Cytologic evidence of increased hemosiderin-laden macrophages (>20%) is also supportive. CT findings of diffuse, bilateral ground-glass opacities or consolidative changes are typical. Early recognition and discontinuation of the offending agent are crucial, as prompt diagnosis and treatment improve survival. Corticosteroids and immunosuppressive agents are often used, although their efficacy in this setting has not been formally evaluated.

Massive and sometimes fatal bleeding has been reported during bevacizumab therapy for treatment of central airway tumors [47]. The inhibition of VEGF is the putative mechanism, which may cause destruction of normal lung tissue and subsequent hemoptysis. Hemoptysis following VEGF inhibitor therapies has been reported more often in association with lung cancers of squamous cell histology, which is likely due to the central location of these tumors [48]. Treatment requires discontinuation of the drug and stabilization of the patient, preferably in an intensive care unit setting. Management of massive hemoptysis is beyond the scope of this chapter but typically includes early bronchoscopy performed with either rigid or flexible endoscope (or both), endovascular embolization, and, in selected cases, surgery, with goals of controlling the bleeding and prevention of aspiration.

Eosinophilic Pneumonia. Eosinophilic pneumonia is characterized by an inappropriate increase in the number of eosinophils and macrophages within alveoli, causing the alveolar septa

to become engorged. Progressive dyspnea, dry cough, and occasionally fever are nonspecific clinical correlates. Elevated peripheral eosinophilia and elevated IgE levels and nonsegmental homogeneous opacities with peripheral and upper-lobe distribution (reverse batwing sign, also known as reverse pulmonary edema sign) are important clinical clues. Causative agents include the taxanes, methotrexate, gemcitabine, fludarabine, and interferon- α . Drug-related EP may resolve with cessation of therapy and initiation of systemic steroids.

Pleural Effusions. Drug-induced pleural effusions may occur as an isolated toxicity to the pleura (following methotrexate, dasatinib, bosutinib, docetaxel, ATRA, and granulocyte colony-stimulating factor (G-CSF) administration) or as a manifestation of a generalized pleuroparenchymal abnormality [49, 50]. These small- to moderate-sized effusions are typically exudative and lymphocyte predominant and may be unilateral or bilateral. Withdrawal of the offending agent may result in spontaneous resolution in some cases.

Pulmonary Vascular Disorders (PVD). The development of thromboembolic disease, pulmonary hypertension, and pulmonary veno-occlusive disease has been described following conventional chemotherapeutic, molecularly targeted, and immunomodulating agents. Increased rates of venous thromboembolism (pulmonary embolism and deep venous thrombosis) have been reported with the ALK inhibitor crizotinib, Bcr-Abl inhibitor ponatinib, and VEGF inhibitors bevacizumab, sunitinib, sorafenib, and pazopanib [51, 52]. In addition, the angiogenesis inhibitors (thalidomide, revlimid, pomalidomide) in combination with steroids, doxorubicin, or BCNU are associated with 14–43% increased risk of thromboembolic events. Other agents, including hormonal therapies, growth factors, and erythropoietic agents, contribute to cancer-associated venous thromboembolism. The development of pulmonary arterial hypertension (PAH) has been associated with several drugs, including bleomycin, busulfan, BCNU, interferon, and dasatinib. Severe PAH following dasatinib, a multi-kinase Bcr-Abl tyrosine kinase inhibitor (TKI), is well described. Once dasatinib-associated

PAH develops, drug withdrawal without rechallenge is recommended. There are no reports of PAH following exposure to the more selective Bcr-Abl targeted TKIs (imatinib and nilotinib), which may be safely used in dasatinib-induced PAH [16, 53–55]. Bleomycin and BCNU have also been implicated in the development of PVOD, an irreversible and often fatal form of pulmonary hypertension that is characterized by fibrous obliteration of pulmonary venules.

