Pulmonary toxicity from novel antineoplastic agents

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Background: The pulmonary side-effects induced by novel antineoplastic agents have not been well characterized.

Methods: To further investigate this topic, relevant English and non-English language studies were identified through Medline. For our search we used the generic names of novel cytotoxic or non-cytotoxic antineoplastic agents and the key phrases: pulmonary/lung toxicity, dyspnea, pneumonitis, acute lung injury, acute respiratory distress syndrome and alveolar damage. The references from the articles identified were reviewed for additional sources. Abstracts from International Meetings were also included. Furthermore, information was obtained from the Pneumotox website, which provides updated knowledge on drug-induced respiratory disease as well as from pharmaceutical websites.

Results: Most novel antineoplastic drugs may induce pulmonary toxicity, which involves mainly the parenchyma, and less frequently the airways, pleura or the pulmonary circulation. Furthermore, a subset of these agents impairs pulmonary function tests. The exact incidence of lung toxicity remains unclear. The most common patterns consist of dyspnea without further details and infiltrative lung disease (ILD), denoting changes in the interstitium or alveoli. The diagnosis is one of exclusion. ILD is usually benign and responds to appropriate treatment; however, fatalities have been reported.

Conclusions: Clinicians should be aware of the potential of most novel antineoplastic agents to cause lung toxicity. A high index of suspicion is required if these are combined with other cytotoxic drugs or radiation.

Key words: acute respiratory distress syndrome, dyspnea, novel antineoplastic agents, pneumonitis, pulmonary function tests, pulmonary toxicity

introduction

About 10% of patients receiving well-established antineoplastic agents develop pulmonary toxicity. The diagnosis depends upon a history of drug exposure, and, most importantly, the exclusion of other causes leading to lung damage, including infections, fluid overload, pulmonary edema, pulmonary embolism or lung involvement from the underlying neoplasm. Infiltrative lung disease (ILD) is the most common form of antineoplastic agent-induced respiratory disease. ILD corresponds to several histological patterns reflecting interstitial lung damage or alveolar filling processes. Entities include non-specific interstitial pneumonitis, hypersensitivity pneumonitis, interstitial lung fibrosis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS), also termed diffuse alveolar damage, and alveolar hemorrhage [1, 2].

Little is known about the potential of novel antineoplastic (cytotoxic and non-cytotoxic) agents to induce pulmonary toxicity. Thus, the aim of the current review article is to provide further insight into this topic.

methods

Relevant English and non-English language studies were identified through Medline. For our search we used the generic names of novel cytotoxic or non-cytotoxic antineoplastic agents; these include antimitabolites (gemcitabine, fludarabine, cladribine, pentostatin), taxanes (paclitaxel, docetaxel), topoisomerase I inhibitors (irinotecan, topotecan), platinum analogs (oxaliplatin), tyrosine kinase inhibitors (gefitinib, imatinib mesylate, erlotinib), monoclonal antibodies, thalidomide and bortezomib.

The key phrases pulmonary/lung toxicity, dyspnea, pneumonitis, acute lung injury, acute respiratory distress syndrome and alveolar damage were entered for the purpose of our search. The references from the identified articles were reviewed for additional sources. Abstracts from International Meetings were also included. Furthermore, information was obtained from the Pneumotox website, which provides updated knowledge on drug-induced respiratory disease. If no reference of lung toxicity was found in these sources, the respective pharmaceutical company website was searched and, in case of no additional information, the Medical Department of the company was contacted.

The main results of our investigation are summarized in Table 1 and are described in detail below.

