

Chemotherapy-induced lung disease

Andrew H. Limper, MD

Thoracic Diseases Research Unit, Division of Pulmonary, Critical Care and Internal Medicine, Mayo Clinic and Foundation, 8-24 Stabile, Rochester, MN 55905, USA

Chemotherapeutic agents are used extensively in solid and hematologic malignancies and are increasingly used for their immunosuppressive properties in the management of inflammatory disorders. Pulmonary diseases that are induced by chemotherapy represent particular challenges for pulmonary and critical care practitioners. These pulmonary reactions can be severe and rapidly fatal. In addition, the presentations of drug-induced pulmonary disease must be rapidly and effectively differentiated from other causes, including pulmonary infection, whose clinical presentations of fever and diffuse radiographic abnormalities may be virtually identical to chemotherapy-induced pulmonary reactions. Chemotherapy-induced lung disease was first recognized in the early 1960s in association with busulfan [1]. Over the past 15 years these reactions have become a major problem, particularly in relation to therapeutic regimens that contain bleomycin, methotrexate, cyclophosphamide, and a host of newer agents. Virtually all patients who take these drugs are immune suppressed, from their underlying disease as well as from the chemotherapy agents themselves. This makes them susceptible to a variety of usual and atypical infections, as well as lung recurrence of their underlying disease, that are important competing diagnoses that need to be excluded.

Universal criteria for the diagnosis of drug-induced pulmonary disease are not available. The diagnosis of cytotoxic lung damage generally depends upon an appropriate history of drug exposure, histologic evidence of lung injury, and, most importantly,

the exclusion of other causes of the lung damage. Unfortunately, there is no single diagnostic test or tissue biopsy that definitively can confirm the diagnosis of chemotherapy-associated lung disease. Thus, a careful and thorough evaluation to eliminate the possibilities of other conditions that produce these effects, particularly infection, is warranted. Clinicians who care for these patients must be aware of the myriad of chemotherapeutic agents that can injure the lungs. Overall, less than 10% of patients who receive chemotherapeutic agents develop pulmonary toxicities [2,3]. Thus, the clinician must maintain a high index of suspicion and be aware of factors that are associated with increased risk of pulmonary injury from these agents [2–12].

A wide variety of chemotherapeutic agents have been associated with pulmonary toxicities (Box 1). The clinical presentation of many drug effects is similar; however, some present more acutely, whereas others are insidious in their onset. In general, dyspnea, nonproductive cough, and, often, fever, begin weeks to years after the medication is first taken. Fever is common with most chemotherapeutic drug-induced pulmonary injuries, but it may not be consistently present. Chills are usually absent; weight loss is prevalent. The chest radiograph during chemotherapy-induced lung disease may be unremarkable for days or weeks before showing typical changes of a diffuse interstitial infiltrative pattern. Alternatively, there may be a diffuse mixed alveolar-interstitial pattern that, on occasion, may be useful in recognizing early drug effects [2]. These patterns are, however, not diagnostic. There is no characteristic radiographic pattern that is specific for a particular chemotherapy agent, with the possible exception of hilar lymphadenopathy that is associated with meth-

E-mail address: limper.andrew@mayo.edu

Box 1. Pharmacologic action of selected chemotherapeutic agents with associated pulmonary toxicities

Antibiotics

Bleomycin
Mitomycin C

Alkylating agents

Busulfan
Cyclophosphamide
Chlorambucil
Melfhalan

Antimetabolites

Methotrexate
6-mercaptopurine
Azathioprine
Cytosine arabinoside
Gemcitabine
Fludarabine

Nitrosamines

Bischloroethyl nitrosourea (BCNU)
Chloroethyl cyclohexyl nitrosourea (CCNU)
Methyl CCNU

Podophyllotoxins

Etoposide
Paclitaxel
Docetaxel
Novel antitumor agents
All trans retinoic acid (ATRA)
Gefinitnib
Imatinib mesylate
Irinotecan

Immune modulatory agents used in malignancy

Interferons (IFNs)
Interleukin (IL)-2
Tumor necrosis factor (TNF)- α

Other miscellaneous chemotherapy agents

Procarbazine
Zinostatin
Vinblastine

otrexate lung [13,14]. Auscultation of the lungs usually reveals crackles, which is a nonspecific finding. In some instances, small pleural effusions may be present during adverse drug reactions, but these are not present consistently enough to be of any diagnostic benefit. Clubbing has not been reported in any chemotherapeutic pulmonary toxicities.