Drug-Induced Airway Disease. Virtually all chemotherapeutic and targeted agents may trigger an infusion reaction (IR), a sometimes life-threatening acute reaction that may be associated with dry cough, dyspnea, wheezing, chest pain, and hypoxia. IRs may manifest as IgE-mediated, type I hypersensitivity reactions (carboplatin, oxaliplatin, and L-asparaginase) or as anaphylactoid reactions, mediated by cytokine release. The latter reaction is often seen following the administration of several monoclonal antibodies (mAbs). IRs may be triggered by the drug itself or in response to the vehicle in which the drug is formulated. This is particularly true of the taxane class of drugs. For example, paclitaxel is formulated in Cremophor EL, a highly allergenic polyoxyethylated castor oil solvent. Docetaxel is formulated in polysorbate 80. Both vehicles may induce mast cell/basophil activation and subsequent hypersensitivity reaction. Other drugs that are formulated in Cremophor EL (cyclosporine, teniposide, ixabepilone) or polysorbate 80 (etoposide) may trigger similar reactions and should be avoided in patients with a history of IRs following taxane administration [56, 57]. Histamine receptor antagonists and steroids are recommended as standard prophylaxis prior to taxane administration, which has reduced the incidence of taxane-induced bronchospasm from 30% to 2% [58]. IRs may occur within minutes to several hours following drug exposure. Close monitoring during and immediately following drug infusion is critical, as breakthrough IRs may occur despite prophylaxis. Although vinca alkaloids are rarely associated with lung toxicity, severe bronchospasm has been described when these agents are given with concurrent or sequential administration of mitomycin therapy [59].

Infections. Lung infections are frequent sequelae of aggressive immunosuppressive regimens. The conventional chemotherapeutic agents as well as molecular-targeted therapies may promote recalcitrant and sometimes life-threatening opportunistic pneumonias [60–77]. Increased infection risk in this setting is primarily due to the development of drug-related neutropenia, lymphopenia, and/or impairment of T cell and B cell function. Reactivation of tuberculosis has been reported following anti-PD-1 therapies [78]. Agents that are more frequently linked to an increased infection risk are listed in Table 3.

Methemoglobinemia. Methemoglobinemia is a rare but potentially fatal blood disorder in which the iron of heme is oxidized in excess to the ferric (Fe^{+++}) state. Ferric hemes of methemoglobin exhibit an impaired affinity for oxygen, while the remaining heme sites within the same tetrameric hemoglobin that are in ferrous state demonstrate an increased affinity for oxygen. This imbalance results in poor oxygen delivery, tissue hypoxia. As methemoglobin levels increase, clinical symptoms of shortness of breath, cyanosis, fatigue, exercise intolerance, dizziness, shock, neurologic disturbances (headache, mental status changes, seizures, coma), and death may ensue. Severe symptoms may occur at lower levels of methemoglobin in the setting of preexisting conditions, such as anemia, coexistent glucose-6-phosphate dehydrogenase (G6PD) deficiency, and chronic lung or heart disease. Exposure to dapsone, topical anesthetic agents, and other oxidant drugs are the most common precipitating agents associated with acquired methemoglobinemia. Two chemotherapeutic agents, cyclophosphamide, and a structurally similar compound, ifosfamide, are important causes of methemoglobinemia. This diagnosis should be considered in the differential of patients who develop acute shortness of breath, cyanosis, respiratory depression, or altered sensorium during treatment with one of these agents [79]. Hypoxia that is refractory to supplemental oxygen, abnormal chocolate coloration of the blood, and clinical cyanosis in the presence of normal PaO_2 are important diagnostic clues. Drug withdrawal is the mainstay of therapy. Depending on the clinical presentation, blood

