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CHEST Special Feature

Pulmonary Complications of Novel Antineoplastic Agents for Solid Tumors*

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Antineoplastic agent-induced pulmonary toxicity is an important cause of respiratory failure. Although the incidence of antineoplastic agent-induced pulmonary toxicity seems to be low, more cases can be expected, with increasing numbers of patients receiving the new generations of antineoplastic agents. Antineoplastic agents have previously been associated with bronchospasm, hypersensitivity reactions, venous thromboembolism, and pulmonary hemorrhage. Physicians should be aware of the clinical and radiographic presentations of the pulmonary toxicities associated with the newer antineoplastic agents. The approach to diagnosis, risk factors, and possible mechanisms of antineoplastic agent-induced pulmonary toxicity are discussed in this article. ***(CHEST 2008; 133:528–538)***

Key words: chemotherapy; pneumonitis; pulmonary toxicity; respiratory failure

Abbreviations: CML = chronic myelogenous leukemia; DVT = deep venous thrombosis; EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor; KL-6 = Krebs von den Lunge-6; mTOR = mammalian target of rapamycin; NSCLC = non-small cell lung cancer

Antineoplastic agent-induced pulmonary toxicity is an important cause of respiratory failure. New antineoplastic agents and regimens are constantly being added to the list of available treatments for cancer patients. These novel antineoplastic agents either have new mechanisms of action such as tyrosine kinase inhibitors or old agents with new indications like thalidomide. Since more patients are being treated with these agents, associated acute respiratory failure is more commonly being recognized. Critical care physicians should be aware of the clinical and radiographic presentations of antineoplastic agent-induced pulmonary toxicities. Unfortunately, the diagnosis of antineoplastic agent-induced pulmonary toxicity is complicated. Antineoplastic agent-induced pulmonary toxicity is a diagnosis of exclusion, and other causes of respiratory failure including pneumonia, cardiogenic pulmonary edema, and diffuse alveolar hemorrhage should be excluded. These conditions are not easily differentiated based on clinical presentation and radiographic findings. Furthermore, as patients usually receive multiple antineoplastic agents, it is usually difficult to identify the culprit agent. Open-lung biopsy may be necessary in selected cases to exclude the alternative diagnoses. Regardless of these difficulties, antineoplastic agent-induced pneumonitis and respiratory failure should be considered in patients receiving chemotherapeutic agents. The cessation of the implicated causative agent and treatment with systemic corticosteroids may result in rapid improvement.[1,2]

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Clinical Manifestations and Diagnosis

Several clinical syndromes have been described in patients with presumed antineoplastic agent-induced lung toxicity (Table 1). The definition of these clinical syndromes may be confusing due to the different criteria used in the literature. Most clinical trials do not report the details of pulmonary toxicity. Authors describe the pulmonary toxicities based

Table 1—*Definitions of Clinical Syndromes**

Syndromes	Description
Bronchospasm	Evidence of airflow obstruction (*eg*, wheezing and prolonged exhale)
Hypersensitivity reaction	Bronchospasm plus other hypersensitivity-related symptoms: angioedema; rash; urticaria; hypotension; arthralgia; nausea; vomiting; hypotension; or hypertension
Infusion reaction	Hypersensitivity reaction during infusion or shortly (within minutes) thereafter
Pneumonitis	Clinical and radiographic manifestation compatible with interstitial pneumonitis
Noncardiogenic pulmonary edema	Pulmonary edema not associated with heart failure or increased left atrial pressures
Capillary leak syndrome	Noncardiogenic pulmonary edema associated with diffuse edema and intravascular hypovolemia
Acute lung injury	1. Noncardiogenic pulmonary associated with evidence of acute inflammation like: fever; and elevated neutrophils in BAL fluid 2. Diffuse bilateral pulmonary infiltrates, no evidence of elevated left atrial pressure, and Po_2/Fio_2 ratio < 300
ARDS	Diffuse bilateral pulmonary infiltrates, no evidence of elevated left atrial pressure, and Po_2/Fio_2 ratio < 200
Eosinophilic pneumonia	Pulmonary infiltrates, hypoxemia, and BAL fluid eosinophilia

*Fio_2 = fraction of inspired oxygen.

either on clinical criteria (*eg*, acute lung injury, ARDS, noncardiogenic pulmonary edema, or pneumonitis) or pathologic findings (*eg*, diffuse alveolar damage, organizing pneumonia, nonspecific pneumonitis, or neutrophilic alveolitis). In this review, we will use the definitions outlined in Table 1.

