Published in final edited form as:

Expert Rev Anticancer Ther. 2018 October ; 18(10): 1041–1057. doi:10.1080/14737140.2018.1500180.

Anticancer therapy and lung injury: molecular mechanisms

Li Li^{1,2}, Henry Mok¹, Pavan Jhaveri¹, Mark D Bonnen¹, Andrew G Sikora³, N. Tony Eissa⁴, Ritsuko U Komaki⁵, and Yohannes T Ghebre, Ph.D.^{1,4}

¹Department of Radiation Oncology, Baylor College of Medicine, Houston, Texas, USA

²Department of Endocrinology, Xinqiao Hospital, Third Military Medical University, Chongqing, China

³Department of Otolaryngology - Head and Neck Surgery, Baylor College of Medicine, Houston, Texas, USA

⁴Department of Medicine, Section on Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas, USA

⁵University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Introduction: Chemotherapy and radiation therapy are two mainstream strategies applied in the treatment of cancer that is not operable. Patients with hematological or solid tumor malignancies substantially benefit from chemotherapeutic drugs and/or ionizing radiation delivered to the site of malignancy. However, considerable adverse effects, including lung inflammation and fibrosis, are associated with the use of these treatment modalities.

Areas covered: As we move towards the era of precision health, we are compelled to understand the molecular basis of chemoradiation-induced pathological lung remodeling and to develop effective treatment strategies that mitigate the development of chronic lung disease (i.e. fibrosis) in cancer patients. The review discusses chemotherapeutic agents that are reported to induce or associate with acute and/or chronic lung injury.

Expert commentary: There is a need to molecularly understand how chemotherapeutic drugs induce or associate with respiratory toxicities and whether such characteristics are inherently related to their anti-tumor effect or are collateral. Once such mechanisms have been identified and/or fully characterized, they may be able to guide disease-management decisions including

Corresponding author: Yohannes T Ghebre, Ph.D., Department of Radiation Oncology, Baylor College of Medicine, Houston, Texas 77030, USA., yohannes.ghebre@bcm.edu, Tel: 713-798-3619, Fax: 713-798-6923.

Declaration of interest

YT Ghebre has received funding from the National Institutes of Health and is a co-founder of Altitude Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Reference annotations

* Of interest

** Of considerable interest

effective intervention strategies for the adverse effects. In the meantime, radiation oncologists should be judicious on the dose of radiation delivered to the lungs, the volume of lung irradiated, and concurrent use of chemotherapeutic drugs.

Keywords

chemotherapy; lung fibrosis; lung inflammation; pulmonary toxicity; radiation therapy

1.0. Introduction

Chemotherapeutic drugs and radiation procedures are the cornerstone of radiation oncology and its critical role in the treatment of hematological and solid tumor malignancies. As part of the standard of care approach for the treatment of various cancer types, these treatment modalities have contributed towards achieving remarkable outcomes in reducing tumor burden, metastasis, cancer relapse, and overall mortality to positively impact the lifespan and quality of life of cancer patients. For example, small molecule- and antibody- based systemic therapies have been used to target processes such as DNA replication and repair or to specifically inhibit molecular pathways that support the proliferation and/or growth of cancer cells throughout the body. By contrast, ionizing radiation is directly focused on body regions containing tumors in order to directly kill the tumor cells. In this regard, conformal thoracic radiotherapy is directed to the chest and chest wall to treat cancers of the lung and breast, mediastinal malignancies and lymphomas. Unfortunately, chemotherapies such as bleomycin and ionizing radiations such as x-rays are often associated with significant pulmonary toxicities including the development of pneumonitis and fibrosis. Acute chemoradiation-induced pneumonitis is characterized by wide-spread inflammation of the lungs and occurs in up to 15% of all irradiated patients typically within few weeks after completing therapy. Although the pneumonitis eventually subsides in some of the patients, some reports indicate that the majority of these patients progress to developing lung fibrosis. Pulmonary fibrosis is a deadly disease characterized by scarring (collagen deposition) and stiffening of the lungs leading to persistent shortness of breath (dyspnea) and eventual death within 3 to 4 years of diagnosis. Unfortunately, there is no drug that can reverse established lung fibrosis and the principal option for patients at late stages of the disease is lung transplantation, which is often complicated by immunological and logistical issues.

The effect of chemoradiation on the pulmonary system may be attributed to the biological mechanisms by which these treatment modalities work including induction of DNA damage and oxidative stress to induce senescence and cell death. The inability of senescent cells to proliferate coupled with increased death of resident cells exposes the lungs and its vascular network to impaired physiological repair mechanisms and accelerated injury.

2.0. Chemotherapeutic agents and lung injury

2.1. Animal models of lung injury

There are several animal models of lung injury that reportedly recapitulate the inflammatory and fibrotic phases of chronic lung disease perpetrated by chemotherapeutic drugs, radiation and other agents. Among these preclinical models, the mouse model of bleomycin-induced

lung injury is widely accepted. In this model, C3H/HeJ, C57BL/6 or other mouse strains are subjected to single or repeated doses of bleomycin intratracheally. Lung inflammation develops within the first two weeks following administration of bleomycin and subsequently progresses to fibrosis in the ensuing 2–3 weeks [1]. Given the similarities in the induction of direct cell injury via DNA damage, other chemotherapeutic drugs may be tested in this animal model for their potential lung toxicity. By contrast, the C3H/HeJ strain is resistant to radiation-induced lung injury in comparison to the C57BL/6 strain which develops vascular remodeling and lung fibrosis upon exposure to 12 to 15 Gy of ionizing radiation. Overall, the inflammatory and fibrotic response to various agents including chemotherapy and radiation is strain-dependent. Therefore, additional mouse strains such as the C3H/HeN, NZB, MRL/MpJ and CBA/J and Balb/c should be considered when screening for lung toxicity of anti-cancer drugs. Below is a description of various chemotherapeutic drugs that have been reported to be associated with cases of lung injury.

2.2. Antitumor antibiotics

A number of antimicrobial agents have been evaluated for their potential to treat neoplastic disorders. Some of these antineoplastic antimicrobials include macrolides (e.g. azithromycin), glycopeptides (e.g. bleomycin), glycyclcyclines (e.g. tigecycline), tetracyclines (e.g. doxycycline) and amphenicols (e.g. chloramphenicol). Among the glycopeptides, bleomycin is by far the most common drug associated with lung injury in cancer patients.

2.2.1. Bleomycin—Isolated in the 1960s from gram-positive bacteria, bleomycins (bleomycin A₂ and pingyangmycin) are widely used natural products for the treatment of various malignancies including Hodgkin's and non-Hodgkin's lymphomas, ovarian, cervical, bladder, lung, and head and neck cancers. Depending on the type of cancer being treated, bleomycin A₂ (bleomycin) is administered through various routes including intravenous (IV), subcutaneous (SC), intramuscular (IM), and intratumoral (IT). The drug is associated with acute and chronic side effects including hair loss, emesis, loss of weight, lung inflammation (pneumonitis), scarring (fibrosis), and loss of lung function (e.g. decrease in the diffusion capacity of the lungs for carbon monoxide; DLCO). The pulmonary toxicities occur in over 40% of cancer patients treated with bleomycin-containing chemotherapeutic regimen [2]. Although the precise mechanism by which bleomycin causes lung injury is not known, some studies indicate that these effects might be inherently associated with its anti-cancer effect including generation of reactive oxygen species (ROS), induction of DNA damage and inhibition of new DNA synthesis [3]. The increase in oxidative stress upon bleomycin treatment is part of the mechanism by which bleomycin facilitates the degradation of nucleic acids (DNA and RNA). This concept is further supported by preclinical data that demonstrate suppression of bleomycin-induced lung injury using antioxidants [4].

Additional studies also indicate that inflammatory cytokines and chemokines including tumor necrosis factor alpha (TNF- α), interleukin 1 beta (IL-1 β), monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor beta (TGF- β) are involved in the process of bleomycin-induced lung injury [4]. The induction of lung TNF- α by bleomycin is

reported to involve T-lymphocytes and macrophages, and significantly contribute to inflammation of the alveoli (alveolitis), overproliferation of fibroblasts and excess deposition of collagen [5]. Additional mechanisms identified in bleomycin-induced lung injury are activation of death signals such as the Fas-Fas Ligand and caspases, as well as sequestration of redox-active metals such as iron and copper from cellular processes [6]. Other contributors of bleomycin-induced lung injury are age, the total drug dose received, history of radiation therapy to the chest, exposure to high levels of oxygen therapy, and pre-existing interstitial lung disease [7].

A great deal of the lessons learned about the adverse pulmonary effects perpetrated by bleomycin come from animal models of bleomycin-induced lung injury [8]. In small animal models (mouse, rat and hamster), instillation of bleomycin through the trachea induces acute inflammatory response that involves recruitment of inflammatory cells and pro-inflammatory molecules, as well as injury or death to alveolar epithelial and vascular endothelial cells. Within 2 weeks, the inflammatory phase, which lasts about 10 days, is followed by upregulation of profibrotic cytokines including TGF- β , increased proliferation of lung fibroblasts and transdifferentiation into myofibroblasts resulting in accumulation of extracellular matrix (ECM) components such as collagen. As a result, the lungs become fibrosed with significant loss in compliance including forced vital capacity (FVC). Despite recapitulating many of the clinical features of bleomycin-induced lung injury in humans, main limitation of this animal model is the reversibility of the lung injury induced by bleomycin [8].

2.2.2. Mitomycin C—Is an anticancer drug used for over 40 years in the treatment of cancers of the breast and upper gastrointestinal tract. As an antitumor antibiotics, one of its main mechanisms in killing bacteria and cancer cells is the potent DNA cross-linking activity by which mitomycin is chemically transformed to mitosene; a DNA reactive compound [9]. As a result, mitomycin C is involved in inhibition of DNA synthesis, induction of genetic recombination events and mutagenesis of mammalian DNA. In addition, the drug is involved in the generation of ROS and other species that are highly tissue reactive and capable of causing apoptotic cell death and tissue injury [10]. One of the tissues that suffer collateral damage upon mitomycin C treatment is the lungs. The use of mitomycin C in some cancer patients is associated with higher incidences of interstitial pneumonitis, pulmonary fibrosis and pulmonary veno-occlusive disease (PVOD) [11]. Mechanistically, mitomycin C-induced pulmonary injury might be associated with the downregulation of members of the SMAD signaling pathway and inhibition of the general control nonderepressible 2 protein (GCN2); a protein encoded by the Eukaryotic Translation Initiation Factor 2 α Kinase 4 (EIF2 α K4) [11]. Genetic mutations in the EIF2 α K4 gene are reported to be associated with hereditary PVOD [12].

2.2.3. Actinomycin D—Actinomycin D was the first of the antibiotics demonstrated to possess antitumor activity. Ever since, it has been used as an anti-cancer agent in the treatment of various cancers including Wilm's tumor and Ewing's sarcoma [13]. Similar to bleomycin and mitomycin C, actinomycin D is associated with lung injury in patients treated with this agent. In addition, actinomycin D increases the severity of pulmonary toxicity

when combined with radiation therapy in patients undergoing thoracic irradiation [14]. The likely mechanism by which actinomycin D induces lung injury is the interference with DNA replication and subsequent elongation of RNA chains [15].

2.2.4. Anthracyclines—These are a class of antitumor antibiotics used to treat hematological and solid tumor malignancies. Members of this class include doxorubicin, daunorubicin, epirubicin and idarubicin. Their interference with nucleic acid synthesis and protein production, inhibition of topoisomerase II enzymatic activity, as well as stimulation of ROS production are key mechanisms of action for the antitumor effect of anthracyclines. Although cardiotoxicity is the more common side effect of anthracyclines in patients, pulmonary complications can be a significant issue associated with the use of anthracyclines. For example, the treatment of angiosarcoma patients with doxorubicin has been reported to be associated with severe pulmonary toxicity including fibrosis [16].

2.3. Alkylating agents

Alkylating antineoplastic agents are a class of chemotherapeutic drugs that recognize and directly interact with DNA by transferring their alkyl group to the DNA base. Alkylating agents are very effective in treating several cancer types including hematologic malignancies, breast cancer and lung cancer. Examples of alkylating antineoplastic agents include nitrogen mustards (e.g. cyclophosphamide, chlorambucil), nitrosureas (e.g. carmustine, streptozocin), hydrazines (procarbazine, temozolomide), alkyl sulfonates (e.g. busulfan), and metal salts (cisplatin, carboplatin). Preclinical studies and case reports indicate that these agents have significant adverse effects including causing lung toxicity that extends from acute pneumonitis, to late-onset pneumonitis that progresses into fibrosis [17].