Table 3 Chemotherapeutic agents and infection risk

Agent class	Infection risk	Mechanism	Refs
Conventional chemotherapy			
Alkylating agents Chlorambucil Cyclophosphamide Bendamustine	Bacterial Fungal HBV reactivation (bendaustine, chlorambucil)	Neutropenia Lymphopenia (T cell dysfunction) Lymphopenia (B and T cell dysfunction, bendamustine, cladribine, pentostatin)	[113]
Purine/pyrimidine analogues Fludarabine Cladribine Pentostatin 6-Mercaptopurine Cytosine arabinoside Azathioprine	Listeria, PJP, nocardia Mycobacterial infections Opportunistic fungal infections Viral (CMV, VZV, HSV)	Lymphopenia (T cell dysfunction – fludarabine) Lymphopenia (B and T cell dysfunction – cladribine, pentostatin)	[114]
Targeted agents			
Bruton tyrosine kinase inhibitors Ibrutinib Acalabrutinib	Opportunistic fungi (<i>Aspergillus</i> , <i>Cryptococcus</i> , PJP, <i>Fusarium</i>) HBV reactivation	Lymphopenia (B-cell dysfunction, ? T cell dysfunction)	[115]
Proteasome inhibitors Carfilzomib Bortezomib	Viruses (VZV)	T cell dysfunction	[116]
Anti-CD20-target Rituximab Obinutuzumab Ofatumumab	Viruses (herpesvirus-CMV, HSV, VZV, enterovirus, JC virus); HBV reactivation	Lymphopenia (B cell dysfunction) Neutropenia (obinutuzumab)	[64]
Anti-CD-52 target Alemtuzumab	Viruses (herpesviruses – CMV, HSV, VZV) Fungal (PJP, <i>Aspergillus</i> , <i>Zygomycetes</i> , <i>Candida</i>)	Lymphopenia (B, T and NK cell dysfunction)	[65]
mTOR inhibitors Temsirolimus Everolimus Sirolimus	Bacterial Fungal	B and T cell dysfunction	[66]
PI3K inhibitors Idelalisib Brigatinib	Bacterial Fungal (PJP, <i>Aspergillus</i>)	Neutropenia Lymphopenia (B and T cell dysfunction)	[69]
BCL2 inhibitors Venetoclax	Bacteria Viruses (enterovirus)	Neutropenia Lymphopenia (B and T cell dysfunction)	[70]
Jak-1 inhibitors Ruxolitinib	Fungal (PJP, <i>Cryptococcus</i>) Mycobacteria (MTB); HBV reactivation	T cell dysfunction	[71–73]
Immunomodulators Thalidomide Lenalidomide	Viral Fungal	Neutropenia Lymphopenia (B and T cell dysfunction)	[75]
Anti-cytokines IFN- α TNF- α (infliximab)	Fungal (PJP, <i>Cryptococcus</i>) Mycobacteria (MTB) HBV reactivation	T cell dysfunction	[77]
Immune checkpoint inhibitors			
Anti-PD-1 therapies	TB reactivation	Anti-PD-1 activity	[78]

transfusions, methylene blue, and intensive care monitoring for stabilization of the airway and hemodynamics should be considered.

Lung Injury Associated with Cancer Immunotherapies

Immune Checkpoint Blocking Agents

A key responsibility of the host immune system is to target and destroy cancer cells. This process is mediated via a series of tightly regulated co-stimulatory and co-inhibitory immunomodulatory signals that result in a dynamic state of equilibrium between immune attack and immune tolerance. Immune-related adverse events (IrAEs) may involve virtually every major organ system, including the lungs. Lung involvement is infrequent; however, pneumonitis associated with immune checkpoint inhibitors (ICIs) represents one of the most severe and potentially fatal forms of IrAEs. The incidence of ICI-related pneumonitis ranges from 5% to 11%, with the most frequent and severe events occurring following combination strategies using concurrent or sequential anti-CTLA-4/PD-1 regimens [80–84]. Nonspecific symptoms of new or worsening dry cough, fatigue, and shortness of breath typically occur within the first 3–6 months of initiation of therapy. Fever and chest pain have also rarely been described. Tachycardia and hypoxia are ominous signs which may presage advance disease. Bronchoscopy and lung biopsy can be helpful in excluding competing diagnoses, such as lymphangitic carcinomatosis, pneumonia, pulmonary edema, alveolar hemorrhage, or preexisting lung disease. A lymphocyte-predominant bronchoalveolar lavage (BAL) fluid is common. Occasionally, peripheral and BAL eosinophilia, suggestive of eosinophilic pneumonia, may be seen. Histopathologic findings of a cellular interstitial pneumonitis, organizing pneumonia, or diffuse alveolar damage may progress to traction bronchiectasis with pulmonary fibrosis (Fig. 2). Ground-glass and reticular changes with subpleural and basilar predominance and patchy, consolidative changes on chest imaging studies are also nonspecific. These findings do not distinguish