The results of lung function studies are abnormal in virtually every patient who has chemotherapeutic drug disease when compared with pretreatment testing. The carbon monoxide diffusing capacity may decrease before decreased volumes are detected. In addition, the decrease in carbon monoxide diffusing capacity may precede the onset of symptoms and radiographic changes by days or weeks [15]. In several prospective studies, diffusing capacity was used to detect the early onset of pulmonary reaction, at which time, the drug or drugs were discontinued to minimize progression into clinical disease [16,17]. Gallium (^{67}Ga) uptake was shown to increase in most of these chemotherapeutic drug reactions; this shows that the lungs are affected before the chest radiograph becomes abnormal. Bronchoalveolar lavage (BAL) may be another means of assessing early lung damage from these drugs; however, the results are variable. In general, the greatest usefulness of BAL in the diagnosis of chemotherapy-associated lung disease is to exclude atypical or typical infections.

Some reactions that are related to chemotherapeutic agents were associated with cytologic atypia in affected pulmonary tissues. The histologic findings of markedly atypical type II pneumocytes, with relative fewer type I cells, was reported. The type II pneumocytes may exhibit a “bizarre” appearance. The nuclear to cytoplasmic ratio remains normal, however, and there is no increased number of mitoses in these cells [4]. Therefore, these changes should not be interpreted as malignant. The presence of cytologic atypia cannot be used to establish definite chemotherapy-associated lung injury. For instance, cytologic atypia may be present in an occasional patient who is treated with busulfan and does not have clinical, radiographic, or pathologic evidence of lung disease.

Hence, cytologic atypia does establish the presence of significant drug exposure but is not diagnostic of toxicity [16]. In addition, tissue examination in chemotherapy-associated lung injury may demonstrate a prominent inflammatory reaction in the interstitium as well as deposition of fibrin and collagen in the septal walls. Lung remodeling can progress to the point of severe fibrosis and result in respiratory insufficiency.

Antibiotic chemotherapy agents

Bleomycin

Bleomycin pulmonary toxicity is the most prevalent and best-defined chemotherapeutic-induced pulmonary disease [16]. Investigations of surveillance pulmonary function testing and chest radiographs reveal that as many as 20% of patients who are treated with bleomycin develop clinical pulmonary disease; as many as 1% die from pulmonary consequences of bleomycin therapy [15]. The incidence of bleomycin-related pulmonary disease is significantly greater in those who received a total dose of more than 450 U, with a 10% death rate in those who received a cumulative dose of more than 550 U. Pulmonary toxicity can develop after low doses of the drug, however. Pulmonary toxicity also is increased in patients who are older than 70 years of age and in those who have pre-existing lung disease or renal failure. In these investigations, frequent monitoring of the carbon monoxide diffusing capacity predicted subsequent clinical deterioration. Progressive decreases in the carbon monoxide diffusing capacity should prompt withdrawal of bleomycin therapy [18]. In addition, the enhanced sensitivity of CT imaging may be useful in establishing an early diagnosis of bleomycin pneumonitis [19,20]. In one study of 100 patients who received bleomycin therapy, thoracic CT imaging was abnormal in 38%, whereas the chest radiographs were abnormal in only 15% [19].

Several other agents synergistically predispose patients to developing bleomycin pneumonitis. Previous or concomitant thoracic radiation therapy is associated with a substantially increased incidence of severe bleomycin pulmonary toxicity. In addition, there is strong evidence of a synergistic effect between previous bleomycin exposure and subsequent exposure to high-inspired oxygen concentrations (Fig. 1). This is a problem during anesthesia and in the post-operative recovery period [21,22]. It is not known for how long after bleomycin exposure that breathing a



Fig. 1. Diffuse lung injury pattern in a patient who received bleomycin for a hematologic malignancy and subsequently underwent general anesthesia with supplemental oxygen.

high-inspired oxygen concentration predisposes to bleomycin toxicity. In particular, exposures within the previous 6 months should be considered highly risky, although the hazard may extend for month or years beyond this period. High-inspired oxygen concentrations should be avoided whenever possible. In addition, there seems to be synergistic toxicity between bleomycin and concomitant administration of cyclophosphamide.

Bleomycin pulmonary toxicity may be reversible if minimal changes have occurred and further bleomycin therapy is withheld. One study demonstrated that if the patient survives the acute event, the pulmonary findings may improve substantially [23]. If significant fibrosis is present, however, the process may progress insidiously, despite the administration of corticosteroids. Histologically, end-stage bleomycin pneumonitis may be indistinguishable from idiopathic usual interstitial pneumonitis.