2.3.1. Nitrogen mustards—Are mustard gas-derived chemotherapeutic agents that work through alkylation of DNA molecules to form interstrand crosslinks that stimulate apoptotic pathways. Examples of nitrogen mustard-based chemotherapeutics include cyclophosphamide, chlorambucil, melphalan and busulfan.

2.3.1.1. Cyclophosphamide: This alkylating agent has been used for over 50 years as both anticancer and immunosuppressive drug. As an anticancer drug, cyclophosphamide has been used in combination therapy to treat many cancer types including acute and chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, breast, ovarian, and lung cancers. Meanwhile, its suppressive action on cells of the immune system (e.g. regulatory T cells) makes it a useful drug to treat autoimmune diseases including multiple sclerosis, rheumatoid arthritis and to suppress organ rejection in transplant recipients. Although it is not one of the most common side effects that follow cyclophosphamide treatment, lung toxicity is a notable complication that accounts for up to 1% of patients treated with regimens that contain cyclophosphamide [18, 19]. The incidence of cyclophosphamide-associated lung toxicity is likely higher if patients are on concurrent treatment regimens such as oxygen therapy, radiation therapy or receiving other alkylating agents. A case series study reported that cyclophosphamide-induced lung toxicity was associated with significant respiratory abnormalities including shortness of breath, nonproductive cough, bilateral pleural thickening, gas exchange abnormalities, pulmonary hypertension, and death due to

respiratory failure [18]. Histopathological studies indicate that cyclophosphamide-induced lung toxicity has nonspecific features including vascular sclerosis, overproliferation of type II pneumocytes and accumulation of nonresident cells in the alveolar and bronchiolar epithelium [20].

Mechanistically, cyclophosphamide-induced lung toxicity involves increased expression of TGF β , fibronectin and procollagen. However, the precise mechanism by which cyclophosphamide induces expression of the profibrotic molecules is not known. Additional studies suggest the contribution of DNA damage and oxidative stress to the processes involved in cyclophosphamide-induced lung toxicity [21].

2.3.1.2. Chlorambucil: This nitrogen mustard derivative is associated with interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP) and lung fibrosis in patients receiving this agent for lymphoproliferative malignancies including chronic lymphocytic leukemia (CLL), myeloproliferative disorders such as polycythemia vera, and autoimmune diseases such as sarcoidosis [22, 23]. Several case studies have reported patients with chlorambucil-induced lung injuries [22–24]. Some of the defined pulmonary features in these case reports include shortness of breath, reduced DLCO, increased interstitial opacities, alveolitis, as well as intraalveolar and interstitial fibrosis.

Although no specific mechanisms linked to chlorambucil-induced lung injury have been reported, it is speculated that its mechanism of action is similar to that of other alkylating agents including generation of ROS, and disruption in physiological alveolar repair mechanisms that results in diffuse alveolar damage including fibrosis [25, 26].

2.3.1.3. Melphalan: This alkylating agent is frequently used to treat patients with multiple myeloma and infrequently used in patients receiving stem cell therapy [27]. Pulmonary complications associated with this agent include acute bronchoconstriction, diffuse interstitial pneumonitis and fibrosis. Preclinical studies with melphalan exposure have found excessive generation of proinflammatory molecules such as IL-1 β , IL-6 and IL-23 in the airways, as well as infiltration of neutrophils and other immune cell types in the lungs [28]. Overexpression of interleukins (e.g. IL-1 β) is known to induce acute lung injury and sustain higher expression of profibrotic molecules including TGF β in animal models of lung injury [29].

2.3.1.4. Busulfan: This is an alkylating agent used in the treatment of chronic myeloid leukemia (CML) or as part of conditioning regimen prior to bone marrow transplantation. Significant pulmonary toxicity occurs in about 5% of patients receiving this agent. The common respiratory symptoms that occur following busulfan therapy include cough, shortness of breath, alveolar hemorrhage, bronchiolitis obliterans, as well as progressive intraalveolar and interstitial fibrosis up to about a decade following exposure to busulfan [30].

The mechanism(s) by which busulfan induces acute and chronic lung injury is largely unknown. However, common mechanisms associated with alkylating agents including

oxidative stress and overactivation of signaling pathways associated with inflammation and cell proliferation is a possibility.

2.4. Platinoids

Platinum-based chemotherapeutic drugs (platinoids) are commonly used to treat a number of malignancies in up to 50% of cancer patients including patients with cervical, testicular, and lung cancers [31]. Examples of platinoids include cisplatin, carboplatin and oxaliplatin. Their mechanism of action in killing cancer cells is inhibition of DNA synthesis and repair to halt transcription. Although the most pronounced side effect in patients treated with platinum-based chemotherapy is neurotoxicity, lung injury has been among the reported complications in lung cancer patients exposed to the platinoids.

2.4.1. Cisplatin—Is a chemotherapeutic drug used in the treatment of cancers including head and neck, ovarian, testicular, breast and lung. The drug inhibits cancer cell proliferation by interfering with their DNA replication through crosslinking and subsequent activation of apoptotic signaling [32]. In addition, cisplatin increases intracellular concentration of free radicals. Side effects associated with cisplatin therapy include nephro-, neuro-, and cardio-toxicities. Regarding the association of cisplatin use and lung injury, a case report indicates the induction of eosinophilic pneumonia by this drug [33]. In addition, concomitant use of cisplatin with bleomycin may reduce the renal clearance of bleomycin and consequently increase the risk of lung toxicity.

2.4.2. Carboplatin—This platinoid is used in the treatment of ovarian, brain and lung cancers. Although it is a relatively safe drug compared to cisplatin, incidents of severe lung fibrosis have been documented when carboplatin is combined with alkaloid agents such as vinorelbine and radiation therapy [34]. Another case study reported that combination of carboplatin with paclitaxel induced significant decline in DLCO ($99\% \pm 36\%$ of the predicted value Vs. $74\% \pm 31\%$ of the predicted value) for at least 5 months following completion of the chemotherapy in a subset of cancer patients [35]. Similar to cisplatin and carboplatin, isolated cases of interstitial pneumonitis and pulmonary fibrosis have been reported for oxaliplatin, mainly when used as an adjuvant therapy. However, it is very rare for the platinoids as monotherapy to cause lung injury.

2.5. Antimetabolites

This class of chemotherapeutic agents is composed of metabolite-like structures that often mimic folic acid, purines, and pyrimidines. Antimetabolites interfere with cellular metabolic pathways including folic acid and DNA synthesis to treat a range of malignancies including leukemia, ovarian, breast and colon cancers. Examples of antimetabolites include analogs of folic acid (e.g. methotrexate), purines (e.g. fludarabine, thioguanine, pentostatin), and pyrimidines (5-Fluorouracil (5-FU), gemcitabine). Examples of each analog that are associated with lung toxicity are described below.

2.5.1. Methotrexate—Is a folic acid analogue chemotherapy used in the treatment of cancers of the lung, breast, skin, head and neck. In addition, the drug is used in the treatment of autoimmune diseases including rheumatoid arthritis. The later indication is due to

methotrexate's immunomodulatory effect including regulation of cell proliferation and inflammation. Studies indicate that up to 7% of arthritis patients treated with methotrexate manifest pulmonary toxicity [36]. In addition, several case studies of cancer patients report methotrexate-associated lung toxicities including hypersensitivity pneumonitis, bronchiolitis obliterans, and pulmonary fibrosis [37, 38]. Although the mechanism by which methotrexate causes lung injury is unclear, the induction of excessive free radicals in cellular compartments may dysregulate mitochondrial function and enhance alveolar epithelial cell injury and aberrant lung remodeling [39]. Additional studies have linked methotrexate treatment with induction of interleukins and activation of several members of the p38 MAPK that are known to be involved in lung inflammation and fibrosis [40].

2.5.2. Fludarabine—Is a purine nucleoside analog that is used to treat chronic lymphoproliferative disorders including lymphoma and leukemia. The use of fludarabine in chronic lymphocytic leukemia (CLL) patients has been associated with pulmonary nodules, interstitial pneumonitis and pulmonary fibrosis [41]. As a purine analog, interference with DNA replication and induction of endonuclease-independent apoptosis are the likely mechanisms by which fludarabine is involved in the killing of the rapidly proliferating cancer cells and depletion of immune cells [42]. However, it is unclear whether these are also the mechanism by which the use of fludarabine promotes lung inflammation and fibrosis. Notably, the lung toxicity associated with fludarabine use is responsive to corticosteroid therapy including resolution of abnormal radiographic findings suggesting that the mechanism of action might involve the immune response [41].

2.5.3. Gemcitabine—Is a pyrimidine nucleoside analog associated with several pulmonary complications including dyspnea, noncardiogenic pulmonary edema, pulmonary veno-occlusive disease, pleural effusion, diffuse alveolar damage, interstitial pneumonitis and lung fibrosis [43] that may lead to abnormal lung function tests. First approved for medical use in the 1990s, gemcitabine is used to treat multiple cancer types including breast and lung cancers. Although the incidence of lung toxicity is below 1%, combination of gemcitabine with other chemotherapeutic drugs such as bleomycin and/or radiation therapy increases the incidence rate by up to 40-fold [44, 45]. Mechanistically, gemcitabine is known to induce the systemic release of pro-inflammatory molecules including cytokines and interleukins. A study has reported the direct correlation of TNF- α levels with the severity of lung toxicity [46]. The later effect of gemcitabine is expected to damage the pulmonary vasculature and drive the lung inflammation seen in cancer patients exposed to gemcitabine therapy [47]. This possibility is further supported by the clinical response of gemcitabine-associated pulmonary toxicity to corticosteroid therapy [48].

2.6. Nitrosoureas

Are a class of nitrogen mustard related alkylating agents used in the treatment of neoplastic disorders including multiple myeloma and small cell lung cancer. Examples of nitrosoureas include carmustine, lomustine, semustine and streptozocin. Although nitrosoureas are rarely associated with lung toxicity, administration of large and/or repeated doses of select members has been reported to be associated with an increased risk of pulmonary fibrosis.

Below is a brief description of the most common nitrosourea, carmustine, in the context of lung toxicity.

2.6.1. Carmustine—Is a commonly used nitrosourea in the treatment of brain cancers including glioblastoma multiforme and medulloblastoma. In addition, carmustine is used as an immunosuppressive agent in multiple myeloma and in preparation to stem cell or organ transplantation. Whether used in the treatment of cancer or autoimmune disease, carmustine is associated with significant pulmonary toxicity in 30% or more of patients receiving this drug [49, 50]. In fact, this alkylating agent is used to deliberately induce lung injury in preclinical animal models [51]. Clinically, histologic and radiologic findings include pneumothorax, pneumonitis and interstitial fibrosis. Pulmonary function testing also shows reduced DLCO [52]. The differential targeting of lung glutathione disulfide (GSSG) reductase by carmustine [53] might drive oxidative stress in the pulmonary microenvironment to disrupt lung homeostasis and augment toxicity. In addition, carmustine has been reported to induce the expression of fibrogenic cytokines including platelet-derived growth factor-B (PDGF-B) and insulin-like growth factor I (IGF-I) in alveolar macrophages and type II pneumocytes [54]. Other nitrosourea members including lomustine and semustine have also been reported to cause pulmonary toxicity; albeit at a lower frequency than carmustine [55, 56].

3.0. Receptor Tyrosine Kinase Inhibitors

Are cell membrane bound receptors for several major growth factors including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). Collectively, they significantly regulate cell fate including proliferation and survival. Many of the receptor tyrosine kinases and their ligands have been linked to the development of cancer and hence have been pharmacologically targeted by various agents including small molecules. Several studies have reported pulmonary toxicities associated with receptor tyrosine kinase inhibitors (RTKIs) including inhibitors of the receptors for VEGF, FGF, EGF and PDGF. Surprisingly, over 50% of the currently approved RTKIs are associated with interstitial lung disease [57]. Below is brief description of the most commonly used RTKIs that have been associated with lung toxicity.