The clinical manifestations of drug-induced pneumonitis are nonspecific and include cough, fever, dyspnea, and hypoxemia. The pulmonary involvement may be rapidly progressive, resulting in respiratory failure and ARDS. The timing of clinical manifestations is unpredictable; they may present during the first cycle of treatment or following subsequent cycles.[1,2] Concurrent treatment with corticosteroids may not prevent the development of drug-induced pneumonitis.[3–7] Elevated WBC count in peripheral blood, elevated erythrocyte sedimentation rate, and elevated C-reactive protein levels are also common nonspecific laboratory findings. Chest imaging may show diffuse or patchy, unilateral or bilateral, ground-glass opacities or consolidations. Reduced lung volumes and diffusion capacity are commonly reported. BAL fluid cell counts are usually elevated with neutrophilia, lymphocytosis, or, rarely, eosinophilia.[1,2]

Elevated serum Krebs von den Lunge-6 (KL-6) levels have been reported in patients with drug-induced pneumonitis. KL-6 is a mucin-like high-molecular-weight glycoprotein that is expressed by type II alveolar pneumocytes. Elevated levels of KL-6 (*ie*, ≥ 500 U/mL) can also be seen in patients with idiopathic interstitial pneumonitis, pneumonitis related to collagen vascular disease, and hypersensitivity pneumonitis.[8] Furthermore, only 53.3% of patients with drug-induced pneumonitis have elevated serum KL-6 levels.[9] However, KL-6 levels do not increase in patients with pneumonia, pulmonary aspergillosis, asthma, bronchiectasis, emphysema, eosinophilic pneumonia, or organizing pneumonia.[8] Other causes of elevated KL-6 levels include hypersensitivity pneumonitis, radiation pneumonitis, viral pneumonia, pneumocystis pneumonia, sarcoidosis, tubulointerstitial nephritis uveitis syndrome, liver disease (*eg*, hepatitis C, cirrhosis, or hepatocellular carcinoma), and malignancy (*eg*, breast cancer or malignant thymoma).[8–15]

One unique presentation of antineoplastic agent-induced pneumonitis is so-called *radiation recall pneumonitis*. Radiation recall pneumonitis is seen in patients who have received previous radiation therapy to the chest. Shortly after the initiation of therapy with the antineoplastic agent, the fever, cough, dyspnea, and hypoxemia develop in the patient. The chest imaging shows pulmonary infiltrates in exactly the same field as in previous radiation therapy. Subsequent progression to diffuse bilateral pneumonitis can be expected in severe cases. The exact mechanism of radiation recall pneumonitis is not known. Irradiation may cause subclinical injury to the lung parenchyma, which may have an additive effect in precipitating lung injury when another pulmonary insult is encountered at a later date. Other possible mechanisms include injury to type II pneumocytes in the radiotherapy field, which reduces the ability of the lung to repair itself and drug hypersensitivity reactions. Other manifestations of radiation recall are dermatitis, mucositis, and myositis. The antineoplastic agents associated with radiation recall pneumonitis are adriamycin, carmustine, doxorubicin, etoposide, gefitinib, gemcitabine, paclitaxel, and trastuzumab.[16–22]

The differential diagnosis of antineoplastic agent-induced pneumonitis is extensive. Infection is a very common cause of pulmonary infiltrates and respiratory failure in cancer patients. Appropriate cultures and serology can be helpful to differentiate pneumonitis from infectious pneumonia. Bronchoscopy with BAL is very useful to exclude an infectious process. Bronchoscopy with BAL is also important to exclude alveolar hemorrhage. In patients with alveolar hemorrhage, the BAL fluid return is hemorrhagic and contains hemosiderin-laden macrophages. The presence of malignant cells in BAL fluid suggests the lymphangitic spread of the cancer. ARDS secondary to aspiration, sepsis, and pancreatitis may be suspected based on history, physical examination results, and other laboratory workup findings. Cardiogenic pulmonary edema is suggested if the echocardiogram shows left ventricular dysfunction and serum B-type natriuretic peptide is elevated. Bilateral transudative pleural effusions and rapid improvement in pulmonary status after diuresis are typically observed in patients with cardiogenic pulmonary edema.[1,2]

