Therapy-induced Toxicity of the Lungs: An Overview

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Abstract. Pulmonary toxicity induced by novel antineoplastic agents has not been well characterized because of the simultaneous or sequential use of drugs and a multimodality therapeutic approach. To further investigate this topic, relevant studies were identified through Medline. The generic names of novel antineoplastic agents and the key words pulmonary toxicity, dyspnea and pneumonitis were used for the search. References from the articles identified were also reviewed for additional sources. Most novel antineoplastic drugs may induce pulmonary toxicity. The most recognized patterns of lung toxicity consist of unspecified dyspnea and interstitial lung disease (ILD). Exclusion diagnosis of possible underlying diseases is necessary. Genetic predisposition, autoimmune conditions or superimposed disease may also be involved in the development of lung toxicity. Conclusion: Clinicians should be aware of potential pulmonary toxicity as a complication in the treatment of cancer and focus on its early detection or prediction.

Pulmonary toxicity is a complication in the treatment of lung cancer. With the current trends in lung cancer therapy, pulmonary toxicity is unavoidable. It is estimated that the frequency of this complication is anywhere between 10-30% depending on the type of treatment.

Anticancer agents for lung cancer have been implicated in lung injury and interstitial lung disease (ILD). ILD comprises histopathological patterns of acute lung injury (ALI), nonspecific interstitial pneumonitis (NSIP), diffuse alveolar damage (DAD), bronchiolitis obliterans with organizing pneumonia, eosinophilic pneumonia, and pulmonary hemorrhage (1). The clinical manifestations of disease range from cough and low-grade fever to serious severe dyspnea and respiratory failure. Understanding of the mechanisms involved is limited although it is considered to be a multistep process. Simultaneous or sequential use of drugs and a multimodality therapeutic approach make assessment of toxicity to a specific agent difficult.

This review focuses on cell injuring mechanisms, potential pulmonary toxicity of the novel antitumor agents for lung cancer (cytotoxic and targeted therapies) and future developments in the early detection or prediction of the candidates for ILD from the therapy.

To further investigate this topic, relevant studies were identified through Medline. The generic names of novel antineoplastic agents (docetaxel, gemcitabine, paclitaxel, irinotecan, gefinitib, erlotinib and bevacizumab) were used in the search. The key phrases pulmonary toxicity, dyspnea, pneumonitis, apoptosis and radiotherapy were used for better results. The references from the articles identified were also reviewed for additional sources.

Pathogenesis

Chemotherapeutic agents appear to affect both normal and neoplastic cells. Drug-associated lung injury results either from cellular dysfunction generating the cell-death mechanism (apoptosis) or by impairing the cell and tissue repair sequence.

Apoptotic dysfunction. The normal activation of apoptosis seems to play an important role in the remodeling of lung tissue after acute lung injury, for the clearance of excess epithelium and mesenchymal cells from resolving lesions (2, 3).

The type II pneumocyte is the stem cell of the alveolar epithelium and is primarily responsible for re-epithelization and the restoration of the integral alveolar architecture. During normal cell turnover or lung damage, these cells...
divide and differentiate into the predominant alveolar type I pneumocytes (4). Widespread loss of integrity of non-neoplastic pneumocytes type I and II appears to be the primary cause of DAD (5).

Activation of the apoptotic procedure follows two fundamental pathways: the death receptor and the mitochondrial pathway. These two are intimately connected via caspase 8 and BID (BCL-2-interacting domain). Caspases, a family of cysteine proteases, can activate degradation enzymes that destroy the cell. The first pathway is initiated by cell surface receptor-mediated activation of caspase (Figure 1). The death receptors (Fas, tumor necrosis factor receptor-1 and tumour necrosis factor receptor-2) interact with soluble proteins or membrane-bound proteins such as the Fas ligand (FasL). FasL is a cell surface molecule expressed predominantly in activated T-lymphocytes and natural killer cells (6, 7). It is accumulated in soluble form at sites of tissue inflammation and has the potential to initiate the apoptosis of leukocytes, epithelial cells and other parenchymal cells (7-9).