3.1. Gefitinib

Is an EGF receptor (EGFR) inhibitor approved in 2003 for the treatment of glioma and cancers of the esophagus, breast and lung. Although the drug is commonly associated with several side effects, pulmonary toxicity including pneumonitis and interstitial lung disease are seen infrequently (below 1% of patients) [58, 59]. In the affected patients, High Resolution Computed Tomography (HRCT) scans show progressive ground-glass opacities, consolidation and bronchiectasis. Clinical assessment also shows cough and shortness of breath. Mechanistically, studies have found significant elevation of the chemokine interferon-inducible protein-10 (IP-10) expression and speculated the involvement of Th1 response in gefitinib-induced pulmonary toxicity [58]. In addition, the targeted inhibition of EGFR by gefitinib is expected to downregulate EGFR phosphorylation and subsequently reduce the proliferative and regenerative capacity of alveolar epithelial cells. EGFR-

activated tyrosine kinase is known to regulate cell growth, differentiation and apoptosis. In addition, EGFR is known to directly interact with TGF- α [60]; a molecule with profound role in lung inflammation and fibrosis. Similar to gefitinib, other orally active small molecule inhibitors of EGFR such as erlotinib and cetuximab have also been associated with pulmonary toxicity [61, 62].

3.2. Imatinib

Is a potent PDGF receptor (PDGFR) inhibitor that has been in use for over 15 years in the treatment of gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia with Philadelphia chromosome translocation. Although the primary mechanism of action is inhibition of tyrosine kinase enzymes including the Abelson proto-oncogene (Abl), c-Kit (CD117) and PDGFR, imatinib also targets additional signaling pathways such as Src kinases, Ras/MAPK and JAK/STAT pathway. Pulmonary toxicity including progressive shortness of breath, pulmonary edema, pleural effusion, interstitial pneumonitis and fibrosis have been observed in patients who received imatinib therapy [63, 64]. In addition, infiltration of inflammatory cells such as macrophages and eosinophils have been observed in bronchoalveolar lavage (BAL) of patients receiving imatinib therapy. In rare cases, pulmonary alveolar proteinosis, where surfactant accumulates in lung air sacs, has been reported following imatinib therapy [65]. However, in some patients, some of the imatinib-induced respiratory complications are reversible upon discontinuation of imatinib and/or initiation of steroid therapy [66, 67]. Although the differential mechanism by which imatinib induces lung-specific toxicity is not clear, as an inhibitor of an essential growth factor receptor (i.e. PDGFR), imatinib may impair the regenerative capacity of lung epithelial cells following an injury, which may in turn compromise barrier function and accelerate pulmonary toxicity [68].

3.3. Sorafenib

Is a multikinase inhibitor targeting receptors for VEGF and PDGF, as well as other family of kinases including Raf/MEK/ERK to treat kidney, liver, and thyroid cancers. Several case reports indicate that treatment of cancer patients with sorafenib is associated with various lung toxicities including interstitial pneumonitis and diffuse alveolar damage [69, 70]. Mechanistically, sorafenib regulates epithelial-to-mesenchymal transition (EMT), autophagy and angiogenesis to suppress tumor growth and vascularity [71, 72]. This antitumor effect as well as complications including lung toxicity are likely to be due to the effect of the drug on the VEGF pathway. Reduction of intrapulmonary VEGF has been associated with lung injury including decreased lung perfusion whereas its restoration correlates with recovery and cell survival at the preclinical level and in patients with high-altitude pulmonary edema (HAPE), idiopathic pulmonary fibrosis (IPF) and acute respiratory distress syndrome (ARDS) [73–75]. Similar to sorafenib, sunitinib is another multikinase inhibitor that has been associated, albeit very rarely, with pulmonary toxicity including recall pneumonitis [76].

4.0. Topoisomerase Inhibitors

Topoisomerases are enzymes centrally involved in the catalysis of DNA backbone breakage and rejoining during cell cycle. Inhibition of topoisomerases is an attractive target for cancer

therapy due to inhibition of a critical step in the repair of DNA strand breaks and subsequent induction of cell death. Several inhibitors of topoisomerase I and II are in clinical use as chemotherapeutic agents including etoposide, irinotecan, topotecan and doxorubicin. Although rarely, some of these agents are associated with pulmonary toxicity.

4.1. Etoposide

Is a chemotherapy used in the US for over 30 years to treat lymphoma, leukemia, neuroblastoma and sarcomas, as well as ovarian, testicular and lung cancer. The drug is associated with multiple side effects including bone marrow suppression and hypotension. As a topoisomerase II inhibitor, etoposide works by complexing with DNA to induce double strand breaks and prevent rejoining of the strands by the topoisomerase II enzyme to eventually block DNA synthesis. Few cases of pulmonary toxicity have been reported in relation to the use of etoposide [77, 78]. For example, a case report indicates the development of bilateral diffuse interstitial and alveolar infiltrates including fibrosis and respiratory failure in lung cancer patients [78]. Due to the limited cases of etoposide-induced lung toxicity, no mechanistic insights have been provided in the literature about how etoposide may affect the lung tissue. However, its significant inhibition on DNA synthesis, cell division and survival may cause collateral damage to normal resident lung cells including alveolar epithelial cells.

4.2. Irinotecan

Is a topoisomerase I inhibitor used in the treatment of colorectal, gastric and lung cancers often in combination with other chemotherapeutic agents including 5-FU, cisplatin, paclitaxel and/or radiation therapy [79, 80]. Notably, concurrent use of irinotecan and radiotherapy in lung cancer patients increased the risk of interstitial pneumonitis by about 40% in comparison to these receiving radiotherapy alone [81]. Additional studies have reported interstitial lung disease in cancer patients exposed to a single [82] or repeated dose of irinotecan [83]. The pulmonary toxicity seen in many of the patients improves following steroid therapy [83]. In addition, bronchoalveolar lavage from irinotecan-treated patient who developed interstitial pneumonitis revealed predominance of lymphocytes [83] suggesting that there is significant involvement of the immune system in the development and/or progression of pulmonary injury induced by irinotecan.

4.3. Topotecan

It is a topoisomerase I inhibitor and semi-synthetic analog of irinotecan that is being used in the treatment of ovarian cancer and small-cell lung cancer. This agent is rarely associated with pulmonary toxicity. In few case reports, some of the pulmonary-related complications of topotecan include diffuse alveolar damage, nonspecific interstitial pneumonia (NSIP), and obliterative bronchiolitis [84].

5.0. Proteasome Inhibitors

Are drugs that inhibit degradation of proteins by proteasomes. In oncology, proteasome inhibitors may inhibit the degradation of tumor-suppressor proteins to prolong their bioavailability and extend their anti-tumor effect including cell-cycle arrest and induction of

apoptosis. So far, 3 proteasome inhibitors have been approved in the US for the treatment of several cancer types including lymphoma and multiple myeloma. Of the proteasome inhibitors, bortezomib is by far the most commonly used chemotherapeutic agent. Isolated case reports over the last 12 years indicate that the agent can be associated with limited pulmonary toxicity.

5.1. Bortezomib

Is the first FDA-approved proteasome inhibitor for the treatment of multiple myeloma and mantle cell lymphoma. A few case studies have reported progressive interstitial lung disease, pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary hypertension or complete respiratory failure in patients treated with bortezomib [85–87]. It is hypothesized that bortezomib-induced pulmonary complications are due to deregulation of the NF κ B pathway and subsequent activation of inflammatory cascade in the lungs [88]. In addition, circulating levels of proinflammatory cytokines including IL-6 and TNF- α are reported to increase following bortezomib therapy [89]. These insights together with the favorable response of bortezomib-induced lung inflammation to corticosteroid therapy indicate that dysregulation of inflammatory pathway is a possible mechanism, at least in part, in inducing lung injury [86].

6.0. mTOR Inhibitors

Are chemicals that inhibit the kinase enzyme mammalian target of rapamycin (mTOR). More specifically, mTOR is a member of the phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs) that selectively phosphorylates serine/threonine residues in a given protein in order to regulate cell fate. Several small molecule inhibitors of mTOR have been developed for the treatment of various tumor types including renal cell carcinoma. Examples of the most common mTOR inhibitors include sirolimus (rapamycin), everolimus and temsirolimus. Some of these inhibitors that have been associated with pulmonary toxicity are discussed below.

6.1. Sirolimus

Is a member of the natural products known as macrolides that possess potent immunosuppressive activity. Medically, it is often used in the modulation of immune cell function following organ transplantation, and to treat a rare form of lung disease known as lymphangioleiomyomatosis (LAM) [90]. Several adverse effects that affect various organ-systems have been noted in patients treated with sirolimus therapy. In the respiratory system, for example, the use of sirolimus has been linked to the development of granulomatous interstitial pneumonitis, lymphocytic alveolitis, alveolar hemorrhage, BOOP and fibrosis [91, 92]. Although it is not certain whether the mechanism of action related to pulmonary toxicity of sirolimus is due to direct toxicity or is immune-mediated, the speculation is that both mechanisms may contribute to lung toxicity via direct damage to expose key alveolar antigens and the subsequent autoimmune response that targets the lungs [93]. In addition, findings from a preclinical study indicate that sirolimus inhibits the interaction of mTOR with the transcription factor STAT1 and deregulates STAT1 dependent apoptosis genes (e.g. Fas and caspases) to promote cell death and lung injury [94].

6.2. Everolimus

Is an analog of sirolimus and mTOR inhibitor that is indicated for the treatment of metastatic renal cell carcinoma and prevention of organ transplant rejection. In general, everolimus works by a similar mechanism of action as sirolimus to inhibit mTOR. However, everolimus is more selective in targeting one of the 2 mTOR protein complexes (mTORC1) and thus has fewer adverse effects in some organ-systems compared to sirolimus. In the respiratory system, however, the use of everolimus is associated with reports of severe cases of pulmonary toxicity including hypersensitivity pneumonitis and diffuse alveolar hemorrhage [95]. A meta-analysis study reported that the incidence rate of everolimus-associated severe pulmonary toxicity is 2.4% while mild-grade pulmonary toxicity reaches up to 10% [96]. The mechanism involved in everolimus-induced pulmonary toxicity is believed to be immune-mediated rather than direct toxicity [97]. This speculation is based on the findings of skewed CD4/CD8 ratio in everolimus-treated patients with no prior history of lung disease or co-prescriptions.

Similarly, several case reports indicate that temsirolimus, like sirolimus and everolimus, is associated with significant pulmonary toxicity including dyspnea and abnormal radiological findings such as pneumonitis, ground glass opacities and lung parenchymal consolidation [98]. Since temsirolimus is a prodrug of sirolimus and is known to be metabolized to sirolimus *in vivo*, it is predicted to work by similar mechanism of action.

7.0. Taxanes

Are a class of chemotherapeutic agents that are derived from *Taxus* plants. They have been widely used for the treatment of many cancer types including breast, cervical, ovarian, gastric and lung. They exert their antitumor effect by interfering with cell division through interference with microtubule depolymerization and trafficking [99]. Examples of the most commonly used taxanes include paclitaxel and docetaxel. These 2 agents have been associated with numerous cases of pulmonary toxicity including interstitial pneumonitis. Below is a brief description of paclitaxel and docetaxel including their association with pulmonary toxicity.

7.1. Paclitaxel

Commonly known as taxol has been in clinical use for almost 25 years to treat a broad range of cancers. Cases of interstitial pneumonitis and pulmonary fibrosis have been reported in patients treated with paclitaxel [100]. However, the incidence is much greater in patients concurrently treated with paclitaxel and other agents including platinoids [101], antimetabolites [102] monoclonal antibody [103] or radiation therapy [104]. Mechanistically, both immunological and non-immunological factors are implicated in paclitaxel-induced pulmonary toxicity. Immunologically, a delayed-type (type IV) hypersensitivity reaction involving impaired helper/suppressor T cell ratio is indicated in patients treated with paclitaxel monotherapy [105]. In combination therapy involving paclitaxel and radiation, severe depletion of lymphocytes including CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and B cells is implicated in creating the basis for opportunistic infections that may

contribute to interstitial pneumonia ^[104], as well as to the loss in lung function manifested by decreased FVC and DLCO ^[106].

7.2. Docetaxel

Used in the treatment of head and neck cancer, breast cancer, prostate cancer and lung cancer, docetaxel is another anti-microtubule chemotherapeutic agent within the taxane family. It has been in clinical use for over 20 years and has been reported to be associated with numerous side effects including low blood cell counts, skin rash, muscle pain, hypotension, shortness of breath, and capillary leak syndrome ^[107]. In addition, emerging reports indicate that the use of docetaxel is associated with significant pulmonary toxicity including severe interstitial pneumonitis ^[108], diffuse and bilateral ground-glass opacities on chest radiography ^[109] and fatal respiratory failure ^[110]. Although the specific mechanism(s) by which docetaxel causes pulmonary toxicity is unknown, the response of patients with such complications to steroid therapy ^[111] suggests that there is an immune component that is involved in the development and/or progression of the disease.