Transbronchial or open-lung biopsy can be helpful in demonstrating the presence of pneumonitis and excluding alternative diagnoses, like lymphangitic carcinomatosis, vasculitis, and pneumonia. Nonspecific pneumonitis, organizing pneumonia, eosinophilic pneumonia, pulmonary fibrosis, and diffuse alveolar damage are commonly seen on lung biopsy specimens. These pathologic patterns are nonspecific and should not be considered diagnostic of drug-induced lung disease. The diagnosis of chemotherapy-induced pneumonitis can be made when pneumonitis develops shortly after the initiation of treatment (*ie*, hours to weeks), lack of an alternative explanation for respiratory failure, and the resolution of pneumonitis after corticosteroid treatment and withdrawal of the presumed agent.

Pathogenesis and Risk Factors

The pathogenesis of antineoplastic agent-induced lung injury is poorly understood. Several mechanisms have been suggested. Direct injury to pneumocytes (chemical alveolitis) or the alveolar capillary endothelium and the subsequent release of cytokines and recruitment of inflammatory cells may be responsible, along with some of the cytotoxic medications. The systemic release of cytokines by chemotherapeutic agents (*eg*, gemcitabine) may also result in capillary leak and pulmonary edema. Positive lymphocyte stimulation test results and an elevated CD4/CD8 cell ratio suggest cell-mediated lung injury due to the activation of lymphocytes, and alveolar macrophages may also play a role. Free oxygen radicals may also be involved especially with mitomycin-C pulmonary toxicity. Epidermal growth factor receptors (EGFRs) are expressed on type II pneumocytes and are involved in alveolar wall repair. EGFR tyrosine kinase inhibitors, by impairing the alveolar repair mechanisms, may potentiate the effect of lung injury due to other causes, including sepsis, radiation, and other medications.[23–26]

Combination chemotherapy may have an additive effect with a higher frequency of pulmonary toxicity. Preexisting pulmonary disease such as idiopathic pulmonary fibrosis, COPD, radiation therapy, extensive pulmonary metastatic disease, and poor functional status have also been associated with increased pulmonary toxicity. A high inspired oxygen concentration may increase the incidence or severity of mitomycin-C-induced pneumonitis.[23,24]

Antineoplastic Agents

Table 2 summarizes the pulmonary complications associated with the newer antineoplastic agents used in the treatment of solid tumors.[27–112] Each agent is discussed separately below.

Alkylating Agents

Chlorozotocin

Chlorozotocin is an alkylating agent with activity against advanced islet-cell carcinoma. Two reported cases[28,29] of mild subacute interstitial pneumonitis have been reported with this agent. Mild dyspnea, dry cough, and pulmonary infiltrates developed in one patient after the third dose of chlorozotocin. Pulmonary function test results showed reduced diffusion capacity and lung volumes. Acute pneumonitis developed in the second patient after receiving chlorozotocin and mitomycin-C. Pneumonitis resolved with prednisone therapy with no residual pulmonary fibrosis.[28,29]

Ifosfamide

Ifosfamide is an alkylating agent that is active against a variety of solid tumors including breast cancer, lung cancer, ovarian cancer, and sarcomas. Ifosfamide pulmonary toxicity has been noted in combination with other antineoplastic therapies. Fatal interstitial pneumonitis has been reported with ifosfamide therapy for soft-tissue sarcoma.[30] In a phase II trial[31] of docetaxel and ifosfamide, interstitial pneumonitis developed after combination chemotherapy in three patients (6%) with non-small cell lung cancer (NSCLC). Two of three patients died due to respiratory failure.[31] The ifosfamide metabolite, 4-thioifosfamide, is known to react with glutathione and deplete the RBC antioxidant reserve. This reaction may rarely result in methemoglobinemia.[32]

Oxaliplatin

Oxaliplatin is a new cytotoxic agent that is mainly used in the treatment of colorectal cancer combined with fluorouracil and leucovorin. Interstitial pneumonitis with fibrosis has been reported after 3 to 6