results

antimetabolites

(i) Gemcitabine. Gemcitabine is a pyrimidine analog that is active against various solid tumors. Serious pulmonary toxicity seems to be uncommon following gemcitabine treatment. Two consecutive analyses including large numbers of patients showed incidence of lung toxicity of 1.4% and <1%, respectively, among patients treated with gemcitabine [3, 4].
Lung toxicity has been reported in patients treated with gemcitabine alone or in combination with other agents and/or radiation. The most recognized clinical pattern consists of self-limiting dyspnea of uncertain etiology, in some cases involving bronchoconstriction [5–8]. Dyspnea associated with non-specific interstitial pneumonitis has been described in clinical studies [9, 10] and case reports [11–19]; pneumonitis may respond to steroids promptly [12, 14, 17]; however, fatalities have been observed [11, 17]. A small number of alveolar damage and/or ARDS cases have also been reported [11, 20–25]. More rare side-effects are diffuse alveolar hemorrhage [26], veno-occlusive disease [27], pleural effusion [28] and interstitial lung fibrosis [5]. Clinicians should be aware of the potential of gemcitabine to impair pulmonary function tests (PFTs). A retrospective analysis investigated patients with advanced non-small-cell lung cancer who received gemcitabine and cisplatin followed by surgery and/or radiation. It was found that diffusion capacity for carbon monoxide (DLCO) decreased significantly after treatment [29]. Recently, our group studied prospectively the effects of gemcitabine on PFTs in patients with non-thoracic malignancies. We showed that a subset (24%) of patients developed a clinically silent, reversible decrease in DLCO. The other lung function indices, such as lung volumes or forced vital capacity (FVC) and forced expiratory volume in one sec (FEV₁), remained unaffected [8].

Gemcitabine shares close structural features to cytosine arabinosine and the proposed mechanism of pulmonary injury is thought to represent a toxic damage on the endothelium of pulmonary capillary vessels, causing a capillary leak syndrome [11]. Hypersensitivity reactions have also been implicated because of the presence of pathologic inflammation and the improvement seen with steroids [12, 14–17].

(ii) Fludarabine. Fludarabine monophosphate is a nucleoside analog that is used widely in the treatment of low-grade lymphomas and chronic lymphocytic leukemia (CLL). The most well described effect on the lungs is an increased risk of opportunistic infections [30]. The direct effects of fludarabine on the lungs have not been well characterized. Cases have been reported where certain respiratory symptoms were speculated to be due to fludarabine exposure, reflecting interstitial or eosinophilic pneumonitis [31–37]. In most of these cases lung toxicity was poorly defined, while previous exposure to alkylation agents confounded the contribution of fludarabine to the described syndromes. Recently, Helman et al. [38] reported a detailed analysis in which fludarabine-related pulmonary toxicity was well characterized and evaluated in 105 patients with chronic lymphoproliferative disorders. Nine patients (8.6%) with pulmonary toxicity were identified. All patients had interstitial and/or alveolar infiltrates on plain chest X-ray and/or chest computed tomography (CT) scan, while two patients had small pleural effusions. Biopsy specimens revealed diffuse chronic interstitial inflammation and fibrosis. In all cases lung toxicity was initially successfully treated with steroids. Nevertheless, steroid tapering was not possible in one case, which eventually proved to be fatal. One patient was rechallenged with fludarabine, but again developed lung toxicity, which was successfully treated with steroids [38].

(iii) Pentostatin. Pulmonary toxicity has not been reported in large randomized and non-randomized trials using this agent. Nevertheless, prescribing information of this drug (www.supergen.com/subpages/products/nipent) includes pulmonary toxicity, especially in patients pretreated with interferon. In addition, prescribing information strongly advises against the use of pentostatin/fludarabine combination, since four of six patients who received this combination for the treatment of refractory CLL of pulmonary toxicity. Although pulmonary toxicity of fludarabine is well established, suggesting a more important role of the latter agent in the toxicity caused by the combination, the contribution of pentostatin cannot be excluded.

(iv) Cldadibine. This agent has not been associated with interstitial lung toxicity.
taxanes