8.0. Monoclonal Antibodies

Several monoclonal antibodies targeting an array of antigens including tyrosine kinase receptors have recently entered clinical practice to improve the quality and quantity of life of cancer patients ^[112]. Examples of monoclonal antibodies in use as anti-cancer drugs with reports of pulmonary complications include cetuximab (Erbix), trastuzumab (Herceptin), bevacizumab (Avastin), panitumumab (Vectibix), gemtuzumab ozogamicin (Mylotarg) and rituximab (Rituxan). Some of these monoclonal antibodies and their pulmonary toxicities are discussed below.

8.1. Cetuximab

Is a mouse/human chimeric monoclonal antibody that competitively targets EGFR for the treatment of squamous cell carcinoma of the head and neck, and metastatic cancers of the colon and lung. Although there are fewer reports of pulmonary toxicity related to the use of cetuximab compared to other EGFR inhibitors described above, there are a number of case reports that highlight lung toxicities including dyspnea, BOOP and interstitial pneumonitis associated with cetuximab monotherapy or in combination ^[62, 113]. There is no mechanistic pathway that is differentially implicated in cetuximab-induced pulmonary toxicity. However, due to the similarities in target engagement to that of RTKIs (e.g. gefitinib), it is possible that the mechanism(s) of pulmonary complications are in common. For example, inhibition of EGFR by cetuximab is expected to downregulate EGFR phosphorylation and subsequently reduce the proliferative and regenerative capacity of alveolar epithelial cells. In addition, cetuximab has been shown to downregulate the expression of key components of the extracellular matrix including matrix metalloproteinase and VEGF ^[114]. These findings may compromise physiological lung remodeling and stimulate aberrant repair.

8.2. Panitumumab

Similar to cetuximab, panitumumab is an EGFR inhibitor that is used for the treatment of refractory EGFR-positive metastatic colorectal carcinoma. In addition to common skin and

ocular toxicities associated with the use of panitumumab, pulmonary fibrosis and interstitial lung disease with diffuse alveolar damage have been reported in about 1% of patients treated with combination therapies that include panitumumab [115, 116]. The mechanism of action for panitumumab-associated pulmonary toxicity might be similar to that of cetuximab involving disruption of physiological angiogenesis and resident lung cell proliferation [117].

8.3. Bevacizumab

Is a humanized monoclonal antibody that targets VEGF signaling for the treatment of renal cell carcinoma, glioblastoma, colorectal and lung cancer. Although inhibition of tumor angiogenesis is an important mechanism to control the growth and metastasis of cancer cells, targeting a chief growth factor such as VEGF by bevacizumab is also a major concern in impairment of physiological angiogenesis as in wound healing during recovery from lung injury and pulmonary vasodilation [118, 119]. In the pulmonary system, combination of bevacizumab with chemotherapy has been associated with increased incidences of pulmonary hemorrhage [120]. Similarly, concurrent administration of bevacizumab with thoracic radiotherapy in lung cancer patients has been reported to be associated with heightened pulmonary parenchymal toxicity [121]. These observations are believed to be due to the increased cell death when chemoradiation therapy is combined with antiangiogenic drugs, as well as due to the suppressive effect of bevacizumab on proliferation- and DNA repair- related genes and transcription factors [122, 123]. Additional mechanisms may include strategies shared by antiangiogenic tyrosine kinase inhibitors such as sorafenib [57].

8.4. Rituximab

This monoclonal antibody is in clinical use for the treatment of CD20-expressing follicular lymphoma and chronic lymphocytic leukemia, as well as autoimmune diseases. Although shortness of breath is one of the infusion-related adverse events that manifest within hours after the administration of the drug, more prolonged and life threatening pulmonary complications are also noted in patients receiving rituximab therapy. For example, case series reports indicate that interstitial pneumonitis and alveolar hemorrhage can be uncommonly induced by rituximab monotherapy [124, 125]. Although the mechanism driving rituximab-induced pulmonary toxicity is not well-characterized, it has been demonstrated that the drug causes the activation of the complement cascade, lysis of B cells, and release of pro-inflammatory cytokines including TNF- α , interferon- γ , and interleukins [126, 127]. In addition, rituximab-induced interstitial pneumonitis appears to effectively resolve following corticosteroid therapy [124] indicating involvement of the immune system (e.g. immune cells, cytokines and complement) in the development and/or progression of rituximab-induced pulmonary toxicity.

8.5. Trastuzumab

This is a humanized monoclonal antibody directed against EGF receptor 2 (HER2) to control tumor cell proliferation in breast cancer cells overexpressing this receptor. The HER2 pathway is involved in activation of several kinase pathways including the MAP kinase and PI3K/Akt pathways in order to activate the NF κ B pathway, suppress cell cycle checkpoints, and support rapid growth and proliferation of cancer cells. To this end, the HER2 gene is overexpressed in up to 30% of breast cancers [128]. By contrast, trastuzumab

blocks HER2-mediated signaling pathways, in part through upregulation of the cyclin-dependent kinase (CDK) inhibitor protein p27Kip1, to control cancer cells [129]. Although most of the reported toxicities related to the use of trastuzumab is to the cardiovascular system including increased risk of cardiac dysfunction and heart failure, there are case reports that suggest acute and delayed respiratory toxicities associated with trastuzumab therapy. In the acute phase, severe infusion reactions such as bronchospasm and respiratory distress have been reported in less than 1% of patients receiving trastuzumab. Some of the delayed pulmonary complications of adjuvant trastuzumab therapy include BOOP and interstitial pneumonitis along with decline in lung function [130, 131]. The mechanism(s) involved in respiratory toxicities associated with trastuzumab therapy is not known. However, the pulmonary complications appear to resolve with anti-inflammatory drugs [131, 132].

8.6. Gemtuzumab ozogamicin

Is a drug-conjugated anti-CD33 monoclonal antibody initially marketed for the treatment of patients with CD33-expressing acute myeloid leukemia (AML). A decade after it had been in clinical use, gemtuzumab ozogamicin was withdrawn from the US market in 2010 due to lack of efficacy and increased mortality. However, the drug was reintroduced this year for the treatment of newly-diagnosed or treatment resistant/relapsed CD33-positive AML. Although the main complications of gemtuzumab ozogamicin therapy including severe myelosuppression are related to collateral destruction of CD33-expressing normal hematopoietic cells, isolated cases of serious respiratory complications including diffuse alveolar hemorrhage have been reported [133].

9.0. Immune checkpoint Inhibitors

Are newly developed immunomodulatory antibodies that target the programmed cell death 1 (PD-1) receptor, its ligand (PD-L1) or the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Examples include nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq) and ipilimumab (Yervoy). These immune check point inhibitors are very powerful tools in the arsenal to fight cancer. However, many of them have been reported to be associated with cases of pulmonary toxicity including pneumonitis, ARDS, granulomatous sarcoid-like disease, and organizing bronchiolitis syndrome. Below is a brief description of the main findings related to lung toxicity.

9.1. PD-1 Inhibitors

Are immune checkpoint inhibitors that target the cell surface receptor PD-1 in order to allow activated T cells unleash their cytotoxic effect on cancer cells. Nivolumab and pembrolizumab are PD-1 inhibitors in clinical use as first- or second- line of treatment for unresectable or metastatic melanoma, renal cell carcinoma and squamous non-small cell lung cancer. Although the mechanism of action of PD-1 inhibitors allows the immune system to launch potent anti-tumor response, it is also tied to several serious immune-mediated adverse effects including dyspnea, cough, respiratory tract infection and lung inflammation [134]. More specifically, a meta-analysis study found that up to 2% of patients treated with PD-1 inhibitors can develop severe pulmonary toxicity while the overall

pulmonary toxicity can reach up to 9% [135]. Notably, the risk of pneumonitis extends for up to 24 months following PD-1 inhibitor therapy [136]. In addition, the incidence rates of pneumonitis are likely higher when PD-1 inhibitors are combined with other immune checkpoint inhibitors or systemic therapies that are associated with pulmonary toxicity [137]. Hyperactivation of the immune system [136], constitutive expression of PD-1 on effector T cells in the lung [138], as well as expression of PD-L1 in the respiratory epithelium might contribute to dysregulation of the airway PD-1/PD-L1 axis and drive adverse effects of nivolumab or other PD-1 inhibitors like pembrolizumab on the respiratory system.

9.2. PD-L1 Inhibitors

Are monoclonal antibody directed against the PD-L1 ligand that is predominantly expressed in tumor cells. As a result, PD-L1 inhibitors block the interaction between PD-1 and PD-L1 to favor activation of immune cells and subsequent anti-tumor response. In this class of drugs, atezolizumab is the only one that is currently FDA-approved for the treatment of non-small cell lung cancer that is refractory to other FDA-approved therapeutic agents. Since the drug has only been in clinical use for the last 2 years, it is difficult to comprehensively assess its effect on the respiratory system. However, data from a large clinical study suggest that atezolizumab has a similar pulmonary toxicity profile as that of PD-1 inhibitors [139].

9.3. CTLA-4 Inhibitors

Are monoclonal antibody that selectively block T cell receptors (CTLA-4) that normally inhibit lymphocyte activation. Through this derepression of T cell activation, CTLA-4 inhibitors enhance immune response including cytotoxic T lymphocytes (CTLs) against cancer cells. Ipilimumab is an FDA-approved CTLA-4 inhibitor for the treatment of unresectable or metastatic melanoma. Overactivation and overproliferation of T cells is an underlying drawback that is associated with many of the immune-related adverse reactions of ipilimumab. Emerging case reports indicate that the use of ipilimumab alone or in combination with other immune checkpoint inhibitors is associated with pulmonary toxicities including organizing pneumonia, autoimmune alveolitis, ARDS and sarcoid-like granulomatosis [140, 141]. Although no specific molecular mechanism has been linked to ipilimumab-induced pulmonary toxicity, the enhanced immune response to normal host tissues of patients treated with immune checkpoint inhibitors, the established role of immune cells in at least some of these pulmonary conditions, and the resolution of ipilimumab-induced pulmonary complications following corticosteroid therapy suggest an immune-mediated mechanism(s) [140].

10.0. Surgical resection

When a given cancer patient is a suitable candidate for surgery, the premier choice to remove a primary tumor is surgical resection. In that case, the patient might be prescribed with pre-operative chemotherapy with or without radiation therapy. However, if the patient's condition does not allow for surgery, definitive chemoradiotherapy is the remaining option to control the tumor. In these unresectable patients, it is likely that high dose of radiation is administered to the tumor. As a result, significant off-target effects including normal tissue toxicity are likely to be experienced especially when the radiation therapy is combined with

chemotherapy. Radiation-induced lung injury is one of such complications and is described below.

11.0. Radiation therapy and pulmonary toxicity

Deliberate or inadvertent exposure to ionizing radiation is often associated with significant surge in life-threatening outcomes. Therapeutically, the application of conformal ionizing radiation therapy (RT) with concurrent chemotherapy for surgically unresectable or medically inoperable thoracic malignancies is a standard of care approach for the treatment of various cancers, including cancer of the lungs, mediastinal malignancies and several types of lymphoma.

The use of radiation therapy in lung cancer is particularly notable. Lung cancer is a leading cause of death in the United States and worldwide. In 2017, it is estimated that there are 222,500 new cases of and 155,870 deaths related to lung cancer in the United States alone [142], of which 80–85% are non-small cell lung cancers (NSCLC) and up to 80% of these patients are unresectable [143]. In these patients, the standard of care approach is definitive thoracic radiotherapy with chemotherapy [144]. It is estimated that 64% of NSCLC patients require radiotherapy at least once and 45% receive it as part of their initial treatment regimen [145].

This targeted strategy has proven to be effective in extending the survival and improving the quality of life of cancer patients, especially with the advancement of radiation technology and delivery techniques [146]. However, overall treatment outcomes remain suboptimal and local tumor failure is a problem for these patients. One main reason for this is the dose-limiting toxicity of radiation fibrosis. It has been established that local tumor control and survival is correlated with increasing radiation dose in NSCLC [147]. However, due to the predictable increase in radiation-induced lung injury (RILI) with increased dose, prescription radiation dose is limited to 60 Gy [148]. Unfortunately, even at this dose, cancer survivors often suffer from the harmful effects of radiation including pneumonitis and pulmonary fibrosis that often leads to fulminant failure of the lungs.