On the other hand, the mitochondrial pathway is composed of members of the B-cell leukemia (Bcl) family of proteins. The Bcl family has both proapoptotic members, such as Bcl-2 associate X protein (BAX), Bcl-2 associate K protein (BAK) and BID, and antiapoptotic members, such as B-cell leukemia 2 (Bcl-2). When cells are exposed to an apoptotic stimulus, for example anticancer drugs, radiation and reactive oxygen radicals, proapoptotic proteins are activated through posttranslational modifications or changes in their conformation. These proteins increase the permeability of the outer membrane of the mitochondria resulting in the release of cytochrome c. In the cytosol, cytochrome c activates a caspase cascade that ultimately leads to cell death (10).

**Impaired repair.** Members of the epidermal growth factor (EGF) family [i.e. EGF, transforming growth factor alpha (TGF-α)] are likely to be important regulators of epithelial repair by virtue of their ability to stimulate cell migration, proliferation, differentiation and survival. EGF belongs to a family of growth factors that exert their biological effect by binding to a transmembrane tyrosine kinase receptor epidermal growth factor receptor (EGFR also known as e-erbB1). In the normal lung, the distribution of EGF and EGFR has been demonstrated by immunohistochemistry, with expression observed in the basal cell layer of the bronchial epithelium (11, 12) and in occasional type II alveolar pneumocytes (13).

Angiogenesis also plays a key role in wound healing. Normal wound repair generates an angiogenic response to deliver nutrients and inflammatory cells to the injured tissue. The mediators of wound angiogenesis include soluble factors such as vascular endothelial growth factor (VEGF), TNF-α, TGF-β, fibroblastic growth factor (FGF) and platelet-derived growth factor (PDGF) which have been identified in several wound models (14).

As EGF signaling and angiogenesis may represent an important mechanism that helps coordinate the process of recovery from lung injury (15, 16), it is possible that their inhibition would partly reduce the ability of pneumocytes to respond and repair. The alteration of repair mechanisms and/or abnormal apoptotic function leads to disruption of the alveolar-capillary membrane and clinical, pathological and radiographic manifestations of ALI.

**Radiotherapy**

Radiation can cause acute or chronic injury in non-neoplastic type I and II pneumocytes, endothelial cells and stromal fibroblasts (17). At a pathological level, pulmonary damage is present as ILD and/or fibrosis. The incidence of toxicity can occur early, within weeks after completion of treatment, or later within the first year (18). The injury of normal lung tissue depends on the total dose (19), dose received from the lung and mean lung dose (20). Alterations in apoptotic and repair mechanisms can also explain the pathogenesis of radiation pneumonitis, as implied by the role of multiple cytokines (e.g. TGF-β, TNF-α, interleukin-1 (IL-1), IL-6 and PDGF) in the pathogenesis and early detection of toxicity (21). Initial DNA damage instigates the repair mechanisms or the process of inflammation and finally cell death and fibrosis. Pulmonary function tests should be used as markers or predictors of the incidence and severity of pneumonitis. Furthermore, the predictive value of clinical data such as the site of the radiated lung, the age of the patient and smoking history have been investigated in the context of radiation pneumonitis (22).

**Novel Cytotoxic Drugs that Cause Pulmonary Toxicity**

The literature reports a number of chemotherapeutic agents that cause the serious side-effect of pulmonary toxicity. The third-generation chemotherapies, specifically taxanes (docetaxel and paclitaxel) and/or gemcitabine, have been studied because of their broad use in the therapy of non-small cell lung cancer NSCLC (23). The pattern of pulmonary toxicity by these agents is usually a non-specific interstitial pneumonitis, diffuse alveolar damage and pleural effusion (24).

**Docetaxel.** Docetaxel is a taxane derivative with activity in many solid tumors including breast, gastric, ovarian and NSCLC (25). Docetaxel disrupts the microtubular network in cells that is essential for mitotic and interphase cellular functions. Binding to free tubulin, docetaxel produces dysfunctional microtubular bundles which inhibit mitosis. The accumulation of such bundles leads to apoptosis. Furthermore, docetaxel is known to inhibit Bcl-2 antiapoptotic protein, which further encourages apoptosis.
Hypersensitivity reactions seem to be common (26, 27). In one study, such reactions were observed in 42% of the patients and included dyspnea, pruritus, skin rashes, fever and hypotension, and may relate to the formulation of docetaxel with polysorbate-80 or to histamine release and may be blocked with the use of premedication (28). Hypersensitivity pneumonitis in which chest computed tomography scans shows a typical ground glass appearance of the lung parenchyma bilaterally appear to be a frequent type of the injury (24, 29, 30).