ICI-related IP from other causes. A concurrent or sequential history of extrapulmonary IrAEs involving the skin, gut, thyroid, or other organs may occur in more than 50% of patients and should raise the index of suspicion [82, 84–88]. Organizing pneumonia and cellular interstitial pneumonitis represent the most frequent histopathologic findings which may progress to traction bronchiectasis with pulmonary fibrosis with advanced stages of disease. Other ICI-mediated respiratory events include bronchitis, bronchiolitis, pleural disease, sarcoid-like reactions, pulmonary granulomatosis, and pseudoprogression of the underlying malignancy [89–93].

The Common Terminology Criteria for Adverse Events (CTCAE) has been widely utilized to establish guidelines for the management of IrAEs. This scoring system uses organ-specific parameters to stratify the severity of therapy-related organ toxicities. Accordingly, symptom scoring ranges from asymptomatic (grade 1) to severe (grade 4) pneumonitis (Table 4). For grade 1 pneumonitis, withholding the drug with close outpatient monitoring is recommended. Drug rechallenge among this group of patients may be considered on a case-by-case basis, if repeat imaging studies, performed 2–4 weeks after withholding the drug, demonstrate resolution of infiltrates. Current consensus favors inpatient management with initiation of systemic corticosteroid therapy among patients with grade 3–4 pneumonitis and patients with grade 2 pneumonitis who demonstrate progression of toxicity despite drug cessation [7, 87, 94–96]. Early grade (1–2) pneumonitis may rapidly progress to respiratory failure and death in 1–2% of patients. Thus, close monitoring of patients with all grades of pneumonitis is recommended.

Genetically Engineered Immunotherapies

Recent success in the use of genetically engineered T cells in the treatment of hematologic malignancies has inspired tremendous interest in this area. This process involves *ex vivo* modification of the naïve T cell to express a unique high-affinity T cell receptor (TCR) or a chimeric