Table 2—*Pulmonary Complications of Chemotherapeutic Agents*

Chemotherapeutic Agents	Pulmonary Complications
Bevacizumab	Pulmonary hemorrhage and hemoptysis
	Increased risk of DVT and pulmonary embolism
Chlorozotocin	Interstitial pneumonitis
Doxorubicin	Organizing pneumonia
	Infusion reaction
Erlotinib	Acute pneumonitis
	ARDS
Etoposide	Acute pneumonitis
	Diffuse alveolar damage
	Hypersensitivity reaction/bronchospasm
Everolimus	Acute pneumonitis
Gefitinib	Acute pneumonitis
	Diffuse alveolar damage
	Diffuse alveolar hemorrhage
	Pulmonary fibrosis
Gemcitabine	Infusion-related reaction
	Capillary leak syndrome/pulmonary edema
	ARDS
	Diffuse alveolar damage
	Diffuse alveolar hemorrhage
	Bronchospasm
	Pleural effusion
Ifosfamide	Interstitial pneumonitis
	Methemoglobinemia
Imatinib	Acute pneumonitis
	Fluid retention and pulmonary edema
	Pleural effusion
Irinotecan	Moderate-to-severe pneumonitis
	Severe hypoxemia and respiratory failure
Oxaliplatin	Pulmonary fibrosis
	Respiratory failure
	Eosinophilic pneumonia
	Infusion-related reactions
Matuzumab	Bronchospasm
Mitozantrone	Acute pneumonitis
Piritrexim	Acute pneumonitis
Taxanes	Acute pneumonitis
	Infusion-related reactions
	Pleural effusion
Temozolomide	Acute pneumonitis
Temsirolimus	Acute pneumonitis
Thalidomide	Pulmonary embolism
	Organizing pneumonia
	Acute pneumonitis
	Pleural effusion
Teniposide	Hypersensitivity reaction/bronchospasm
Topotecan	Bronchiolitis and organizing pneumonia
Trastuzumab	Acute lung injury
	Acute pneumonitis
	Organizing pneumonia
	Infusion-related reaction
	Bronchospasm

months of therapy. The patients present with slowly progressive cough and dyspnea for several months, but the disease can become accelerated. Deaths due to respiratory failure have been reported 10 to 20 days after presentation even with corticosteroid therapy.[33,34] Eosinophilic pneumonia after oxaliplatin therapy is a rare complication.[35]

Oxaliplatin infusion-related reactions and severe anaphylactic reactions occur with a reported frequency of 1.3%. All reactions appear within 5 to 50 min after starting oxaliplatin infusion and usually last less than a day. A hypertensive crisis resulting in a change in mental status has been reported.[36]

Temozolomide

Temozolomide is a new alkylating agent with preclinical activity against a variety of solid tumors and hematologic malignancies. It is mainly used in the treatment of anaplastic astrocytoma and metastatic melanoma. There are limited data from phase I and II trials[37,38] regarding the safety and efficacy of temozolomide in the treatment of malignancies. In a phase II trial[37] of temozolomide for patients with recurrent or progressive brain metastases from a variety of solid tumors, pneumonitis developed in 4.8% of patients. The patients were treated with 150 to 200 mg/m^2/d for 5 days. The treatment cycles were repeated every 4 weeks. In another phase II trial,[38] 46 elderly patients with acute myeloid leukemia were treated with oral temozolomide, 200 mg/m^2/d for 5 days. One patient died of acute interstitial pneumonitis.[37,38]

Antibiotics

Doxorubicin

Doxorubicin is a cytotoxic antibiotic that inhibits topoisomerase II. It has activity against a variety of solid tumors (*ie*, cancers of the bladder, breast, stomach, lung, ovaries, and thyroid, soft-tissue sarcoma, and others). Lung toxicity is rare. Infusion reaction may be seen in 8% of patients during pegylated liposomal doxorubicin infusion. Dyspnea may develop in patients within 1 to 5 min after infusion, and the symptoms resolve within 5 to 15 min after stopping the infusion. *In vitro* studies[39] have shown that pegylated-liposomal doxorubicin stimulates neutrophil adhesion to human umbilical vein endothelial cells. Since transient relative neutropenia has been detected during pegylated-liposomal doxorubicin infusion, the adhesion and sequestration of neutrophils to the pulmonary circulation have been suggested as a potential mechanism for infusion-related acute dyspnea.[39] Several cases of doxorubicin-induced organizing pneumonia, mostly in patients with lymphoma, have been described in the literature.[40,41]