The exquisite sensitivity of the lungs in general and the alveoli in particular to the effects of radiation is a significant clinical concern shadowing control and cure of the underlying cancer. Radiation pneumonitis and fibrosis are dose-limiting factors in patients undergoing thoracic irradiation for the treatment of lung, larynx, breast and hematological malignancies. RILI is mainly driven by the direct cytotoxic action of ionizing radiation on lung cells [149]. Ionizing radiation is known to generate tissue reactive free radicals that can damage DNA molecules and cause clonogenic death in alveolar epithelial cells. In addition, ionizing radiation is known to cause the release of proinflammatory and profibrotic molecules to sustain the fibroinflammatory response. Currently, the incidence rate of RILI appears to be on the decline due to a number of developments in the fields of radiology and radiation oncology including the implementation of sensitive imaging techniques such as 4 dimensional CT imaging, the use of stereotactic radiation therapy, proton beam therapy, and advances in treatment planning [150]. Nonetheless, RILI continues to be a clinical problem

and the two main complications, radiation pneumonitis and fibrosis need to be completely characterized to facilitate the development of effective intervention.

Acute radiation pneumonitis is characterized by wide-spread inflammation of the lungs and occurs in up to 15% of all irradiated patients, typically within 6 months after the completion of RT [149]. Classic symptoms include low-grade fever, cough, chest congestion, shortness of breath, patchy and ground-glass opacification and worsening in clinical parameters of lung function [151]. In severe cases where patients receive concurrent chemoradiation therapy, the overall rate of grade 3 or worse pulmonary events approaches 20% and the rate of radiation pneumonitis reaches up to 7% [148]. The differential diagnosis (from recurrent tumor) of radiation pneumonitis takes several factors into account including the patient's age, radiation dose administered, the volume of lung irradiated, co-treatment with chemotherapy, onset and duration of the symptoms outlined above and abnormal radiologic features by computed tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography (PET) scans [152]. In addition, more invasive techniques such as bronchoscopy, thoracentesis and/or lung biopsy are occasionally used to make definitive diagnosis of radiation pneumonitis by differentiating it from underlying malignancy or infectious pneumonitis [153].

Although radiation pneumonitis can spontaneously resolve in cases where the lung injury is limited, the vast majority (up to 75%) of cases progress to developing chronic scarring of the lungs (i.e. fibrosis) at the irradiation site within 6 to 12 months [154] of completing RT. Fibrosis is a progressive process that eventually replaces most of the remaining normal lung tissue with scar tissue, resulting in impaired respiration and possibly death within 3–4 years. Lung fibrosis is typically characterized by progressive loss of lung volume, consolidation, chronic scarring and bronchiectasis. Diagnostic findings include medical history such as past or current treatment with drugs that are known to be associated with lung toxicity [155], crackling sounds during examination of the lungs, impaired findings on Six-Minute Walk Test (6MWT), HRCT scan showing scarring and typical radiographic changes, bronchoscopy demonstrating elevated markers of inflammation and fibrosis, lung function test showing impaired diffusing capacity and decreased lung volumes, as well as lung biopsy showing histologic fibrosis. Recently, the American Thoracic Society (ATS) and its sister Associations in Europe (ERS), Japan (JRS) and Latin America (ALAT) outlined evidence-based guidelines for the diagnosis and management of pulmonary fibrosis of unknown cause [156]. Unfortunately, there is no FDA-approved drug specifically for the treatment of radiation-induced lung fibrosis and the clinical intervention at this stage is limited to palliative care and lung transplantation, which is unrealistic option for the majority of cancer patients.

Mechanistically, radiation pneumonitis and fibrosis are mediated by DNA damage and dysregulation of a number of fibro-inflammatory molecules [157–159]. Some of the molecules that are elevated during the inflammatory phase and/or are sustained during the progression to fibrosis include: TNF- α ; interleukins (IL-1 β , IL-1, IL-4, IL-6 and IL-13); adhesion molecules (VCAM1 and ICAM1); cytokines (TGF β); growth factors (PDGF, FGF, IGF and VEGF); transcription factors (NF κ B); reactive oxygen species (ROS) and reactive nitrogen species (RNS) [160]. These molecular dysregulations and the lethality of ionizing radiation to

type 1 pneumocytes, alveolar epithelial and endothelial cells could trigger loss of barrier function and structural denudation to promote recruitment of inflammatory cells, uncontrolled matrix turnover, and aberrant repair.

Fortunately, emerging advances in radiation technology and delivery techniques have ignited optimism about minimizing collateral effects of ionizing radiation. Some of the emerging technologies include stereotactic body radiation therapy (SBRT), intensity-modulated radiotherapy (IMRT), and respiratory-gated radiotherapy. These treatment modalities are able to precisely deliver radiation doses to a tumor while largely sparing normal tissue [146]. In SBRT, for example, imaging-based coordinate system guides the targeted delivery of high dose of radiation to the tumor. Since the technique is highly customizable, patient's anatomy, breathing pattern and organ motion are taken into account to modulate the intensity and direction of the beams. Respiratory-gated radiotherapy is a suitable technique in the irradiation of tumors seeded in tissues that are affected by breathing motion such as the lungs. Here, respiratory motion is incorporated into the treatment planning and, when needed, breathing motion can be reduced using abdominal compression, breath-hold techniques, or respiratory gating. Accordingly, the dose of irradiation on normal surrounding tissue is minimized [144]. Unfortunately though, despite these technological advances, the exquisite sensitivity of the lungs to even low doses of radiation remains a substantial challenge in the locally advanced setting.

12.0. Conclusion

The implementation of sophisticated radiation delivery techniques has decreased exposure of the lungs to excessive ionizing radiation during the treatment of cancer. However, ionizing radiation and several of the chemotherapeutic agents in use continue to present the risk of inducing and/or exacerbating pulmonary injury including pneumonitis and lung fibrosis (Table 1).

Therefore, radiation oncologists should be judicious on the dose of radiation delivered to the lungs, the volume of lung irradiated, and concurrent use of chemotherapeutic drugs or other aggravating agents. They should also involve other professionals including pulmonologists and interstitial lung disease (ILD) experts whenever necessary to plan treatment options for patients at a greater risk of pulmonary toxicity.

13.0. Expert commentary

Given the continued clinical use of chemotherapeutic drugs that are associated with significant pulmonary toxicity, there is a compelling need to molecularly understand how these drugs induce or associate with respiratory toxicities and whether such characteristics are inherently related to their anti-tumor activity or are collateral effects. Once future research identifies and/or fully characterizes such mechanisms, the insights may be able to guide disease-management decisions including effective intervention strategies for the adverse events. In the meantime, it is important to take cautious steps when treating patients with ionizing radiation or chemotherapeutic agents that are known or suspected to induce pulmonary toxicity. Although significant pulmonary toxicity may compromise total lung

capacity, pulmonary function tests or radiological examinations may be within normal range in cases of mild disease. However, for patients that manifest signs and/or symptoms of drug/radiation-induced pulmonary toxicities, it may be necessary to consider dose reducing, delaying, discontinuing or substituting the aggravating agent(s) to avoid the risk of permanent complications. In some patients, glucocorticoid-therapy and/or antibiotics may help resolve pulmonary inflammation and respiratory infections. Additional agents such as amifostine and pentoxifylline with proven potential to reduce the effects of chemoradiation therapy should also be considered to minimize toxicity. Retreatment after resolution of symptoms should be evaluated on a case-by-case basis and recurrent pulmonary toxicity should be monitored closely. Recent developments in radiation delivery techniques such as SBRT, IMRT, SRS, and respiratory-gated radiotherapy that differentially deliver radiation doses to a tumor are expected to substantially reduce normal tissue toxicity including lung inflammation and fibrosis.

Emerging anti-cancer therapies including molecularly targeted agents and Chimeric Antigen Receptor (CAR) T cell therapy safety on the respiratory system should carefully be assessed and comprehensive clinical guidelines should be developed to manage patients who develop respiratory complications following these prescriptions. Given their recent emergence to the market and increasing case reports of pulmonary complications, immune checkpoint inhibitors would also require careful monitoring for adverse effects. Future directions should include testing and development of therapeutic agents for radiation-induced pulmonary complications. Such agents should be searched among peptides, monoclonal antibodies, natural and synthetic small molecules including receptor and non-receptor tyrosine kinase inhibitors, as well as novel class of targeted agents. In parallel, the efficacy of FDA-approved antifibrotic agents such as pirfenidone and nintedanib, as well as other FDA-approved drugs, such as proton pump inhibitors (PPIs), that have antifibrotic potential [161] should be evaluated in the settings of radiation-induced pulmonary complications.

14.0. Five-year view

From drug development and advances in radiation therapy techniques points of view, these are very exciting times for the fields of general oncology and radiation oncology. In the next five years, we expect to gain additional molecular insights on how some of the most common chemotherapeutic drugs work and how they are associated with pulmonary toxicity. We also anticipate to gain important insights on the therapeutic safety of emerging anti-cancer drugs including molecularly targeted agents and immune checkpoint inhibitors. If the increasing trend of pulmonary complications continue with prolonged use of some of these agents, we can clearly see the need to develop comprehensive guidelines to manage patients who suffer from respiratory complications following these treatments.

Overall, we speculate a considerable drop in the total number of cases with pulmonary complications secondary to anti-cancer therapy. This optimism is based on progressively refined mechanistic understanding of how several cancer pharmacotherapies work, and the growing use of precise radiation delivery techniques such as SBRT, IMRT, SRS, and respiratory-gated radiotherapy.

Acknowledgments

Funding

This manuscript has received funding from the National Institutes of Health (K01HL118683 and R01HL137703).

References

1. Moore BB and Hogaboam CM. Murine models of pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2008;294:L152–60 [PubMed: 17993587]
2. Tashiro M, Izumikawa K, Yoshioka D et al. Lung fibrosis 10 years after cessation of bleomycin therapy. *Tohoku J Exp Med* 2008;216:77–80 [PubMed: 18719341]
3. Hecht SM. Bleomycin: new perspectives on the mechanism of action. *J Nat Prod* 2000;63:158–68 [PubMed: 10650103]
4. Hoshino T, Nakamura H, Okamoto M et al. Redox-active protein thioredoxin prevents proinflammatory cytokine- or bleomycin-induced lung injury. *Am J Respir Crit Care Med* 2003;168:1075–83 [PubMed: 12816738]
5. Piguet PF, Collart MA, Grau GE et al. Tumor necrosis factor/cachectin plays a key role in bleomycin-induced pneumopathy and fibrosis. *J Exp Med* 1989;170:655–63 [PubMed: 2475571]
6. Lin PS, Kwock L, Hefter K et al. Effects of iron, copper, cobalt, and their chelators on the cytotoxicity of bleomycin. *Cancer Res* 1983;43:1049–53 [PubMed: 6186368]
7. Carver JR, Shapiro CL, Ng A et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol* 2007;25:3991–4008 [PubMed: 17577017] *This paper reviews clinical evidence on late cardiac and pulmonary toxicities of anti-cancer therapy.
8. Moeller A, Ask K, Warburton D et al. The bleomycin animal model: a useful tool to investigate treatment options for idiopathic pulmonary fibrosis? *Int J Biochem Cell Biol* 2008;40:362–82 [PubMed: 17936056]
9. Tomasz M Mitomycin C: small, fast and deadly (but very selective). *Chem Biol* 1995;2:575–9 [PubMed: 9383461]
10. Shi K, Wang D, Cao X et al. Endoplasmic reticulum stress signaling is involved in mitomycin C (MMC)-induced apoptosis in human fibroblasts via PERK pathway. *PLoS One* 2013;8:e59330 [PubMed: 23533616]
11. Perros F, Gunther S, Ranchoux B et al. Mitomycin-Induced Pulmonary Veno-Occlusive Disease: Evidence From Human Disease and Animal Models. *Circulation* 2015;132:834–47 [PubMed: 26130118]
12. Eyries M, Montani D, Girerd B et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014;46:65–9 [PubMed: 24292273]
13. D'Angio GJ, Evans A, Breslow N et al. The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer* 1981;47:2302–11 [PubMed: 6164480]
14. Cohen IJ, Loven D, Schoenfeld T et al. Dactinomycin potentiation of radiation pneumonitis: a forgotten interaction. *Pediatr Hematol Oncol* 1991;8:187–92 [PubMed: 1863544]
15. Sobell HM. Actinomycin and DNA transcription. *Proc Natl Acad Sci U S A* 1985;82:5328–31 [PubMed: 2410919]
16. Mazzotta M, Giusti R, Iacono D et al. Pulmonary Fibrosis after Pegylated Liposomal Doxorubicin in Elderly Patient with Cutaneous Angiosarcoma. *Case Rep Oncol Med* 2016;2016:8034832 [PubMed: 26904333]
17. Vahid B and Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest* 2008;133:528–38 [PubMed: 18252919]
18. Malik SW, Myers JL, DeRemee RA et al. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med* 1996;154:1851–6 [PubMed: 8970380]