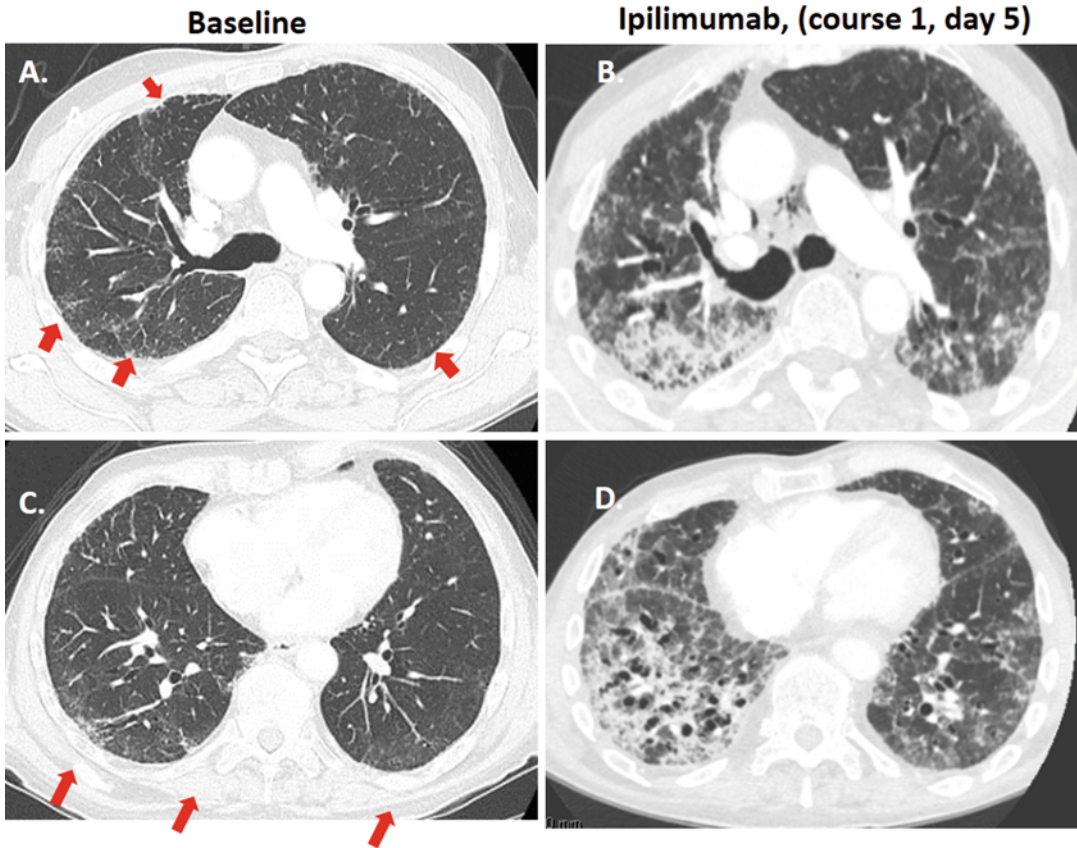


Fig. 2 Ipilimumab-induced lung injury. A 78-year-old man treated with combined ipilimumab monotherapy for melanoma presented 5 days after cycle 1 of therapy with dyspnea and dry cough. Asymptomatic idiopathic pulmonary fibrosis was coincidentally found on CT imaging studies 5 years prior to the cancer diagnosis. Subtle,

subpleural reticular changes at baseline (arrows, **a**, **c**) are consistent with the patient's known history of pulmonary fibrosis. Extensive superimposed areas of bilateral ground-glass densities are seen on the admitting CT (**b**, **d**), which corresponded to organizing pneumonia on lung biopsies, felt to be related to ipilimumab

antigen receptor (CAR). The modified T cells are expanded and infused into the recipient through a process called adoptive cell transfer. The two major classes of engineered T cell therapies, known as chimeric antigen receptor T cells (CAR-T) and bispecific T cell engagers (BiTEs), have advantages over conventional therapies in their ability to target unique antigens on tumor cells with a precision that standard chemotherapy and radiation cannot, resulting in cytologic killing of specific antigen-positive tumor targets. In addition, these agents have the capacity to promote large-scale T cell expansion [96–101]. BiTEs are antibody-derived molecules with dual antigen specificity, allowing them to simultaneously bind unique antigens on the T cell and the tumor cell,

thereby facilitating cytotoxic cell-to-cell interactions and tumor cell killing.

Engineered T cells are “living drugs” which may induce organ toxicity well after discontinuation of the agent. The most prominent toxicity of both CAR-T and BiTE therapies is cytokine release syndrome (CRS), a systemic inflammatory response that is thought to be caused by rapid T cell proliferation with the toxic release of pro-inflammatory cytokines, such as IFN- γ , TNF- α , and IL-6 following therapy. These cytokines may promote damage to the endothelium and other organs, resulting in microvascular leakage, and potentially fatal organ system damage to the heart, liver, lung, and kidneys [102]. Patients may present with rapid onset of

Table 4 CTCAE scoring system and consensus guidelines in the management of lung injury associated with immune checkpoint inhibitor therapies

Pneumonitis grade	Clinical symptoms	Treatment recommendations
1	Asymptomatic	Withhold therapy; close clinical and diagnostic follow-up to determine timing and feasibility of resumption of therapy; if evidence of disease progression, treat as higher-grade pneumonitis
2	Mild symptoms of dyspnea with moderate exertion; minimal interference with activities of daily living	Withhold therapy; initiate corticosteroid therapy in select cases; close clinical and diagnostic follow-up to determine timing and feasibility of resumption of therapy; if evidence of disease progression, treat as higher-grade pneumonitis
3	Dyspnea at rest; dyspnea limits activities of daily living and self-care	Discontinue therapy; hospitalize and initiate corticosteroid therapy; if evidence of disease progression, treat as higher-grade pneumonitis
4	Severe, life-threatening symptoms, respiratory compromise	Permanent discontinuation of therapy; hospitalize with higher-level (ICU) care; initiate corticosteroid therapy

high fever, rigors, chills, myalgias, dyspnea, hypoxia, and hemodynamic instability 4–16 h following drug infusion (Fig. 3). Supportive care, including fluid resuscitation, vasopressor support, supplemental oxygen, and intubation, may be required for patients with severe symptoms. Systemic corticosteroids and treatment with IL-6 receptor-directed therapy with tocilizumab are also used to suppress the intense inflammatory response [96, 103, 104].