Epirubicin

Epirubicin is primarily used against breast and ovarian cancer, gastric cancer, lung cancer, and lymphomas. Epirubicin pulmonary toxicity has been noted in combination with other antineoplastic therapies. Although rare, severe pneumonitis can occur in patients receiving epirubicin within weeks after undergoing irradiation to chest. In one study,[42] interstitial pneumonitis occurred in 9% of patients (4 of 44 patients) with breast cancer treated with 5-fluorouracil, epirubicin, and cyclophosphamide. It is important to note that patients were also treated with granulocyte-stimulating factor, and two patients received one dose of paclitaxel.[42] Although these reports do not support the pulmonary toxicity of epirubicin *per se*, epirubicin may potentiate the pulmonary toxicity of other agents.

Mitoxantrone

Mitoxantrone is a topoisomerase II inhibitor that is mainly used in the treatment of metastatic breast cancer. Severe acute pneumonitis may be seen after mitoxantrone therapy. The lung pathology demonstrates organizing pneumonia and a hypersensitivity pneumonitis-like pattern. Other chemotherapy agents (*ie*, bleomycin, vincristine, cylophosphamide, and chlorambucil) were also included in the chemotherapeutic regimen in most cases. Oral corticosteroids were reported to result in the rapid resolution of pneumonitis.[43–45]

Antimetobolites

Piritrexim

Piritrexim is an orally bioavailable, second-generation antifolate with activity against transitional cell carcinoma. In a phase II trial,[46] piritrexim was administered orally in a dose of 25 mg daily for 5 consecutive days per week for 3 consecutive weeks. In this study,[46] pulmonary toxicity (only 1 of 28 patients had grade 3 pulmonary toxicity) developed in 14% of patients (4 of 28 patients).[46] de Wit et al[47] described a case of diffuse interstitial pneumonitis and respiratory failure after treatment with piritrexim for transitional cell carcinoma of the renal pelvis. The authors concluded that pulmonary disease was probably induced by piritrexim. The respiratory failure resolved after drug discontinuation.[47]

Monoclonal Antibodies

Bevacizumab

Bevacizumab, a monoclonal antibody against endothelial growth factor, has been used to treat patients with a variety of cancers. There are several reported pulmonary toxicities associated with bevacizumab therapy. Pulmonary hemorrhage and hemoptysis has been reported[48–50] in 2.3% of patients with nonsquamous NSCLC. In these patients, pulmonary hemorrhage may lead to respiratory failure, and fatalities have been reported in 1.6% of patients treated with bevacizumab. Severe hemoptysis and pulmonary hemorrhage associated with bevacizumab therapy is more common in patients, with squamous cell carcinoma being reported in up to 31% of patients. Bevacizumab has also associated with increased risk of deep venous thrombosis (DVT) and pulmonary embolism.[48–50]

Matuzumab

Matuzumab is a humanized Ig G1 that blocks the activation of EGFR. Matuzumab is active against EGFR-positive NSCLC. Bronchospasm related to matuzumab has been reported in 5% of patients. Premedication with corticosteroids is effective to prevent bronchospasm.[51]

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that selectively binds to the human EGFR (HER)-2 protein. Trastuzumab is indicated for the treatment of metastatic breast cancers with overexpression of HER-2 protein. The incidence of trastuzumab-induced pneumonitis is 0.4 to 0.6%. Trastuzumab-induced pneumonitis may present with rapidly progressive pulmonary infiltrates and respiratory failure after receiving 1 dose of trastuzumab or after 6 weeks of therapy. The mortality of trastuzumab-induced pneumonitis is about 0.1%. Acute neutrophilic alveolitis and organizing pneumonia after trastuzumab treatment also have been reported. Infusion-related symptoms, including hypotension, angioedema, bronchospasm, dyspnea, fever, chills, and urticaria, has been reported to occur in about 15% of patients. Severe episodes of hypotension, bronchospasm, and hypoxemia leading to death are rare.[52–56]