A more frequent form of bleomycin pneumonitis has been described, namely a hypersensitivity type of bleomycin reaction that is associated with acute onset, fever, and peripheral blood or BAL eosinophilia. Discontinuation of bleomycin and initiating corticosteroids usually causes reversal of this hypersensitivity variant of bleomycin pneumonitis.

In addition, a rare, but clinically important, presentation of bleomycin pneumonitis can occur, the clinical presentation of nodular pulmonary lesions that mimic tumor metastasis [24,25]. These reactions have

been described in the setting of seminoma or lymphoma and sometimes require surgical biopsy to differentiate bleomycin-associated lung injury from recurrence of the primary malignancy. The nodular lesions of bleomycin pneumonitis frequently display the histologic pattern of bronchiolitis obliterans with organizing pneumonitis (BOOP) [4]. Similar, BOOP-like reactions were described in association with other chemotherapeutic agents, including cyclophosphamide, methotrexate, mitomycin, chlorambucil, and interferon, as well as nonchemotherapeutic agents, including amiodarone, gold, and nitrofurantoin [4].

Mitomycin C

Mitomycin C has been used in the management of bladder tumors, lung cancer, metastatic breast carcinoma, anal cancer, esophageal malignancies, and metastatic liver tumors. The exact incidence of mitomycin-induced pneumonitis is uncertain. One series stated that the incidence is approximately 8%; two additional series estimated the incidence from 12% to 39% [26,27]. The symptomatology, radiographic abnormalities, and histologic findings of mitomycin-induced pneumonitis generally are similar to those of other alkylating drug reactions. It was suggested, however, that the carbon monoxide diffusing capacity may not decrease before the onset of clinical symptoms [26]. In addition, the favorable response to corticosteroid therapy was dramatic in several patients, possibly greater than in other forms of chemotherapy-associated lung injury.

In addition to mitomycin-induced pneumonitis, there are accumulating reports of an unusual reaction to mitomycin C that consists of microangiopathic hemolytic anemia with associated renal failure and noncardiogenic pulmonary edema [28]. Most of these patients developed side effects between 6 and 12 months after beginning mitomycin C chemotherapy, but the syndrome has been described several months after termination of treatment. Approximately one half of the patients develop adult respiratory distress syndrome. The mortality of patients who have respiratory complications may be as high as 95%, compared with 50% in patients who do not have lung involvement. Many of these patients with mitomycin C associated hemolytic-uremic syndrome also received fluorouracil (5 FU), an agent without significant known pulmonary toxicity. In some instances, this unusual drug reaction seemed to be precipitated by blood transfusions. Histologically, microangiopathic changes are seen in the kidneys and lungs with intimal hyperplasia of the arterioles (sometimes associated with complete occlusion of the lumen), along

with prominent nuclear atypia of the capillary cells and capillary fibrin thrombi.

Alkylating agents

Busulfan

Busulfan has been used for the management of chronic myeloproliferative diseases in conditioning protocols preceding autologous bone marrow stem cell transplantation. The average time from the initiation of therapy to the onset of respiratory symptoms is approximately 3.5 years and ranges from 8 months to 10 years. Busulfan pulmonary toxicity can occur as early as 6 weeks following initiation of therapy. The incidence of busulfan pulmonary toxicity is estimated to be 6%, with a reported range of 2.5% to 43% [29]. Dyspnea, fever, and cough begin in a more insidious fashion than with most other chemotherapy-associated lung toxicities. Symptoms have been reported to begin months after busulfan therapy was discontinued. Withdrawal of the agent and administration of corticosteroids results in variable clinical response. Although some patients improve, most experience progressive respiratory impairment and death. It is not clear whether busulfan-related injury is a dose-dependent phenomenon. Concomitant radiation therapy may potentiate the effect of busulfan, as it does with some of the other chemotherapeutic agents. The chest radiograph in busulfan toxicity reveals a combined alveolar and interstitial infiltrative process, that is more severe than in other chemotherapy-induced pulmonary reactions. This is likely due to a high degree of desquamation of injured epithelial cells into the alveolar spaces. Accordingly, the alveolar debris was so extensive that it yielded a pattern that was suggestive of alveolar proteinosis in several patients who received busulfan. This form of alveolar proteinosis is more refractory to therapeutic lavage than idiopathic alveolar proteinosis [30–32].