Radiation-Induced Lung Injury

Clinically significant radiation-induced lung injury (RILI) is the most common dose-limiting complication of thoracic radiation therapy (RT), occurring in 5–20% of patients. Recent advances in radiation techniques and delivery systems, such as proton therapy, three-dimensional conformal RT (CRT), intensity-modulated RT (IMRT), and stereotactic body RT (SBRT), purport lower lung injury rates while delivering higher target doses of radiation to the lung. Factors associated with radiation delivery (total radiation dose, dose per fraction, volume of irradiated lung, and beam characteristics and arrangements) and clinical factors (preexisting lung disease, underlying poor pulmonary reserve, prior radiotherapy, multimodality regimens, rapid steroid withdrawal) all potentiate the appearance and severity of radiation pneumotoxicity.

Radiographically apparent lung injury is common with total doses of radiation that exceed 40 Gy and is rare at doses below 20 Gy [105, 106]. Hyperfractionated radiation doses delivered to the smallest lung volume are recommended.

Clinical Presentation

Acute clinical radiation pneumonitis, heralded by dyspnea, low-grade fever, and dry cough, develops insidiously over 1–3 months after completion of radiation. Radiographic changes typically precede clinical symptoms, appearing 3–4 weeks following RT. Discrete ground-glass opacities, ill-defined patchy nodules, or consolidation with air bronchograms and volume loss within the irradiated field are common early findings which evolve over the ensuing 6–23 months, leaving a linear scar. Regional fibrosis is seen in nearly all patients, including those without clinical symptoms, and is characterized by the appearance of a well-demarcated area of volume loss, linear densities, bronchiectasis, retraction of the lung parenchyma, tenting and elevation of the hemidiaphragm, and ipsilateral pleural thickening within the irradiated field (Fig. 4). Post-radiation volume loss, bronchiectasis, and consolidation may occur following the newer modes of RT delivery but typically are less extensive than injury patterns following conventional radiation [107].