(i) Paclitaxel. Paclitaxel is one of the most active chemotherapeutic agents in the treatment of breast, lung and ovarian carcinoma. Up to 30% of patients in early trials experienced a type I hypersensitivity reaction, characterized by dyspnea, chest tightness, bronchospasm, urticaria and hypotension [39]. These symptoms occur within the first 2 or 3 min after the first dose of drug therapy, and may be due to IgE antibodies to paclitaxel or to its Cremophor EL vehicle, or may be mediated by the release of histamine and other vasoactive substances. Premedication subsequently reduced the incidence of such reactions to 1% [40]. ILD in the form of non-specific or hypersensitivity pneumonitis has been described in case reports, clinical studies and small series [41–46]. Systematic investigations focusing on the incidence of ILD following paclitaxel administration have yielded low rates. Khan et al. [47] studied retrospectively 239 patients with various malignancies treated with paclitaxel, etoposide and cyclophosphamide, with or without thoracic radiation. They demonstrated that pneumonitis occurred in three patients (1%). Pulmonary infiltrates and symptoms were evident within 6 h following the drug infusion and the radiological signs resolved in 24–96 h while symptoms responded to steroids [47]. Ayoub et al. [48] reviewed the records of 122 patients with lymphoma treated with single-agent paclitaxel. They found that of the six patients with abnormal radiological findings only one (<1%) had histologic findings suggestive of non-specific interstitial pneumonitis, and that neoplasm along with infections accounted for the chest X-ray abnormalities observed in the remaining patients [48]. It is noteworthy to mention that the incidence of interstitial pneumonitis is much higher if paclitaxel is given concurrently with radiation (47% of patients) [49] or with other agents having the potential to cause lung toxicity, including gemcitabine (33% of patients) [50]. Other rare side-effects are diffuse alveolar damage and lung fibrosis. The former has been described in two patients treated with paclitaxel and gemcitabine [51] and the latter in one patient treated with paclitaxel and carboplatin [52]. A delayed-type hypersensitivity reaction involving immunological and non-immunological mechanisms has been proposed as a possible pathophysiological mechanism [45]. Alternatively, it has been suggested that paclitaxel, especially when combined with radiotherapy, may lead to protracted lymphocytopenia; this results in an immunodeficiency state, thus causing opportunistic infections that account, at least in part, for the interstitial infiltrates [49]. Clinicians should we aware of the potential of paclitaxel to impair the PFTs. Robert et al. [53] studied patients with advanced non-small-cell lung cancer who were treated with paclitaxel, cisplatin and radiation. They found that FVC and especially DLCO decreased significantly. No relationship was found between changes in PFTs and incidence of acute or late pulmonary toxicity. A prospective study from our group showed that the combination of paclitaxel and carboplatin induced an isolated decrease in DLCO in the absence of clinical or radiological evidence of toxicity. The change in DLCO was associated with a higher baseline DLCO and a lower FEV1, whereas it was unrelated to age, gender, smoking history or to cumulative dose of paclitaxel. In a subset of patients the decline in DLCO was present several months after the completion of chemotherapy [54].

(ii) Docetaxel. Docetaxel is a taxane derivative with activity in many solid tumors including breast, gastric, ovarian and non-small-cell lung cancer. Hypersensitivity reactions seem to be frequent; in one study such reactions were observed in 42% of the patients and consisted of dyspnea, pruritus, skin rashes, fever and hypotension. They have been attributed to its formulation with polysorbate-80 or to histamine release and may be blocked with the use of premedication [55]. Acute interstitial pneumonitis has been reported when docetaxel is administered as monotherapy or in combination with other cytotoxic agents [56–63]. Pneumonitis usually responds to steroids [56, 62], but may also be fatal [60, 61]. The coadministration of docetaxel and gemcitabine is associated with a high incidence (23% of patients) of interstitial pneumonitis [64]. Rare side-effects include pleural effusions and diffuse alveolar damage or ARDS. The former has been described in patients treated with docetaxel and thalidomide [65] and the latter in those receiving docetaxel combined with gemcitabine or estramustine [22, 60].

A capillary leak syndrome has also been suggested to explain the formation of pleural effusions in the absence of interstitial lung disease in patients receiving docetaxel [65]. This syndrome causes fluid retention and is associated with the cumulative docetaxel dose: > 50% of patients receiving a total of 500 mg/m2 of the drug developed edema in a recent study [65]. Diuretic treatment offers little help, while daily treatment with 40 mg of methyl-prednisolone the days before and after docetaxel administration, significantly delayed the onset of edema in a recent randomized study [66].

topoisomerase I inhibitors

(i) Irinotecan. Irinotecan is approved in the USA and Europe for the treatment of metastatic colorectal cancer. Pulmonary toxicity, without further specification, has been reported in >20% of patients given irinotecan in US studies; these patients had a history of 5-fluorouracil (5-FU) exposure [67, 68]. Interstitial pneumonitis following irinotecan administration responding to steroids has been described in a few case reports [69, 70]. In general, the incidence of pneumonitis has been found to be low (1.8% of patients) in the early Japanese registration trials; fatalities related to respiratory insufficiency have been described. The contribution of irinotecan to the development of pneumonitis is difficult to assess because these patients had lung tumors and some had pulmonary comorbidities [71, 72]. The incidence of pneumonitis is higher if irinotecan is combined with paclitaxel (12.5% of patients) [73] or with radiotherapy (56% of patients) [74]. The origin of irinotecan-induced pulmonary toxicity remains unclear; an immunopathological mechanism has been suggested, since a number of patients had a history of asthma or seasonal rhinitis [69, 70].