19. Ochoa R, Bejarano PA, Gluck S et al. Pneumonitis and pulmonary fibrosis in a patient receiving adjuvant docetaxel and cyclophosphamide for stage 3 breast cancer: a case report and literature review. *J Med Case Rep* 2012;6:413 [PubMed: 23198815]
20. Segura A, Yuste A, Cercos A et al. Pulmonary fibrosis induced by cyclophosphamide. *Ann Pharmacother* 2001;35:894–7 [PubMed: 11485142]
21. Hoyt DG and Lazo JS. Acute pneumocyte injury, poly(ADP-ribose) polymerase activity, and pyridine nucleotide levels after in vitro exposure of murine lung slices to cyclophosphamide. *Biochem Pharmacol* 1994;48:1757–65 [PubMed: 7980645]
22. Mohr M, Kingreen D, Ruhl H et al. Interstitial lung disease--an underdiagnosed side effect of chlorambucil? *Ann Hematol* 1993;67:305–7 [PubMed: 8280814]
23. Crestani B, Jaccard A, Israel-Biet D et al. Chlorambucil-associated pneumonitis. *Chest* 1994;105:634–6 [PubMed: 8306788]
24. Khong HT and McCarthy J. Chlorambucil-induced pulmonary disease: a case report and review of the literature. *Ann Hematol* 1998;77:85–7 [PubMed: 9760160]
25. Cooper JA, Jr., White DA and Matthey RA Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. *Am Rev Respir Dis* 1986;133:321–40 [PubMed: 3511808]
26. Matsuno O Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. *Respir Res* 2012;13:39 [PubMed: 22651223]
27. Akasheh MS, Freytes CO and Vesole DH. Melphalan-associated pulmonary toxicity following high-dose therapy with autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2000;26:1107–9 [PubMed: 11108311]
28. Ekstrand-Hammarstrom B, Wigenstam E and Bucht A. Inhalation of alkylating mustard causes long-term T cell-dependent inflammation in airways and growth of connective tissue. *Toxicology* 2011;280:88–97 [PubMed: 21129433]
29. Kolb M, Margetts PJ, Anthony DC et al. Transient expression of IL-1beta induces acute lung injury and chronic repair leading to pulmonary fibrosis. *J Clin Invest* 2001;107:1529–36 [PubMed: 11413160]
30. Ringden O, Remberger M, Ruutu T et al. Increased risk of chronic graft-versus-host disease, obstructive bronchiolitis, and alopecia with busulfan versus total body irradiation: long-term results of a randomized trial in allogeneic marrow recipients with leukemia. *Nordic Bone Marrow Transplantation Group. Blood* 1999;93:2196–201 [PubMed: 10090927]
31. Johnstone TC, Alexander SM, Lin W et al. Effects of monofunctional platinum agents on bacterial growth: a retrospective study. *J Am Chem Soc* 2014;136:116–8 [PubMed: 24364388]
32. Dasari S and Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. *Eur J Pharmacol* 2014;740:364–78 [PubMed: 25058905] *This comprehensive review discusses cisplatin, its use and related toxicities with emphasis on molecular mechanisms of action.
33. Ideguchi H, Kojima K, Hirosako S et al. Cisplatin-induced eosinophilic pneumonia. *Case Rep Pulmonol* 2014;2014:209732 [PubMed: 25478274]
34. Kirkbride P, Hatton M, Lorigan P et al. Fatal pulmonary fibrosis associated with induction chemotherapy with carboplatin and vinorelbine followed by CHART radiotherapy for locally advanced non-small cell lung cancer. *Clin Oncol (R Coll Radiol)* 2002;14:361–6 [PubMed: 12555874]
35. Dimopoulou I, Galani H, Dafni U et al. A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. *Cancer* 2002;94:452–8 [PubMed: 11900231]
36. Barrera P, Laan RF, van Riel PL et al. Methotrexate-related pulmonary complications in rheumatoid arthritis. *Ann Rheum Dis* 1994;53:434–9 [PubMed: 7944614]
37. Jakubovic BD, Donovan A, Webster PM et al. Methotrexate-induced pulmonary toxicity. *Can Respir J* 2013;20:153–5 [PubMed: 23762881]
38. Salehi M, Miller R and Khaing M. Methotrexate-induced Hypersensitivity Pneumonitis appearing after 30 years of use: a case report. *J Med Case Rep* 2017;11:174 [PubMed: 28655345] *This paper presents a case of methotrexate-induced lung injury after unusually long period of time.
39. Ohbayashi M, Suzuki M, Yashiro Y et al. Induction of pulmonary fibrosis by methotrexate treatment in mice lung in vivo and in vitro. *J Toxicol Sci* 2010;35:653–61 [PubMed: 20930460]

40. Kim YJ, Song M and Ryu JC. Inflammation in methotrexate-induced pulmonary toxicity occurs via the p38 MAPK pathway. *Toxicology* 2009;256:183–90 [PubMed: 19100307]
41. Garg S, Garg MS and Basmaji N. Multiple pulmonary nodules: an unusual presentation of fludarabine pulmonary toxicity: case report and review of literature. *Am J Hematol* 2002;70:241–5 [PubMed: 12111771]
42. Stoica GS, Greenberg HE and Rossoff LJ. Corticosteroid responsive fludarabine pulmonary toxicity. *Am J Clin Oncol* 2002;25:340–1 [PubMed: 12151960]
43. Turco C, Jary M, Kim S et al. Gemcitabine-Induced Pulmonary Toxicity: A Case Report of Pulmonary Veno-Occlusive Disease. *Clin Med Insights Oncol* 2015;9:75–9 [PubMed: 26380562]
44. Bredenfeld H, Franklin J, Nogova L et al. Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2004;22:2424–9 [PubMed: 15136597]
45. Belknap SM, Kuzel TM, Yarnold PR et al. Clinical features and correlates of gemcitabine-associated lung injury: findings from the RADAR project. *Cancer* 2006;106:2051–7 [PubMed: 16568459]
46. Levitt ML, Kassem B, Gooding WE et al. Phase I study of gemcitabine given weekly as a short infusion for non-small cell lung cancer: results and possible immune system-related mechanisms. *Lung Cancer* 2004;43:335–44 [PubMed: 15165093]
47. Pavlakis N, Bell DR, Millward MJ et al. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer* 1997;80:286–91 [PubMed: 9217042]
48. Vander Els NJ and Miller V. Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. *Chest* 1998;114:1779–81 [PubMed: 9872221]
49. Alessandrino EP, Bernasconi P, Colombo A et al. Pulmonary toxicity following carmustine-based preparative regimens and autologous peripheral blood progenitor cell transplantation in hematological malignancies. *Bone Marrow Transplant* 2000;25:309–13 [PubMed: 10673703]
50. Lohani S, O'Driscoll BR and Woodcock AA. 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004;126:1007 [PubMed: 15364795]
51. Kehrer JP and Klein-Szanto AJ. Enhanced acute lung damage in mice following administration of 1,3-bis(2-chloroethyl)-1-nitrosourea. *Cancer Res* 1985;45:5707–13 [PubMed: 4053044]
52. Cao TM, Negrin RS, Stockerl-Goldstein KE et al. Pulmonary toxicity syndrome in breast cancer patients undergoing BCNU-containing high-dose chemotherapy and autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2000;6:387–94 [PubMed: 10917574]
53. Smith AC and Boyd MR. Preferential effects of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) on pulmonary glutathione reductase and glutathione/glutathione disulfide ratios: possible implications for lung toxicity. *J Pharmacol Exp Ther* 1984;229:658–63 [PubMed: 6726651]
54. Shen YC, Chiu CF, Chow KC et al. Fatal pulmonary fibrosis associated with BCNU: the relative role of platelet-derived growth factor-B, insulin-like growth factor I, transforming growth factor-beta1 and cyclooxygenase-2. *Bone Marrow Transplant* 2004;34:609–14 [PubMed: 15286697]
55. Lee W, Moore RP and Wampler GL. Interstitial pulmonary fibrosis as a complication of prolonged methyl-CCNU therapy. *Cancer Treat Rep* 1978;62:1355–8 [PubMed: 688278]
56. Tucci E, Verdiani P, Di Carlo S et al. Lomustine (CCNU)-induced pulmonary fibrosis. *Tumori* 1986;72:95–8 [PubMed: 3952821]
57. Shah RR. Tyrosine Kinase Inhibitor-Induced Interstitial Lung Disease: Clinical Features, Diagnostic Challenges, and Therapeutic Dilemmas. *Drug Saf* 2016;39:1073–91 [PubMed: 27534751] *This paper comprehensively reviews the diagnostic challenges, clinical outcome and therapeutic options in patients who experience tyrosine kinase inhibitor-related pulmonary toxicity.
58. Kataoka K, Taniguchi H, Hasegawa Y et al. Interstitial lung disease associated with gefitinib. *Respir Med* 2006;100:698–704 [PubMed: 16137874]
59. Hong D, Zhang G, Zhang X et al. Pulmonary Toxicities of Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)* 2016;95:e3008 [PubMed: 26945426] *This systematic review evaluates the overall incidence and risk of gefitinib-related pulmonary toxicity from 1967 to 2015.

60. Madtes DK, Busby HK, Strandjord TP et al. Expression of transforming growth factor-alpha and epidermal growth factor receptor is increased following bleomycin-induced lung injury in rats. *Am J Respir Cell Mol Biol* 1994;11:540–51 [PubMed: 7524566]
61. Liu V, White DA, Zakowski MF et al. Pulmonary toxicity associated with erlotinib. *Chest* 2007;132:1042–4 [PubMed: 17873198]
62. Chua W, Peters M, Loneragan R et al. Cetuximab-associated pulmonary toxicity. *Clin Colorectal Cancer* 2009;8:118–20 [PubMed: 19739274]
63. Ma CX, Hobday TJ and Jett JR. Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003;78:1578–9 [PubMed: 14661689]
64. Ohnishi K, Sakai F, Kudoh S et al. Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006;20:1162–4 [PubMed: 16598305]
65. Wagner U, Staats P, Moll R et al. Imatinib-associated pulmonary alveolar proteinosis. *Am J Med* 2003;115:674
66. Rajda J and Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005;79:80–1
67. Lin JT, Yeh KT, Fang HY et al. Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006;47:1693–5 [PubMed: 16966290]
68. Sakao S and Tatsumi K. Molecular mechanisms of lung-specific toxicity induced by epidermal growth factor receptor tyrosine kinase inhibitors. *Oncol Lett* 2012;4:865–7 [PubMed: 23162612]
69. Guan Y, Meng J, Zhao H et al. Fatal interstitial lung disease after addition of sorafenib to a patient with lung adenocarcinoma who had failed to improve with erlotinib alone. *Case Rep Oncol* 2014;7:273–6 [PubMed: 24926256]
70. Yamaguchi T, Seki T, Miyasaka C et al. Interstitial pneumonia induced by sorafenib in a patient with hepatocellular carcinoma: An autopsy case report. *Oncol Lett* 2015;9:1633–6 [PubMed: 25789013]
71. Prieto-Dominguez N, Ordonez R, Fernandez A et al. Modulation of Autophagy by Sorafenib: Effects on Treatment Response. *Front Pharmacol* 2016;7:151 [PubMed: 27375485]
72. Zhang J, Chen YL, Ji G et al. Sorafenib inhibits epithelial-mesenchymal transition through an epigenetic-based mechanism in human lung epithelial cells. *PLoS One* 2013;8:e64954 [PubMed: 23741434]
73. Meyer KC, Cardoni A and Xiang ZZ. Vascular endothelial growth factor in bronchoalveolar lavage from normal subjects and patients with diffuse parenchymal lung disease. *J Lab Clin Med* 2000;135:332–8 [PubMed: 10779049]
74. Hanaoka M, Droma Y, Naramoto A et al. Vascular endothelial growth factor in patients with high-altitude pulmonary edema. *J Appl Physiol* (1985) 2003;94:1836–40 [PubMed: 12524373]
75. Abadie Y, Bregeon F, Papazian L et al. Decreased VEGF concentration in lung tissue and vascular injury during ARDS. *Eur Respir J* 2005;25:139–46 [PubMed: 15640335]
76. Seidel C, Janssen S, Karstens JH et al. Recall pneumonitis during systemic treatment with sunitinib. *Ann Oncol* 2010;21:2119–20 [PubMed: 20720089]
77. Dajczman E, Srolovitz H, Kreisman H et al. Fatal pulmonary toxicity following oral etoposide therapy. *Lung Cancer* 1995;12:81–6 [PubMed: 7600034]
78. Gurjal A, An T, Valdivieso M et al. Etoposide-induced pulmonary toxicity. *Lung Cancer* 1999;26:109–12 [PubMed: 10568682]
79. Pitot HC, Wender DB, O'Connell MJ et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1997;15:2910–9 [PubMed: 9256135]
80. Yamada K, Ikehara M, Tanaka G et al. Dose escalation study of paclitaxel in combination with fixed-dose irinotecan in patients with advanced non-small cell lung cancer (JCOG 9807). *Oncology* 2004;66:94–100 [PubMed: 15138360]
81. Yamada M, Kudoh S, Hirata K et al. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* 1998;34:71–5 [PubMed: 9624240]
82. Madarnas Y, Webster P, Shorter AM et al. Irinotecan-associated pulmonary toxicity. *Anticancer Drugs* 2000;11:709–13 [PubMed: 11129733]