Docetaxel can cause acute interstitial pneumonitis when used as monotherapy or in combination with other treatments (29-35). The coadministration of docetaxel and gemcitabine can be correlated with an incidence as high as 23% of interstitial pneumonitis (36). Patients receiving docetaxel combined with gemcitabine or estramustine have occasionally suffered from diffuse alveolar damage (33, 37), which may even extend to adult respiratory distress syndrome (ARDS). Docetaxel-related pneumonitis usually responds to steroids (30, 31), which is also indicative of a hypersensitivity reaction. However severe cases have occasionally been reported in which the use of steroids was ineffective and death ensued after long-term ventilatory support (33, 34, 38).

Although in some cases, docetaxel has been connected to edematous states after subsequent cycles, pulmonary edema is rare. In two studies, 20% and 62% of patients treated with docetaxel suffered from fluid retention which was typically peripheral, with pleural effusions reported less often. Notably, docetaxel appears to cause a capillary protein leakage independent of the presence or absence to interstitial lung disease (39). Animal studies of taxanes (paclitaxel and docetaxel) have shown increased albumin extravasation (40). Such toxicity is seen more often in patients receiving a total dose of 500 mg/m² (39). It has also been described in patients treated with docetaxel and thalidomide (35). Although diuretic treatments should not be used to resolve the edematous symptoms, steroids are indicated for the possible prevention or delay of the onset of symptoms if given before and after the administration of docetaxel (41). The usefulness of corticosteroids in combination therapies of docetaxel with radiotherapy or gemcitabine is uncertain and death may still ensue (30, 34, 37).

Non-cardiogenic pulmonary edema, or ALI, which may be precipitated by chemotherapeutic drugs is characterized by the presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiographs and no evidence of left atrial hypertension/congestive heart failure (42). Exclusion of any infectious, metabolic, or cancer-related causes and a response to corticosteroids may further support such a diagnosis.

Gemcitabine. Gemcitabine is a deoxycytidine analog (2',2'-difluoro-deoxycytidine) which interferes with DNA synthesis by inhibiting DNA and RNA polymerase. Inserting itself into...
the growing DNA, by competing with deoxycytidine triphosphate at the cytidine sites, gemcitabine arrests growth at the S-phase and induces apoptosis. This antimetabolite is used in a number of solid tumors including pancreatic, ovarian, breast and esophageal as well as lung cancer. The toxicity profile of gemcitabine is mild compared with other cytotoxics (43) and usually involves myelosuppression which is dose-limiting (44). Higher incidences of neutropenia can be seen more commonly in combination therapy rather than in first-line therapy (45).

Although gemcitabine is considered to be a drug with a reasonable safety profile, cases of pulmonary toxicity have been reported. Studies with a large number of patients have shown an incidence of gemcitabine-related pulmonary toxicity of 4% and lower than 1%, respectively (43, 46). The clinical presentation is frequently sub-acute and nonspecific. Symptoms may even appear weeks after the last given dose and may include progressively worsening dyspnea, fevers, chills and night sweats.Transient dyspnea has been reported to arise within hours after the administration of gemcitabine in about 8-10% of patients (47, 48). More often, this transient dyspnea is associated with bronchospasm and is usually a self-limiting event. The dyspnea might be due to underlying disease such as lung cancer (40% of study population) or pulmonary manifestations of other malignancies. However, severe dyspnea associated with this drug has occurred in about 3-5% (47, 49). Most of these cases could be managed by withdrawing gemcitabine and concomitant administration of diuretics and corticosteroids. More rare side-effects are interstitial lung fibrosis, pleural effusion, alveolar hemorrhage and various airway diseases with bronchospasm (24).