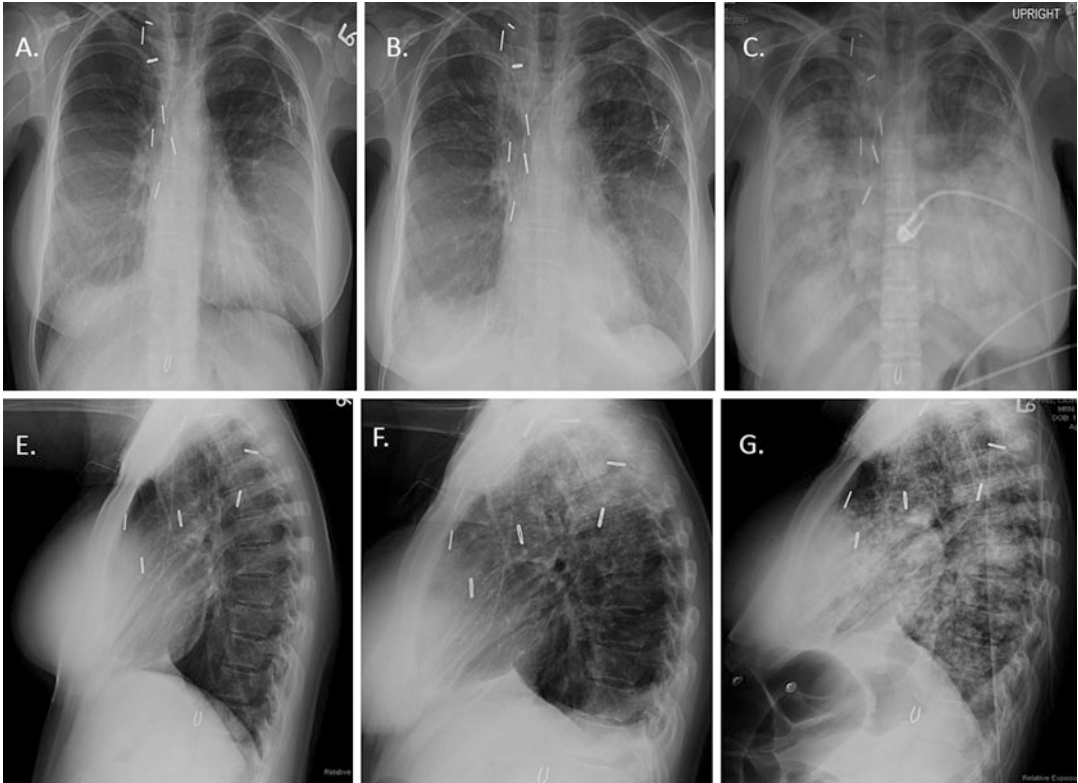


Fig. 3 Cytokine release syndrome associated with blinatumomab therapy. A 47-year-old woman developed acute, severe dyspnea, dry cough, and low-grade fever 7 h following infusion of blinatumomab for refractory ALL. Over the ensuing 24 h, the patient required vasopressor support and was intubated and placed on mechanical

ventilation for hypoxemic respiratory failure. Bronchoscopically obtained distal airway samples were culture negative and without evidence of malignant cells. The patient was started on high-dose steroids and tocilizumab but succumbed to refractory hypoxemia and hypotension, felt to be due to cytokine release syndrome

Radiation Recall Pneumonitis

Radiation recall pneumonitis (RRP) is a rare inflammatory reaction that develops within a previously irradiated field following certain chemotherapy and molecularly targeted therapies. This reaction has been most often observed following taxane- and anthracycline-based therapies. Gemcitabine, etoposide, vinorelbine, trastuzumab, and erlotinib may also trigger this disease [108, 109]. Clinically, RRP is signaled by dry cough, fever, and dyspnea and accompanied by ground-glass opacities and areas of consolidation that conform to the prior radiation treatment portal. RRP may develop during the first or subsequent course of therapy with the inciting agent,

which may be weeks to years following completion of RT. Drug withdrawal and corticosteroid therapy may mitigate symptoms of radiation pneumonitis but have not been shown to be of benefit in the treatment of radiation fibrosis. Drug reintroduction has been successful in some cases [110].

Other Manifestations of Radiation-Induced Lung Injury

Pleural effusions may develop as early (within 6 months) and late (1–5 years) sequelae of RT. Effusions are typically small, ipsilateral, or bilateral. Reactive mesothelial cells with