Cyclophosphamide

Cyclophosphamide is included in several combination chemotherapeutic regimens for hematologic malignancies and solid tumors, including breast carcinoma. This agent is also used extensively, alone, or in combination, with corticosteroids for immune suppression in the vasculitides and other inflammatory conditions. Accumulating evidence suggests that the incidence of cyclophosphamide-induced pneumonitis may be largely underestimated [33]. A comprehensive retrospective review at a tertiary referral center iden-

tified six patients over 20 years in whom cyclophosphamide was the only factor that contributed to pulmonary injury [34]. Clinical features of cyclophosphamide-associated pulmonary toxicity include dyspnea, fever, cough, gas exchange abnormalities, parenchymal infiltrates, and pleural thickening. Two patterns of cyclophosphamide-induced lung toxicity were appreciated in that series. First, an early-onset pneumonitis occurred within the first 1 to 6 months after institution of therapy. This form generally responded to withdrawal of cyclophosphamide. In contrast, a late-onset pneumonitis can develop after months, or years, of therapy, and result in progressive lung fibrosis and bilateral pleural thickening. This late-onset variety has minimal response to withdrawal of cyclophosphamide or to corticosteroid therapy [34]. The dose of cyclophosphamide and the subsequent development of pulmonary disease are not related clearly. There have been rare reports of negative rechallenge with cyclophosphamide (ie, without subsequent recurrence of the pulmonary toxicity); however, this is not generally recommended.

Chlorambucil

This alkylating agent is prescribed primarily for chronic lymphocytic disorders but also has been used as an immunosuppressant. The clinical presentation, chest radiographic abnormalities, and histologic features of chlorambucil-associated pneumonitis are similar to those described in other alkylating agent–induced pulmonary toxicities [3]. The presentation is generally insidious and occurs 6 months to a year or more after beginning therapy. Surveillance of lung function, particularly diffusing capacity, may be beneficial in anticipating which patients will deteriorate and require discontinuation of the agent. Little data are available on the efficacy of corticosteroid therapy in chlorambucil-associated lung toxicity.

Melphalan

Melphalan has been used in the treatment of multiple myeloma. Few well-documented cases of pulmonary toxicity that were associated with melphalan were reported, although the overall incidence may be underestimated [2]. The course of melphalan-associated pulmonary injury varies from acute to subacute. There are no particular clues for predicting which patient will develop side effects. The incidence of pulmonary side effects from melphalan must be low because this agent has been used widely in the treatment of a chronic hematologic malignancy.

Antimetabolites

Methotrexate

Methotrexate is present in many combination programs for neoplasms and also is used extensively for nonmalignant conditions, including psoriasis and rheumatoid arthritis. Several hundred cases of adverse pulmonary reactions that were related to methotrexate have been reported. Methotrexate pneumonitis is unique and has been associated with a few fatalities. Dyspnea, nonproductive cough, and fever usually commence a few days to several weeks after initiation of therapy; in rare cases, symptoms may begin a few months or years after the onset of therapy [35]. Methotrexate-associated pneumonitis is almost always reversible with or without the addition of corticosteroids. Eosinophilia, usually mild, is seen in at least half of the cases; therefore, the disease is believed to represent a hypersensitivity state [3]. The intriguing feature of this reaction is that the drug may be reinstated following resolution of methotrexate pneumonitis without triggering a subsequent recurrence of symptoms or findings. In about one third of the patients, weakly formed granulomas are documented in lung biopsy; this is an unusual finding in other forms of chemotherapy-associated lung disease [4]. There is no cellular atypia, such as is seen in other cytotoxic drug reactions.

The chest radiograph usually reveals a homogeneous infiltrate throughout all lung fields. Hilar adenopathy or pleural effusion occurs in at least 10% of patients who have methotrexate pulmonary toxicity. In contrast to most other chemotherapy pulmonary toxicities, prospective investigations of patients who received methotrexate did not demonstrate a diminished diffusing capacity that might precede subclinical toxicity. In addition, pulmonary toxicity in response to methotrexate does not seem to be dose related. There were a few reports of fatal reactions that occurred from intrathecal methotrexate or from oral ingestion after previous intrathecal injections. Exclusion of opportunistic infections in the setting of methotrexate use is particularly important. *Pneumocystis* pneumonia was reported in patients who received methotrexate, either alone, or in combination with corticosteroids [36]. The clinical presentation, chest radiograph, and other clinical features can be similar to methotrexate lung [36,37].