Acute interstitial pneumonitis related to this agent has been suggested to be a cytokine-mediated hypersensitivity reaction, due to its improvement after the administration of steroids (48). The response to corticosteroids in gemcitabine-associated interstitial lung disease (ILD) is inconsistent (27, 37, 48).

Additionally, this drug appears to have a direct toxic effect on the endothelial cells of the pulmonary capillaries, which causes a capillary leak syndrome. It appears that this capillary event is often mild as patients are asymptomatic and have normal function indices. In these cases, the withdrawal of the drug is sufficient and the use of corticosteroids is not warranted.

The incidence rate of ARDS associated with gemcitabine has been reported to be as low as 0.002% (46). An extreme elevation of the erythrocyte sedimentation rate (ESR) (>100 mm/h) at the time of diagnosis may be used as a guide for ARDS development, according to one study (50).

Although in general serious toxicity is not common with gemcitabine, it has been observed to cause some fatalities (47, 51). More deaths are due to gemcitabine used in combination with other cancer therapies. A retrospective analysis which investigated patients with advanced NSCLC who received gemcitabine and cisplatin followed by surgery and/or radiation found that diffusion capacity for carbon monoxide (DLCO) decreased significantly after treatment (52). Recently, another study investigated the effects of gemcitabine on pulmonary function tests (PFTs) in patients with non-thoracic malignancies in a prospective setting. It showed that a subset (24%) of patients developed a clinically silent, reversible decrease in DLCO. Other lung function indices, such as forced vital capacity (FVC) and forced expiratory volume in one second, remained unaffected (53).

To reiterate, combination chemotherapy with docetaxel and gemcitabine is associated with a higher incidence of interstitial pneumonitis (36, 54). Additionally, diffuse alveolar damage or ARDS has been seen in those receiving docetaxel combined with gemcitabine (37, 54).

Paclitaxel. Like docetaxel, paclitaxel is derived itself from the bark of yew trees and is a spindle poison plant alkaloid. Paclitaxel interferes with the normal function of microtubule growth and arrests microtubule function by ultra-stabilizing its structure. Binding to the β subunit of tubulin, paclitaxel prevents the disassembly of the resulting microtubule/paclitaxel complex. Like docetaxel, paclitaxel also binds to Bcl-2 thus arresting its function of inhibiting apoptosis.

Paclitaxel is one of the most active chemotherapeutic agents in the treatment of breast, lung and ovarian carcinoma and advanced forms of Kaposi’s sarcoma. Paclitaxel, used in the treatment of thoracic-based tumors such as breast and lung cancer is not known to cause significant pulmonary toxicity. However, symptoms occurring within the first five minutes after the first dose of drug therapy, characterized by dyspnea, chest tightness, bronchospasm, urticaria and hypotension, have been seen in up to 30% of patients in early trials which were attributed to a probable type I hypersensitivity reaction (55). These symptoms may be attributed to IgE antibody formation to paclitaxel or to its vehicle, or may be mediated by the release of histamine and other vasoactive substances. Premedication subsequently reduced the occurrence of such reactions to 1% (56). Pretreatment with an antihistamine, a corticosteroid and a histamine 2 blocker (H2-receptor antagonists) mainly prevents this reaction (57).

ILD in the form of nonspecific or hypersensitivity pneumonitis has been described in a number of case reports and clinical studies (58-63). On the other hand, multi-therapeutic studies found the incidence of pneumonitis to be very low (1%), even with radiation therapy (64). The symptoms and radiological findings of pulmonary infiltrates eventually resolved within 24-96 hours after steroid administration (64). In another dose-escalation study, paclitaxel in combination with a fixed-dose of irinotecan in patients with advanced NSCLC was
found to cause pneumonitis grade 1 to 3 (65). On the whole, the incidence of interstitial pneumonitis is much higher if paclitaxel is given concurrently with radiation (47% of patients) (66), or with other agents that may potentially cause lung toxicity, including gemcitabine (33% of patients) (67, 68). The mild interstitial pneumonitis that has been reported was managed with low-dose corticosteroids, which resulted in a good response, even when radiotherapy was administered (58, 63).

Other rarer side-effects are DAD and lung fibrosis. DAD has been documented in two patients treated with paclitaxel and gemcitabine (69), and lung fibrosis has been seen in one patient treated with paclitaxel and carboplatin (70).