83. Michielin O, Udry E, Periard D et al. Irinotecan-induced interstitial pneumonia. *Lancet Oncol* 2004;5:322–4 [PubMed: 15120670]
84. Maitland ML, Wilcox R, Hogarth DK et al. Diffuse alveolar damage after a single dose of topotecan in a patient with pulmonary fibrosis and small cell lung cancer. *Lung Cancer* 2006;54:243–5 [PubMed: 16949700]
85. Miyakoshi S, Kami M, Yuji K et al. Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. *Blood* 2006;107:3492–4 [PubMed: 16410442]
86. Zappasodi P, Dore R, Castagnola C et al. Rapid response to high-dose steroids of severe bortezomib-related pulmonary complication in multiple myeloma. *J Clin Oncol* 2007;25:3380–1 [PubMed: 17664489]
87. Yamaguchi T, Sasaki M and Itoh K. Bortezomib-induced pneumonitis during bortezomib retreatment in multiple myeloma. *Jpn J Clin Oncol* 2012;42:637–9 [PubMed: 22628610]
88. Dhakal A, Belur AA and Chandra AB. Bortezomib Induced Pulmonary Toxicity. *Blood* 2014;124:5731
89. Pitini V, Arrigo C, Altavilla G et al. Severe pulmonary complications after bortezomib treatment for multiple myeloma: an unrecognized pulmonary vasculitis? *Leuk Res* 2007;31:1027–8 [PubMed: 17134751]
90. McCormack FX, Inoue Y, Moss J et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *N Engl J Med* 2011;364:1595–606 [PubMed: 21410393]
91. Pham PT, Pham PC, Danovitch GM et al. Sirolimus-associated pulmonary toxicity. *Transplantation* 2004;77:1215–20 [PubMed: 15114088]
92. Ussavarungsi K, Elsanjak A, Laski M et al. Sirolimus induced granulomatous interstitial pneumonitis. *Respir Med Case Rep* 2012;7:8–11 [PubMed: 26029599]
93. Morelon E, Stern M, Israel-Biet D et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001;72:787–90 [PubMed: 11571438]
94. Fielhaber JA, Carroll SF, Dydensborg AB et al. Inhibition of mammalian target of rapamycin augments lipopolysaccharide-induced lung injury and apoptosis. *J Immunol* 2012;188:4535–42 [PubMed: 22450807]
95. Junpaparp P, Sharma B, Samiappan A et al. Everolimus-induced severe pulmonary toxicity with diffuse alveolar hemorrhage. *Ann Am Thorac Soc* 2013;10:727–9 [PubMed: 24364783]
96. Iacovelli R, Palazzo A, Mezi S et al. Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials. *Acta Oncol* 2012;51:873–9 [PubMed: 22909392]
97. Frija J, Joly D, Knebelmann B et al. Everolimus-related organizing pneumonia: a report establishing causality. *Invest New Drugs* 2012;30:1244–7 [PubMed: 21188465]
98. Duran I, Siu LL, Oza AM et al. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006;42:1875–80 [PubMed: 16806903]
99. Abal M, Andreu JM and Barasoain I. Taxanes: microtubule and centrosome targets, and cell cycle dependent mechanisms of action. *Curr Cancer Drug Targets* 2003;3:193–203 [PubMed: 12769688]
*This review discusses cell cycle dependent mechanisms of action of taxanes.
100. Goldberg HL and Vannice SB. Pneumonitis related to treatment with paclitaxel. *J Clin Oncol* 1995;13:534–5 [PubMed: 7844618]
101. Ostoros G, Pretz A, Fillinger J et al. Fatal pulmonary fibrosis induced by paclitaxel: a case report and review of the literature. *Int J Gynecol Cancer* 2006;16 Suppl 1:391–3
102. Thomas AL, Cox G, Sharma RA et al. Gemcitabine and paclitaxel associated pneumonitis in non-small cell lung cancer: report of a phase I/II dose-escalating study. *Eur J Cancer* 2000;36:2329–34 [PubMed: 11094306]
103. Abulkhair O and El Melouk W. Delayed Paclitaxel-trastuzumab-induced interstitial pneumonitis in breast cancer. *Case Rep Oncol* 2011;4:186–91 [PubMed: 21516267]
104. Reckzeh B, Merte H, Pfluger KH et al. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. *J Clin Oncol* 1996;14:1071–6 [PubMed: 8648359]

105. Fujimori K, Yokoyama A, Kurita Y et al. Paclitaxel-induced cell-mediated hypersensitivity pneumonitis. Diagnosis using leukocyte migration test, bronchoalveolar lavage and transbronchial lung biopsy. *Oncology* 1998;55:340–4 [PubMed: 9663424]
106. Robert F, Childs HA, Spencer SA et al. Phase I/IIa study of concurrent paclitaxel and cisplatin with radiation therapy in locally advanced non-small cell lung cancer: analysis of early and late pulmonary morbidity. *Semin Radiat Oncol* 1999;9:136–47 [PubMed: 10210553]
107. Semb KA, Aamdal S and Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. *J Clin Oncol* 1998;16:3426–32 [PubMed: 9779722]
108. Read WL, Mortimer JE and Picus J. Severe interstitial pneumonitis associated with docetaxel administration. *Cancer* 2002;94:847–53 [PubMed: 11857321]
109. Tamiya A, Naito T, Miura S et al. Interstitial lung disease associated with docetaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* 2012;32:1103–6 [PubMed: 22399640]
110. Morris MJ, Santamauro J, Shia J et al. Fatal respiratory failure associated with treatment of prostate cancer using docetaxel and estramustine. *Urology* 2002;60:1111
111. Genestreti G, Di Battista M, Trisolini R et al. A commentary on interstitial pneumonitis induced by docetaxel: clinical cases and systematic review of the literature. *Tumori* 2015;101:e92–5 [PubMed: 25908033]
112. Scott AM, Allison JP and Wolchok JD. Monoclonal antibodies in cancer therapy. *Cancer Immun* 2012;12:14 [PubMed: 22896759] *This paper provides an overview of the history of antigenic target discovery, development of antibody-based therapy and clinical use.
113. Hoag JB, Azizi A, Doherty TJ et al. Association of cetuximab with adverse pulmonary events in cancer patients: a comprehensive review. *J Exp Clin Cancer Res* 2009;28:113 [PubMed: 19682368]
114. Harding J and Burtneess B. Cetuximab: an epidermal growth factor receptor chimeric human-murine monoclonal antibody. *Drugs Today (Barc)* 2005;41:107–27 [PubMed: 15821783]
115. Yamada T, Moriwaki T, Matsuda K et al. Panitumumab-induced interstitial lung disease in a case of metastatic colorectal cancer. *Onkologie* 2013;36:209–12 [PubMed: 23548971]
116. Osawa M, Kudoh S, Sakai F et al. Clinical features and risk factors of panitumumab-induced interstitial lung disease: a postmarketing all-case surveillance study. *Int J Clin Oncol* 2015;20:1063–71 [PubMed: 25967287] *This paper provides postmarketing surveillance data from over 3000 patients who have been treated with panitumumab.
117. Gemmete JJ and Mukherji SK. Panitumumab (vectibix). *AJNR Am J Neuroradiol* 2011;32:1002–3 [PubMed: 21596817]
118. Nissen NN, Polverini PJ, Koch AE et al. Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. *Am J Pathol* 1998;152:1445–52 [PubMed: 9626049]
119. Erinjeri JP, Fong AJ, Kemeny NE et al. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. *Cancer* 2011;117:1296–301 [PubMed: 21381016]
120. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–50 [PubMed: 17167137]
121. Lind JS, Senan S and Smit EF. Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer. *J Clin Oncol* 2012;30:e104–8 [PubMed: 22331948]
122. Senan S and Smit EF. Design of clinical trials of radiation combined with antiangiogenic therapy. *Oncologist* 2007;12:465–77 [PubMed: 17470689]
123. Koukourakis MI, Giatromanolaki A, Sheldon H et al. Phase I/II trial of bevacizumab and radiotherapy for locally advanced inoperable colorectal cancer: vasculature-independent radiosensitizing effect of bevacizumab. *Clin Cancer Res* 2009;15:7069–76 [PubMed: 19887481]
124. Burton C, Kaczmarek R and Jan-Mohamed R. Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003;348:2690–1; discussion –1 [PubMed: 12826649]
125. Swords R, Power D, Fay M et al. Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004;77:103–4

126. Bienvu J, Chvetzoff R, Salles G et al. Tumor necrosis factor alpha release is a major biological event associated with rituximab treatment. *Hematol J* 2001;2:378–84 [PubMed: 11920277]
127. Hiraga J, Kondoh Y, Taniguchi H et al. A case of interstitial pneumonia induced by rituximab therapy. *Int J Hematol* 2005;81:169–70 [PubMed: 15765788]
128. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177–82 [PubMed: 3798106]
129. Le XF, Pruefer F and Bast RC, Jr., HER2-targeting antibodies modulate the cyclin-dependent kinase inhibitor p27Kip1 via multiple signaling pathways. *Cell Cycle* 2005;4:87–95 [PubMed: 15611642]
130. Radzikowska E, Szczepulska E, Chabowski M et al. Organising pneumonia caused by trastuzumab (Herceptin) therapy for breast cancer. *Eur Respir J* 2003;21:552–5 [PubMed: 12662016]
131. Costa R, Costa-Filho RB, Talamantes SM et al. Interstitial Pneumonitis Secondary to Trastuzumab: A Case Report and Literature Review. *Case Rep Oncol* 2017;10:524–30 [PubMed: 28690527]
132. Vahid B and Mehrotra A. Trastuzumab (Herceptin)-associated lung injury. *Respirology* 2006;11:655–8 [PubMed: 16916343]
133. Lin TS, Penza SL, Avalos BR et al. Diffuse alveolar hemorrhage following gemtuzumab ozogamicin. *Bone Marrow Transplant* 2005;35:823–4 [PubMed: 15735659]
134. Li H, Ma W, Yoneda KY et al. Severe nivolumab-induced pneumonitis preceding durable clinical remission in a patient with refractory, metastatic lung squamous cell cancer: a case report. *J Hematol Oncol* 2017;10:64 [PubMed: 28245875]
135. Abdel-Rahman O, ElHalawani H and Fouad M. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Expert Opin Drug Saf* 2015;14:1507–18 [PubMed: 26394770] *This meta-analysis paper reviews several clinical trials that enrolled patients treated with immune checkpoint inhibitors and provides insights into increased risk of elevated transaminases.
136. Nishino M, Sholl LM, Hodi FS et al. Anti-PD-1-Related Pneumonitis during Cancer Immunotherapy. *N Engl J Med* 2015;373:288–90 [PubMed: 26176400]
137. Naidoo J, Page DB, Li BT et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015;26:2375–91 [PubMed: 26371282] **This paper reviews several clinical studies that investigated anti-PD1 and anti-PD-L1 antibodies and summarizes the major adverse events reported in these studies as well as provides management algorithms.
138. McNally B, Ye F, Willette M et al. Local blockade of epithelial PDL-1 in the airways enhances T cell function and viral clearance during influenza virus infection. *J Virol* 2013;87:12916–24 [PubMed: 24067957]
139. Fehrenbacher L, Spira A, Ballinger M et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46 [PubMed: 26970723]
140. Barjaktarevic IZ, Qadir N, Suri A et al. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. *Chest* 2013;143:858–61 [PubMed: 23460165]
141. Franzen D, Schad K, Dummer R et al. Severe acute respiratory distress syndrome due to ipilimumab. *Eur Respir J* 2013;42:866–8 [PubMed: 24000256]
142. Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30 [PubMed: 28055103]
143. Schaake-Koning C, van den Bogaert W, Dalesio O et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–30 [PubMed: 1310160]
144. Ettinger DS, Wood DE, Aisner DL et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017;15:504–35 [PubMed: 28404761]
145. Tyldesley S, Boyd C, Schulze K et al. Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. *Int J Radiat Oncol Biol Phys* 2001;49:973–85 [PubMed: 11240238]