(ii) Topotecan. Topotecan is used primarily in the treatment of metastatic carcinoma of the ovary and as second-line treatment of small-cell lung cancer. Topotecan-related pulmonary toxicity appears to be very rare; bronchiolitis obliterans has been described in two cases [75, 76].
platinum analogs

(i) Oxaliplatin. Oxaliplatin monotherapy has frequently been associated with adverse reactions from upper respiratory tract, mainly of laryngeal dysesthesia, which is a form of neurosensory effect [77]. Pulmonary toxicity is rare following oxaliplatin monotherapy. The major indication of oxaliplatin is the treatment of advanced colorectal carcinoma, in combination with 5-FU. Recently, a case of acute diffuse alveolar damage following treatment with oxaliplatin and 5-FU plus folinic acid has been reported [78]. This complication occurred after seven cycles of treatment and resolved completely with prednisone. The significance of the combination of the two agents on the development of this toxicity is uncertain. Lung toxicity has not been reported with 5-FU monotherapy but rare cases of ILD have been described when this agent is used in combination with other chemotherapeutic drugs, including cisplatin [79]. Although pulmonary toxicity is rare, it appears that it should be part of the differential diagnosis in cases of alveolar damage, where other possible causes have been ruled out.

(ii) Erlo tinib. Pulmonary toxicity is rare; only one case of interstitial pneumonitis has been reported [100].

Monoclonal antibodies

Monoclonal antibodies are used with increasing frequency in the treatment of various hematopoietic malignancies and solid tumors. Toxicity of these agents represents a challenge of contemporary anticancer treatment, because they have a different toxicity profile from classic chemotherapeutic agents they are now increasingly used in combination with chemotherapeutic agents, but also because of the relatively short period they have entered routine clinical practice. Pulmonary toxicity is not commonly associated with the use of monoclonal antibodies. Bronchospasm has been reported during the infusion of monoclonal antibodies as part of a hypersensitivity reaction, although this manifestation is the least common feature of such reactions [101]. Recent reports suggest that monoclonal antibodies can cause frank lung injury, specifically ILD. These recent data are reviewed in this section.

(i) Rituximab. Rituximab targets CD20+ B lymphocytes. Although it was first approved for the treatment of low-grade follicular lymphoma, it is now also approved for high-grade lymphomas, while it has also been used in other hematological diseases. Rituximab-induced lung injury is rare but well documented. It has been reported in <0.03% of patient receiving the drug according to company data [102]. Most data come from case reports [103–109] and the contribution of the drug is sometimes confounded by the administration of other drugs (e.g. cyclophosphamide, bleomycin) that can also cause lung toxicity. Nevertheless, interstitial pneumonitis has been reported with rituximab monotherapy, thus proving the potential of this agent for lung injury. Alveolar hemorrhage is extremely rare [110]. The underlying mechanism for lung injury is not known but it has been postulated that cytokine release might be responsible, since treatment with rituximab results in complement activation, B-lymphocyte cytolysis and release of tumor necrosis factor [105]. This is strengthened by the fact that serious pulmonary toxicity developed in one patient who showed a marked decrease in lymphocyte count after rituximab administration [106]. In all cases lung toxicity resolved after steroid treatment, with no late sequelae. Nevertheless, it should be mentioned that concomitant administration of steroids may not prevent the occurrence of pneumonitis, as shown in two of the reported cases [106, 107].
(ii) **Trastuzumab**. Trastuzumab is a humanized monoclonal antibody against the epidermal growth factor type 2 (HER2) receptor, which is overexpressed in about 25% of breast cancers. This antibody is now approved in the USA and Europe for the treatment of metastatic breast cancer overexpressing this receptor. Although this antibody has been used in everyday practice only recently, its wide application has shown that lung toxicity is exceptional. Prior to commercial availability no fatal pulmonary adverse events were reported in the context of clinical trials. In an extensive analysis of the safety of the administration of this drug to 25 000 patients, after the approval in the USA, bronchospasm was the only respiratory-associated serious adverse event [111]. In 15 cases (0.04%) these events were fatal [112]. Reactions occurred usually within 2.5 h of administration and most of the fatalities were associated with dyspnea, bronchospasm and/or respiratory distress. Most fatalities were reported in patients with poor performance status and severe underlying pulmonary problems. In several cases patients were oxygen-dependent prior to trastuzumab administration. PFTs are not routinely recommended [112], but caution should be exercised when treating patients with pulmonary compromise. Apart from the infusion-related respiratory-distress events, a case of organizing pneumonia, probably due to trastuzumab administration, has recently been reported [113]. It should be mentioned that previous administration of radiotherapy confounds the association of this toxicity with the administration of the antibody in this case.