Nucleoside Analogs

Gemcitabine

Gemcitabine is a nucleoside analog with activity against a variety of solid tumors, especially NSCLC and pancreatic cancer. A variety of forms of pulmonary toxicity have been described with the use of gemcitabine. Dyspnea developing within hours of infusion has been reported to occur in about 10% of patients. Most patients improve with therapy with diuretics and corticosteroids. Bronchospasm develops in about 0.6% of patients. These infusion-related reactions are usually mild and rarely have resulted in the discontinuation of treatment.[23] Gemcitabine-induced pneumonitis has been reported to occur in up to 13.8% of patients. An analysis[57,58] of pooled data from a large database showed the incidence of gemcitabine-induced pulmonary toxicity to vary from 0.02 to 0.27%. The following three types of gemcitabine-induced pneumonitis have been described: (1) a capillary leak syndrome with pulmonary edema; (2) diffuse alveolar damage; and (3) alveolar hemorrhage. Previous lung disease, chest radiation, and concurrent treatment with other agents (*eg*, paclitaxel, docetaxel, ifosfamide, or granulocyte colony-stimulating factor) are possible risk factors. Restrictive physiology with a marked reduction in diffusion capacity has been reported. Although the mortality rate can be as high as 20%, a rapid response (within days) to prednisone, 60 mg daily, has been described in the literature.[23,57–63]

Podophyllotoxins

Etoposide

Etoposide is a topoisomerase II inhibitor. This agent is used primarily in the treatment of small cell lung cancer. The most common pulmonary toxicity is a hypersensitivity reaction that can present with symptoms of anaphylaxis, angioedema, chest discomfort, bronchospasm, and hypotension.[64] Etoposide-induced acute pneumonitis or acute lung injury, although uncommon, may occur. The pathology of etoposide-induced lung injury is diffuse alveolar damage, fibrin membrane formation, and alveolar wall edema. Fatal cases are rare. Etoposide is also known to increase the risk of radiation pneumonitis. Concurrent treatment with other pneumotoxic agents may increase the risk of pneumonitis.[65,66] Zimmerman et al[67] reported that interstitial pneumonitis developed in 24% of 50 patients treated with etoposide, methotrexate, and cyclophosphamide for small cell anaplastic lung cancer. It has been shown that etoposide increases the intracellular levels of methotrexate. The authors postulated that the pulmonary toxicity was secondary to methotrexate pneumonitis, which was caused by excessive intracellular levels of methotrexate related to the concurrent use of etoposide.[67]

Teniposide

Teniposide is used in the treatment of glioblastoma multiforme. Hypersensitivity reaction to teniposide occurs in 3.6 to 6.5% of patients. urticaria, hypotension or hypertension, dyspnea, bronchospasm, cyanosis, flushing, and vomiting within first 10 to 20 min of teniposide infusion develop in patients. In patients with leukemia, infusion reaction tends to occur after the completion of infusion. However, the timing of the hypersensitivity reaction is unpredictable and may occur during the first treatment cycle or during subsequent treatment cycles.[68]

Rapamycin Analogs

Temsirolimus

Temsirolimus is a rapamycin analog that is active against renal cell carcinoma, endometrial carcinoma, breast cancer, glioblastoma multiforme, and GI neuroendocrine tumors. Temsirolimus binds with immunophilin FK-506 binding protein-12 and forms a complex that inhibits the protein activity of mammalian target of rapamycin (mTOR). mTOR is a serine-threonine kinase that regulates cell growth, proliferation, and apoptosis. Interstitial pneumonitis is a non–dose-dependent complication of temsirolimus. Interstitial pneumonitis has been reported in 1 to 36% of patients treated with 25 to 250 mg/wk. The onset of pneumonitis usually takes place within 16 weeks (range, 2 to 16 weeks) after temsirolimus treatment. In one case series,[69,70] 50% of patients were clinically asymptomatic, with drug-induced pneumonitis diagnosed by chest imaging. The chest CT scan may show ground-glass opacity or consolidation.[69,70]

Everolimus

The pharmacologic effects of everolimus are also mediated through binding to FK-506 binding protein-12 and the inhibition of mTOR. Everolimus has been used as an immunosuppressive agent following organ transplantation, to treat severe psoriasis, and as an investigational antineoplastic agent (*eg*, for the treatment of sarcoma or renal cell cancer). Although clinical data in patients with malignancy are sparse, in one study[71] using everolimus in heart transplant recipients, interstitial pneumonitis developed in 3.3% of patients 4 weeks after switching treatment to everolimus. All patients with pneumonitis required mechanical ventilation.[71]