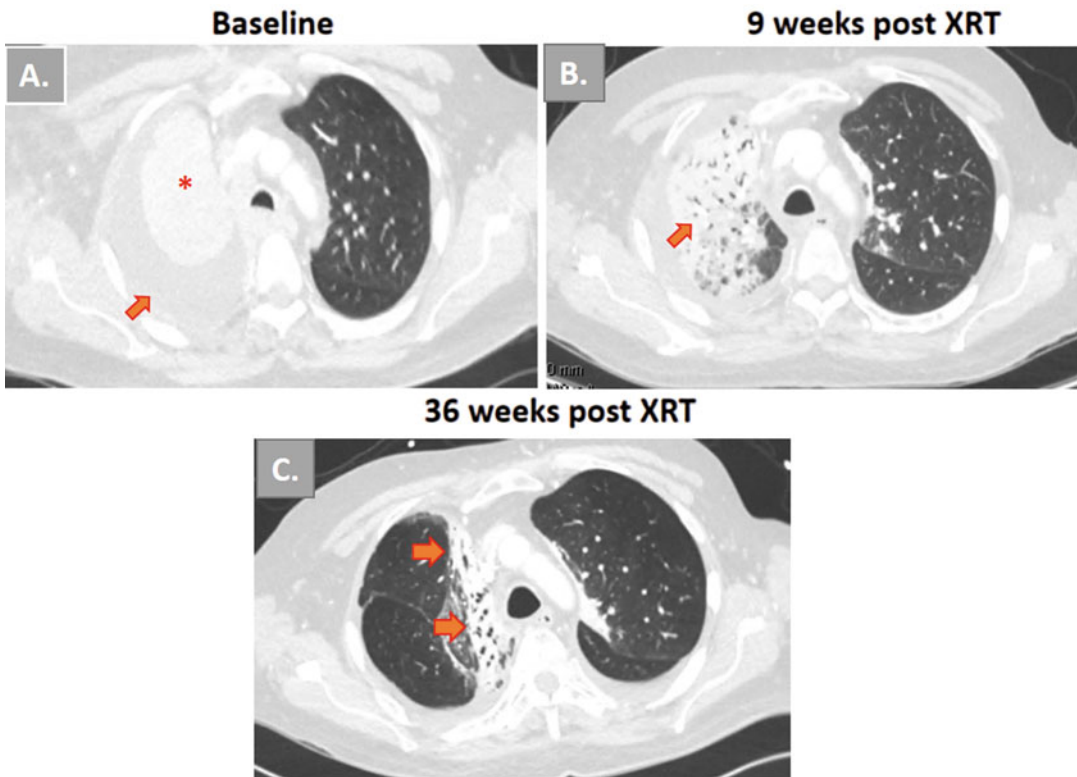


Fig. 4 Evolution of radiation-induced lung injury. A 56-year-old man underwent radiation therapy to the right upper and middle lobes and paramediastinal areas for primary bronchogenic carcinoma. At baseline, (a) a large central mass involving the right upper and middle lobes (*) along with a moderate-sized right pleural effusion (arrow) is seen. Nine weeks after completion of radiation therapy (b), there are dense consolidative opacities in the

right lung (arrow), consistent with evolving radiation changes. The large mass-like consolidation has resolved. Nine months following completion of radiation therapy (c), linear densities outlining a well-demarcated area of volume loss (arrows), bronchiectasis, retraction of the lung parenchyma, and ipsilateral pleural thickening within the irradiated field are seen

negative pleural fluid cytology are common. Most radiation-induced pleural effusions are asymptomatic, although pleuritic chest pain and dyspnea are occasionally presenting symptoms. Radiation-related organizing pneumonia (OP) and eosinophilic pneumonia (EP) have been described in patients with breast cancer and may involve nonirradiated areas of the lung [107, 111]. These lung injury patterns are characterized by migratory pulmonary opacities that develop 1–3 months after completing RT. A prior history of asthma or atopy, coupled with blood or tissue eosinophilia, supports the diagnosis of radiation-induced EP. Both lung injury patterns are typically steroid-responsive.

Management of Radiation-Induced Lung Injury

Treatment recommendations for DILI in the cancer setting are generally provided by collective clinical experience and expert opinion. Pneumonitis grading schemes, based on the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) [112], offer limited guidelines for drug withdrawal and initiation of immunosuppressive therapies based on symptom severity. Permanent drug cessation is recommended for most DILI events associated with cytotoxic drugs; however, indications for drug interruption and resumption may vary with the specific class of agents in

question. Resolution of pulmonary toxicity may occur following drug simple interruption in some patients. Thus, close follow-up while withholding corticosteroid therapy in asymptomatic patients with stable and mild disease is reasonable. Initiation of systemic corticosteroids is generally based on the acuity, severity, and rapidity of worsening of pulmonary impairment as well as the histopathologic patterns of disease. The benefits of corticosteroids in this setting are largely observational and gleaned from anecdotal reports and small case series. Evidence-based guidelines informing the optimal timing, dose, and duration of corticosteroid therapy do not exist. Prednisolone or its equivalent, dosed at 0.5–1 mg/kg/day, is typical, with dosing and tapering schedules guided by the radiologic and clinical symptoms and response to therapy. Additional therapies, such as cyclophosphamide, macrolides, cyclosporine, rituximab, and infliximab, may be indicated in steroid-refractory patients. Evidence favoring a benefit in these cases is also anecdotal and limited to small case series.

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