(iii) **Bevacizumab**. Bevacizumab is an IgG1 recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that blocks binding of human VEGF to its receptors. Bevacizumab has been approved for first-line treatment of advanced colorectal cancer in combination with other agents. Severe pulmonary toxicity has not been usually reported in patients receiving bevacizumab. Nevertheless, hemoptysis was encountered frequently in a randomized phase II study in patients with non-small-cell lung cancer. Although hemoptysis can be a symptom of lung cancer, the incidence was significantly higher among patients receiving bevacizumab (20% versus 6%). Four patients receiving bevacizumab suffered severe hemoptysis. In patients treated with bevacizumab, serious bleeding was also reported in the form of hematemesis [114]. Such bleeding episodes have not been reported in patients with colorectal, renal, breast or prostate cancer [115]. In all cases tumors were centrally located and in the proximity of major blood vessels. Furthermore, squamous histology may possibly present a risk factor for major bleeding and have been excluded from the ongoing trial [114].

(iv) **Alemtuzumab**. Alemtuzumab is a monoclonal antibody directed against the cell surface antigen CD52 on lymphocytes and monocytes. It is a valuable option for salvage therapy in patients with chronic lymphocytic leukemia. Apart from severe bronchospasm (WHO grade IV) responding to steroids [116], patients with chronic lymphocytic leukemia. Apart from severe bronchospasm (WHO grade IV) responding to steroids [116], no other pulmonary side-effect has been reported.

(v) **Cetuximab**. Cetuximab is an anti-EGFR monoclonal antibody that has shown significant activity in colon and head and neck cancer. Dyspnea is the most frequent respiratory side-effect reported. In a recent randomized study dyspnea was severe in 13% of cases [117]. Dyspnea is related to the infusion, and most cases of severe dyspnea have been reported in patients of poor performance status and/or with underlying lung disease. Other forms of lung toxicity have not been reported for this drug.

**thalidomide**

Thalidomide is used in the treatment of multiple myeloma primarily, but also of prostate and renal cancer. It has immunomodulatory and antiangiogenic effects, along with anticytokine activity. The most common pulmonary side-effect is dyspnea without further details, occurring with an incidence from 4% to 54% [118, 119]. Dyspnea may be transient, suggesting that in properly selected patients, thalidomide can be safely reintroduced at a reduced dose once symptoms resolve [120]. The most serious thalidomide-induced pulmonary side-effect is thromboembolic disease, which appears to be higher when the drug is combined with dexamethasone or other chemotherapeutic agents [121]. Rare adverse effects are interstitial pneumonitis and pleural effusion [63, 122, 123].

**bortezomib**

Bortezomib is an inhibitor of 26S proteasome, a large protein complex that degrades ubiquitinated proteins. It has approval for recurrent and/or refractory myeloma. Lung toxicity seems to be uncommon and consists mainly of dyspnea without further specification [124–127]. ILD is very rare; one case of pneumonitis has been reported so far [127]. Most patients receiving bortezomib have been treated previously with other modalities; therefore, it is difficult to conclude whether the aforementioned lung toxicities are caused by bortezomib itself or by prior treatment.

**discussion**

Most novel antineoplastic agents have the potential to induce pulmonary toxicity, which involves primarily the lung parenchyma; the airways, pleura or pulmonary circulation are less frequently affected. The exact incidence of lung toxicity remains currently unclear; this is related to confounding factors, including pulmonary comorbidities and prior or concurrent use of other treatment modalities, such as radiation and antineoplastic drugs. The clinical presentation of many drug-induced effects is similar; however, some present acutely, while others are insidious in their onset. In most instances the symptoms are confined to the lungs, while occasionally they may be part of a systemic syndrome. The most recognized clinical patterns consist of dyspnea without further specification and ILD, which requires the same diagnostic approach as in ILD of other causes. Lung toxicity may respond to appropriate treatment; however, fatalities have been reported.

**references**