Taxanes

Taxanes are mainly used in the treatment of breast, ovarian, and lung cancers. Paclitaxel and docetaxel are known to cause pneumonitis with estimated frequencies of 0.73 to 12% and 7 to 26%, respectively. Dyspnea, cough, hypoxemia, and pulmonary infiltrates usually develop 1 week to 3 months after treatment. Possible risk factors for pulmonary toxicity are weekly or biweekly therapy compared to triweekly therapy and concurrent treatment with gemcitabine and irinotecan. Severe pneumonitis and pulmonary fibrosis resulting in death have been described. Mild cases of pneumonitis tend to resolve spontaneously or after low-dose prednisone therapy (*ie*, prednisone, 40 mg daily for 2 weeks). Mild pneumonitis is not a contraindication to subsequent paclitaxel therapies, and the safe readministration of paclitaxel has been reported. Chest imaging findings include bilateral reticular or reticulonodular opacities, focal consolidation, and bilateral patchy areas of increased attenuation with upper lobe predominance. A hypersensitivity mechanism has been suggested in the pathogenesis on lung injury. Infusion-related reactions and hypersensitivity reactions may cause bronchospasm and hypotension.[72–79]

Topoisomerase I Inhibitors

Irinotecan

Irinotecan is a topoisomerase I inhibitor that is used mainly in the treatment of colon cancer, particularly in combination with other chemotherapy agents. Pneumonitis is a dose-dependent side effect of irinotecan. Moderate-to-severe pneumonitis has been reported in 2 to 16% of patients treated with irinotecan. Severe hypoxemia and respiratory failure requiring mechanical ventilation may develop in about 9% of the patients. Fatalities due to severe pneumonitis have been reported in 1 to 3.5% of patients.[80–83]

Topotecan

Topotecan is a topoisomerase I inhibitor that is mainly used in the treatment of metastatic carcinoma of the ovary or small cell lung cancer. Dyspnea has been reported in 3 to 4% of patients treated for ovarian or lung cancer.[84,85] Few cases of topotecan-induced lung toxicity have been described, and include diffuse alveolar damage, organizing pneumonia, mild interstitial fibrosis with numerous intraalveolar macrophages, and respiratory failure in the setting of preexisting pulmonary fibrosis.[86–88]

Exatecan

Exatecan is a new and experimental topoisomerase I inhibitor that has activity against a number of solid tumors. Although in one phase II study[89] mild to moderate dyspnea developed in 36% of patients treated with exatecan, pulmonary toxicity secondary to exatecan therapy has not been reported.

Thalidomide

Thalidomide was approved in 2006 for the treatment of multiple myeloma. Thalidomide is also being investigated for treatment of several other cancers. Dyspnea in association with thalidomide therapy has been reported[90,91] in 4 to 54% of patients. Opportunistic infections including *Pneumocystis carinii* pneumonia, disseminated herpes zoster, and herpes simplex infections have been described in leukopenic patients receiving thalidomide.[92,93] Several studies[94,95] have found increased incidence of DVT and pulmonary embolism in association with thalidomide therapy. Thromboembolic disease usually occurs at a mean time of 2 months after thalidomide administration. The reported rates of DVT and pulmonary embolism vary from 0 to 43% of treated patients. Higher rates have been observed among patients who received thalidomide in combination with chemotherapy (16%) or dexamethasone (15%) compared to thalidomide alone (5%).[94,95] Thalidomide-induced pneumonitis is extremely rare. Mild interstitial fibrosis, lymphocytic alveolitis, and organizing pneumonia have been described.[4,96,97]

Tyrosine Kinase Inhibitors

Gefitinib

Gefitinib is an oral EGFR tyrosine kinase inhibitor that is active against NSCLC, and ovarian, colon, head and neck, and breast cancers. Gefitinib-induced lung toxicity usually occurs within the first 90 days of treatment with gefitinib. Interstitial pneumonitis, diffuse alveolar damage, alveolar hemorrhage, and pulmonary fibrosis have been described.[98–103] The reported incidence of gefitinib-induced lung toxicity in Japan is between 1% and 2%, which is higher than the incidence of 0.3% that has been reported in the United States.[100–103] Gefitinib-induced pneumonitis is fatal in one third of cases.[104] Risk factors for pneumonitis seem to be the presence of previous lung damage from smoking, chemotherapy, irradiation, infection, or pulmonary fibrosis.[24]

Erlotinib

Erlotinib is a HER type 1/EGFR tyrosine kinase inhibitor. Erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC. Erlotinib-induced pneumonitis has been described[105] in patients treated with erlotinib for the treatment of advanced solid tumors. In a National Cancer Institute of Canada Clinical Trials Group study,[106] erlotinib, 150 mg daily, was compared with placebo.