A delayed-type hypersensitivity reaction involving immunological and non-immunological mechanisms has been proposed as a possible pathophysiological mechanism (62) for ILD. A hypersensitivity reaction as shown by increased lymphocyte and eosinophil counts, along with a decreased helper/suppressor T lymphocyte ratio has been reported (62). Protracted lymphocytopenia can be seen for up to three months, which may invite opportunistic infections to arise accounting for the pulmonary infiltrates (66).

With regard to PFTs, paclitaxel may impair FVC and DLCO, which may decrease (71). No relationship has been established between changes in PFTs and the incidence of acute or late pulmonary toxicity.

**Irinotecan.** Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan is usually used in the treatment of colorectal cancer and is known to cause pneumonitis, whether alone or in combination with other drugs or radiotherapy (72-74). However, severe pulmonary events are infrequent. In clinical studies evaluating the weekly dosage schedule, NCI-CTC (National Cancer Institute-Common Toxicity Criteria, version 3.0) dyspnea grade 3 or 4 was reported in 4% of patients. Over half of the patients with dyspnea had lung metastases, which made it difficult to clarify if irinotecan was the culprit. However, in those who had been exposed to 5-fluorouracil (5-FU), pulmonary toxicity was reported in >20% of the patients given irinotecan (75, 76).

Interstitial pneumonitis, which responded to steroids, has been described in a few case reports (72, 77). A low incidence of pneumonitis at 1.8% was found in the early Japanese trials although fatalities have been described. It is rather difficult to assess clearly the exact contribution of irinotecan to these symptoms as the patients had lung tumors or other pulmonary comorbidities (78, 79). It is clear that the incidence of pneumonitis is higher if irinotecan is combined with paclitaxel (12.5% of patients) (65) or with radiotherapy (56% of patients) (73). Combination chemotherapy with cisplatin and irinotecan and concurrent radiotherapy have been correlated to increased levels of pulmonary fibrosis (80, 81).

**Multimodality Therapy in Lung Cancer and Pulmonary Toxicity**

Multimodality therapy is the current standard in locoregionally advanced and metastatic lung cancer. Many cytotoxic agents are involved in pneumonitis but while traditionally bleomycin, adriamycin, cyclophosphamide, mitomycin C and methotrexate have been reported, these agents are of less importance in lung cancer because they are not commonly used. Among the third-generation agents used with radiation in current practice, docetaxel might be the most toxic. This drug has an unacceptable toxicity of serious (NCI-CTC Grade 3) pneumonitis, in 47% of the patients, in concurrent administration with radiotherapy (23).

When paclitaxel-induced pneumonitis is combined with radiotherapy, immunological as well as non-immunological mechanisms may be involved. A hypersensitivity reaction, as evidenced by increased lymphocytes and eosinophils, along with a decreased helper/suppressor T lymphocyte ratio, has been reported (62). Protracted lymphocytopenia can be seen for up to three months and may indeed invite opportunistic infections to arise.

Chemotherapy with the cisplatin-irinotecan combination and concurrent radiotherapy correlates with increased of pulmonary fibrosis (80). Serious pneumonitis (NCI-CTC grade 3-4) has also occurred in 7.7% of patients treated with combination chemotherapy (cisplatin and vinorelbine) and radiation therapy according to one study (82).

Pemetrexed, a new multitarget antifolate, is currently used in malignant pleura mesothelioma and in first and second-line treatment of NSCLC (83). When this agent is combined with platinum based chemotherapy and radiation, it may be associated with fatal pneumonitis (84).

**Targeted Therapies and Pulmonary Toxicity**

Several studies of the last decade have indicated the pivotal role of angiogenesis and EGFR activation in tumor growth and metastatic dissemination (85). This has led to an ‘explosion’ of targeted therapies in lung cancer treatment. New single and multitarget agents have been developed. EGF tyrosine kinase inhibitors (TKIs) (namely gefinitib and erlotinib) have been used as salvage treatment in refractory NSCLC (83, 86, 87). VEGF-TKIs (namely sorafenib and sunitinib) (88) and monoclonal antibodies against the VEGF receptor VEGFR (bevacizumab) (89) are combined with chemotherapy in standard first-line treatment or in phase II and III first- and second-line clinical trials in NSCLC.