146. Chun SG, Hu C, Choy H et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol* 2017;35:56–62 [PubMed: 28034064]
147. Auperin A, Le Pechoux C, Rolland E et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–90 [PubMed: 20351327]
148. Bradley JD, Paulus R, Komaki R et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187–199 [PubMed: 25601342] **This paper reports the outcome of a phase III study that compared fractionated radiation of two total prescription doses in patients that received concurrent chemotherapy and/or an immune checkpoint inhibitor for the treatment of non-smal cell lung cancer.
149. Geara FB, Komaki R, Tucker SL et al. Factors influencing the development of lung fibrosis after chemoradiation for small cell carcinoma of the lung: evidence for inherent interindividual variation. *Int J Radiat Oncol Biol Phys* 1998;41:279–86 [PubMed: 9607342]
150. Kong FM and Wang S. Nondosimetric risk factors for radiation-induced lung toxicity. *Semin Radiat Oncol* 2015;25:100–9 [PubMed: 25771414] *This reviews discusses patient-related risk factors other than dosimetry for radiation-induced pulmonary toxicity.
151. McDonald S, Rubin P, Phillips TL et al. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys* 1995;31:1187–203 [PubMed: 7713782]
152. Guerrero T, Johnson V, Hart J et al. Radiation pneumonitis: local dose versus [18F]-fluorodeoxyglucose uptake response in irradiated lung. *Int J Radiat Oncol Biol Phys* 2007;68:1030–5 [PubMed: 17398033]
153. Choi YW, Munden RF, Erasmus JJ et al. Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. *Radiographics* 2004;24:985–97; discussion 98 [PubMed: 15256622]
154. Nozaki Y, Hasegawa Y, Takeuchi A et al. Nitric oxide as an inflammatory mediator of radiation pneumonitis in rats. *Am J Physiol* 1997;272:L651–8 [PubMed: 9142938]
155. Daba MH, El-Tahir KE, Al-Arifi MN et al. Drug-induced pulmonary fibrosis. *Saudi Med J* 2004;25:700–6 [PubMed: 15195196]
156. Raghu G, Rochwerg B, Zhang Y et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19 [PubMed: 26177183] *This paper provides official Thoracic Society guidelines for the treatment of lung fibrosis of idiopathic cause.
157. Rubin P, Johnston CJ, Williams JP et al. A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis. *Int J Radiat Oncol Biol Phys* 1995;33:99–109 [PubMed: 7642437]
158. Hallahan D, Kuchibhotla J and Wyble C. Cell adhesion molecules mediate radiation-induced leukocyte adhesion to the vascular endothelium. *Cancer Res* 1996;56:5150–5 [PubMed: 8912850]
159. Provatopoulou X, Athanasiou E and Gounaris A. Predictive markers of radiation pneumonitis. *Anticancer Res* 2008;28:2421–32 [PubMed: 18751429]
160. Wang S, Campbell J, Stenmark MH et al. Plasma Levels of IL-8 and TGF-beta1 Predict Radiation-Induced Lung Toxicity in Non-Small Cell Lung Cancer: A Validation Study. *Int J Radiat Oncol Biol Phys* 2017;98:615–21 [PubMed: 28581403]
161. Ghebre YT and Raghu G. Idiopathic Pulmonary Fibrosis: Novel Concepts of Proton Pump Inhibitors as Antifibrotic Drugs. *Am J Respir Crit Care Med* 2016;193:1345–52 [PubMed: 27110898]

Key issues

- Many classes of chemotherapeutic drugs are associated with several patterns of lung injury that culminates to acute bronchoconstriction, interstitial pneumonitis, pulmonary veno-occlusive disease, pulmonary hypertension, bronchiolitis obliterans organizing pneumonia, intraalveolar fibrosis and complete respiratory failure.
- Some of the classes of chemotherapeutic drugs whose members are associated with lung injury include antitumor antibiotics, alkylating agents, platinoids, antimetabolites, nitrosurea, receptor tyrosine kinase inhibitors, topoisomerase inhibitors, taxanes, and immune checkpoint inhibitors.
- Traditionally, radiation therapy has been associated with significant cases of lung inflammation and fibrosis. However, emerging developments in radiation delivery techniques such as stereotactic body radiation therapy (SBRT), intensity-modulated radiotherapy (IMRT), stereotactic radiosurgery (SRS), and respiratory-gated radiotherapy that precisely deliver radiation doses to a tumor are expected to substantially reduce pulmonary toxicity.
- Interventional strategies to manage lung injury secondary to chemoradiation therapy requires, at least in part, greater understanding of the mechanism(s) by which these agents interact with the pulmonary system. Such refined understanding may eventually help in guiding disease-management decisions and in addressing whether it is possible to tease out off-target effects.
- It is important to be vigilant when treating patients with ionizing radiation or chemotherapeutic drugs that are known or suspected to induce pulmonary toxicity. For patients that manifest signs and/or symptoms of drug/radiation-induced pulmonary toxicities, it may be necessary to consider dose reducing, delaying, discontinuing or substituting the aggravating agent(s) to avoid the risk of permanent complications.

Table 1:

Summary of pulmonary toxicity associated with chemoradiation therapy

Class	Agent	Patterns of lung injury	Potential mechanism(s) of action
Antitumor Antibiotics	Bleomycin	- Inflammation - Fibrosis	- DNA damage - Oxidative stress - Induction of Inflammatory molecules - Activation of death signals
	Mitomycin C	- Interstitial pneumonitis - Fibrosis - Pulmonary veno-occlusive disease (PVOD)	- DNA damage - Oxidative stress - Downregulation of SMAD signaling - Inhibition of GCN2
	Actinomycin D	- Pneumonitis - Fibrosis	- Inhibition of DNA replication
	Antracyclines	- Fibrosis	- Inhibition of nucleic acid synthesis - Inhibition of topoisomerase II activity - Oxidative stress
Alkylating Agents	Cyclophosphamide	- Dyspnea - Bilateral pleural thickening - Pulmonary hypertension - Respiratory failure	- Increased expression of profibrotic molecules: TGF β , fibronectin, procollagen - DNA damage - Oxidative stress
	Chlorambucil	- Interstitial pneumonitis - Intraalveolar fibrosis - Interstitial fibrosis - Bronchiolitis Obliterans Organizing Pneumonia	- Generation of reactive oxygen species - Impaired alveolar repair
	Melphalan	- Acute bronchoconstriction - Interstitial pneumonitis - Interstitial fibrosis	- Upregulation of Fibroinflammatory molecules: IL-1 β , IL-6, IL-23
	Busulfan	- Dyspnea - Alveolar hemorrhage - Bronchiolitis obliterans - Intraalveolar fibrosis - Interstitial fibrosis	- Oxidative stress - Dysregulation of pathways associated with fibroinflammation
Platinoids	Cisplatin	- Eosinophilic pneumonia	- Oxidative stress - Inhibition of physiological lung repair
	Carboplatin	- Fibrosis	- Oxidative stress - Inhibition of physiological lung repair
	Oxaliplatin	- Interstitial pneumonitis - Fibrosis	- Oxidative stress - Inhibition of physiological lung repair
Antimetabolites	Methotrexate	- Hypersensitivity pneumonitis - Bronchiolitis obliterans - Intraalveolar fibrosis	- Generation of free radicals - Upregulation of Fibroinflammatory molecules - Activation of p38 MAPK
	Fludarabine	- Pulmonary nodules - Interstitial pneumonitis - Fibrosis	- Inflammation mediated
	Gemcitabine	- Dyspnea - Noncardiogenic pulmonary edema - Pulmonary veno-occlusive disease (PVOD) - Diffuse alveolar damage - Interstitial pneumonitis - Fibrosis	- Systemic release of Proinflammatory cytokines and interleukins
Nitrosurea	Carmustine	- Pneumothorax - Pneumonitis - Fibrosis	- Targeting of lung glutathione disulfide (GSSG) reductase - Induction of fibrogenic cytokines in alveolar macrophages and type II pneumocytes

Class	Agent	Patterns of lung injury	Potential mechanism(s) of action
Receptor Tyrosine Kinase Inhibitors	Gefitinib	- Pneumonitis - Interstitial lung disease - Ground-glass opacification - Bronchiectasis	- Upregulation of chemokine interferon-inducible protein-10 (IP-10) expression - Th1 response - EGFR inhibition Associated impairment of alveolar epithelial cell proliferation and repair - Dysregulated interaction with profibrotic molecules (e.g. TGF- α)
	Imatinib	- Dyspnea - Pleural effusion - Pulmonary edema - Interstitial pneumonitis - Fibrosis	- Dysregulation of lung cell growth, differentiation and apoptosis
	Sorafenib	- Interstitial pneumonitis - Diffuse alveolar damage	- Inhibition of intrapulmonary VEGF and subsequent inhibition of cell growth
Topoisomerase Inhibitors	Etoposide	- Diffuse interstitial and alveolar infiltrates - Fibrosis	- Inhibition of DNA synthesis, cell division and survival in resident lung cells
	Irinotecan	- Interstitial pneumonitis	- Immune-mediated Including Inflammatory molecules and cells
	Topotecan	- Diffuse alveolar damage - Non-specific Interstitial pneumonia - Bronchiolitis obliterans	- Immune-mediated Including Inflammatory molecules and cells
Proteasome Inhibitors	Bortezomib	- Interstitial lung injury - Pneumonitis - Bronchiolitis Obliterans Organizing Pneumonia - Pulmonary hypertension	- Dysregulation of NF κ B pathway - Activation of lung Inflammatory cascade
mTOR inhibitors	Sirolimus	- Granulomatous interstitial pneumonitis - Lymphocytic alveolitis - Alveolar hemorrhage - Bronchiolitis Obliterans Organizing Pneumonia - Fibrosis	- Exposure of alveolar antigens via direct toxicity - Autoimmune response to exposed antigen - Dysregulation of mTOR-STAT1 interaction to impact cell death and lung injury
	Everolimus	- Hypersensitivity pneumonitis - Diffuse alveolar hemorrhage	- Immune-mediated including involvement of CD4/CD8 cells
Taxanes	Paclitaxel	- Interstitial pneumonitis - Pulmonary fibrosis	- Immunological and non-immunological
	Docetaxel	- Interstitial pneumonitis - Ground-glass opacification	- Immune-mediated Involving inflammation
Monoclonal Antibody	Cetuximab	- Dyspnea - Bronchiolitis Obliterans Organizing Pneumonia - Interstitial pneumonitis	- Inhibition of major growth factor receptor involved in the proliferation and regeneration of lung cells - Inhibition of matrix metalloproteinases
	Panitumumab	- Interstitial lung disease - Fibrosis	- Inhibition of major growth factors and physiological angiogenesis in the lungs
	Bevacizumab	- Pulmonary hemorrhage - Hemoptysis - Pulmonary Parenchymal toxicity	- Inhibition of a major growth factor (i.e. VEGF) - Inhibition of proliferation- and DNA repair- related genes and transcription factors
	Rituximab	- Interstitial pneumonitis - Alveolar hemorrhage	- Activation of complement cascade - Release of Proinflammatory cytokines
	Trastuzumab	- Bronchospasm - Respiratory distress - Bronchiolitis Obliterans Organizing Pneumonia - Interstitial pneumonitis	- Immune-mediated Involving inflammation
Immune Checkpoint Inhibitors	PD-1 inhibitors	- Dyspnea	- Overstimulation of immune system

Class	Agent	Patterns of lung injury	Potential mechanism(s) of action
		<ul style="list-style-type: none"> - Respiratory tract infection - Pneumonitis 	<ul style="list-style-type: none"> - Collateral targeting of PD-1 on effector T cells and PD-L1 in the respiratory epithelium
	CTLA-4 inhibitors	<ul style="list-style-type: none"> - Organizing pneumonia - Autoimmune alveolitis - Acute respiratory distress syndrome - Sarcoid-like granulomatosis 	<ul style="list-style-type: none"> - Overstimulation of immune system - Immune-mediated Involving inflammation
Radiation	Ionizing radiation	<ul style="list-style-type: none"> - Dyspnea - Pneumonitis - Ground-glass opacification 	<ul style="list-style-type: none"> - DNA damage - Oxidative and nitrosative stress - Dysregulation of Fibroinflammatory molecules