Patients with locally advanced or metastatic NSCLC after failure to respond to at least one prior chemotherapy regimen were enrolled into this study. The incidence of pneumonitis in this study was 0.8%.[106] In a phase III trial[107] of erlotinib hydrochloride combined with carboplatin and paclitaxel chemotherapy in patients with advanced NSCLC, severe pneumonitis and respiratory failure developed in five patients in the erlotinib arm (1.0%) and one patient in the placebo arm (0.2%). All six cases of pneumonitis were fatal.[107] The clinical presentation and nature of these interstitial lung diseases were not reported in these trials. Vahid and Esmaili[108] described two cases of erlotinib-induced pneumonitis that resulted in respiratory failure. The patients presented 4 to 6 days after the initiation of erlotinib therapy with fever, cough, and hypoxemia. Bilateral ground-glass opacities seen on chest imaging and elevated BAL fluid cell counts with high neutrophil percentages (76% and 89%, respectively) were found. One patient improved with high-dose corticosteroid therapy and was extubated in 4 days. Septic shock developed in the second patient, and the patient died.[108]

Imatinib

Imatinib is a potent tyrosine kinase inhibitor that is mainly used in the treatment of patients with chronic myelogenous leukemia (CML). It is also effective in patients with GI stromal tumor. Although most cases of imatinib-induced pulmonary adverse events have been reported in patients with CML (0.2 to 1.3% in patients with early chronic phase CML), there have been rare cases of pneumonitis described in patients with GI stromal tumor treated with imatinib. Dyspnea during imatinib therapy is most often related to fluid retention and pulmonary edema. Fluid retention may be due to prolonged platelet-derived growth factor inhibition by imatinib. Platelet-derived growth factor pathways are involved in the regulation of interstitial fluid homeostasis.[109] Imatinib pneumonitis develops 10 to 282 days (median time, 49 days) after treatment with imatinib (range, 200 to 600 mg daily). Dyspnea, hypoxemia, fever, eosinophilia, and elevated KL-6 levels are usually seen. The chest CT scan shows diffuse or patchy ground-glass opacity, consolidation, or fine nodular opacity. The lung pathology may show interstitial pneumonitis and fibrosis, destruction of alveolar septa, lymphocytic alveolitis, plasma cell infiltrates, or type II pneumocyte hyperplasia. The resolution of pneumonitis after corticosteroid therapy has been reported. Ohnishi et al[109] reported that pneumonitis developed in 4 of 11 patients with a history of imatinib-induced pneumonitis after reexposure to imatinib.[110–115] Pleural effusions (unilateral and bilateral) have been described after the initiation of imatinib therapy. It is important to acknowledge that although drug toxicity and the subsequent development of pleural effusions is possible, it is extremely difficult to exclude volume overload and the progression of primary disease as a cause of pleural effusion in reported cases. The nature of these drug-induced effusions has not been described.[116]

Treatment

The mainstay of therapy for drug-induced pneumonitis is the cessation of the presumed culprit agent and systemic corticosteroids. Although corticosteroids are used widely to treat drug-induced pneumonitis, this treatment has not been evaluated in controlled clinical trials. It is important to exclude an infectious etiology prior to initiating corticosteroid therapy. We recommend therapy with methylprednisolone, 1 g/d for 3 days, in patients with respiratory failure. Lower doses of corticosteroids (methylprednisolone, 60 mg every 6 h) may be used in less severe cases of pneumonitis.[1,2] In our experience, therapy with systemic corticosteroids results in a rapid improvement in oxygenation and may lead to mechanical ventilation liberation. Supportive care, bronchodilators, IV fluid, vasopressors, and mechanical ventilation are indicated in patients with severe hypersensitivity reactions and circulatory collapse.

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