Treatment with gefinitib and erlotinib has been correlated with interstitial pneumonitis in 1% and 0.8% of treated patients (90, 91). Symptoms such as dyspnea, cough and low-grade fever, start from day five up to nine months after starting therapy (92). The pathogenesis of ILD is likely to
be an effect of EGFR involvement in the repair process and not a result of biotransformation or chemical injury as with radiotherapy and chemotherapy (5, 93). However, further research to elucidate the key cell types involved is needed.

Monoclonal antibodies are used in the treatment of various hematopoietic malignancies and solid tumors. Most recently, bevacizumab has been used in lung cancer (83) and has been correlated with serious and fatal hemoptysis (94), while bleeding episodes have not been reported in patients with colorectal, renal, breast or prostate cancer (95). Squamous NSCLC histology, a central location of the tumor and proximity to large vessels may present risk factors for pulmonary bleeding adverse events (89).

Supportive and Prophylactic Treatment in Lung Cancer Patients

Chemotherapy regimens are dose limited by their adverse effect on bone marrow and myelosuppression. Colony-stimulating growth factors (G-CSF) (e.g., filgrastim and pegfilgrastim) are of great importance in the supportive care of cancer patients. They are effective in reducing the nadir and duration of neutropenia by permitting the optimum dose intention when necessary (96). Pulmonary injury has been described with the use of marrow stem cell growth factor (97). Since in all the reports the pulmonary symptoms started during or after neutropenia recovery, it appears that the proposed mechanism of toxicity is mediated by neutrophilic invasion into the lungs with release of cytokines. Capillary-leak syndrome and ALI are the pathological patterns displayed. Since most cases have been reported as recurrent exacerbation by G-CSF of chemotherapy-related pulmonary toxicity, it is possible that the stem-cell growth factors may strengthen the lung toxicity of several chemotherapeutic agents (42, 97). Given the importance of neutrophils in the onset of toxicity, high-risk patients must be under close monitoring and should discontinue G-CSF administration as soon as the leukocyte count rises to 1,000 cells/μl (97).

Positron-emission Tomography (PET)

The increased metabolic activity of tumors sites can be demonstrated by PET scan. This novel imaging technique has proved its effectiveness in lung cancer staging and the current literature is focusing on other serviceable uses. The accumulation of cells and cytokines as well as the generation of the apoptotic mechanism after lung injury suggest alteration of the metabolic activity of the lung cells. In a small, but very interesting study by Hassaballa et al. (98) in lung cancer patients after radiation and chemotherapy, PET distinguished changes in the shielded normal lung tissue after treatment. Imaging with PET may provide an early barometer of pulmonary toxicity. Further investigation is needed, but based on these early data, this novel imaging tool could prove to be useful in monitoring or even predicting high risk patients for lung toxicity.

Summary and Future Prospects

Novel antineoplastic agents have the potential to induce pulmonary toxicity. The exact incidence of lung toxicity is currently unclear. The clinical presentation of many drug-induced effects is similar; however, some are presented acutely and are severe. The most recognizable clinical pattern consists of unspecified dyspnea and as this mimics lung cancer symptoms it has to be distinguished from disease progression. The development of ILD associated with anticancer treatment strategies is considered to be a multistep process and one of the initiating factors is likely to be the apoptosis of non-neoplastic type I and II pneumocytes. The mitochondrial mediated apoptotic pathway may also be involved in the pathology of the disease. The fact that only a small fraction of cancer patients develop lung toxicity from the unselective action of radiotherapy and chemotherapy implies that genetic predisposition, autoimmune conditions, or superimposed disease may be also involved. The fundamental requirement of up-to-date oncology is for patients to be treated as individuals with a specific care plan for each one. This need will be addressed in the future by pharmacogenomics. To date, relatively few pharmacogenomic findings have made a transition from “bench to bed-side” (99), but candidate gene approaches may lead to clinical tests for toxicity avoidance and efficacy prediction.

Conflict of Interest

The authors declare no conflict of interest.

References


637