Azathioprine

Azathioprine is frequent component of several combination chemotherapy regimens for malignan-

cies and is being used increasingly for its immune suppressive properties during inflammatory conditions and following organ transplantation. There are more than one dozen case reports of azathioprine pneumonitis. The net overall incidence must be low, because of the widespread use of this agent for neoplastic and nonneoplastic conditions [2]. Regardless, the possibility of an azathioprine pneumonitis must be considered in any individual who receives this agent. Azathioprine is metabolized to 6-mercaptopurine and there has been a handful of reports that detailed cytotoxic interstitial pneumonitis in association with this metabolite [6]. Many of these patients received other drugs that potentially could be implicated in the lung injury described.

Cytosine arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent that is used to induce remission in acute leukemia and other hematologic malignancies before bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiac pulmonary edema [38]. Histologic examination of lung tissue during ara-C pulmonary toxicity reveals marked intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration that is described with other cytotoxic drugs. In two large series, 13% to 28% of the patients who had toxicity developed respiratory distress during the administration of the drug; nearly one half developed symptoms within a month of completing drug administration [38,39]. The mechanism that underlies this reaction is unknown and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive, with mechanical ventilation, careful management of fluid status, and surveillance for superimposed infectious complications.

Gemcitabine

Gemcitabine is a pyrimidine analog, with structural similarities and activities parallel to cytarabine (ara-C). It is highly active against nonsmall cell lung cancer, pancreatic carcinoma, and breast and ovarian cancers. It is generally well-tolerated; most toxicities are bone marrow suppression, nausea, rash, transaminase increase, and edema. The incidence of pulmonary toxicity in association with gemcitabine has emerged only recently and probably has been underestimated [40]. Dyspnea was reported in 10% of treated patients; severe dyspnea was found in up to 5% [41–43]. There are three major patterns of res-

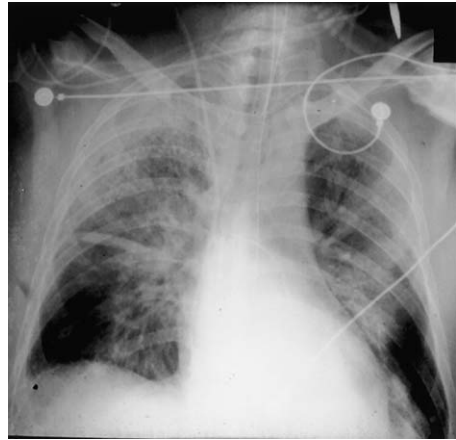


Fig. 2. BCNU lung injury is frequently associated with bilateral upper lobe infiltration as demonstrated on this chest radiograph. Discontinuation of the agent and institution of corticosteroid yields little sustained improvement.

piratory involvement in gemcitabine-related pulmonary toxicity. The first pattern is a nonspecific, self-limiting dyspnea that occurs within hours to days of treatment. A second, uncommon pattern is an acute hypersensitivity reaction with bronchospasm. A third pattern of severe respiratory involvement is seen occasionally. This is a severe idiosyncratic reaction with marked dyspnea and pulmonary infiltrates that may progress to life-threatening respiratory insufficiency (Fig. 2). Most cases of gemcitabine-related pulmonary toxicity resolve with discontinuation of this agent. In cases of severe symptoms, discontinuation of the agent, with institution of corticosteroids, careful fluid management, and diuretic therapy may be warranted [42].

Fludarabine

Fludarabine is another nucleoside analog that is widely used in the management of chronic lymphoproliferative disorders. The incidence of pulmonary toxicity related to fludarabine was estimated to be 8.6% [44]. Affected individuals experience dyspnea as early as 3 days after the first cycle of chemotherapy, although later onset of pulmonary symptoms have been described. The chest radiograph reveals either interstitial or mixed interstitial-alveolar infiltrates. Most patients seem to respond to discontinuation of this drug and receive symptomatic and objective benefits from corticosteroid therapy.

Nitrosamines

Nitrosourea compounds have activity in treatment regimens for gliomas and other central nervous system tumors, as well as in conditioning protocols that precede autologous bone marrow stem cell transplantation. Pulmonary toxicity that is related to nitrosoureas have been known since the 1970s and represents one of the most common side effects of these agents [45]. In particular, BCNU (carmustine) was reported to induce acute onset pulmonary injury and delayed-onset pulmonary fibrosis, with a predilection for the upper lobes [45]. The incidence of pulmonary toxicity that is associated with the administration of BCNU varies from 1.5% to 20% and seems to be dose related, with up to a 50% incidence of lung disease in patients who received a total dose of more than 1500 mg/m² [46]. There also have been reports of pulmonary effects that occurred with much lower doses [46]. The duration of therapy before the onset of pulmonary toxicity for the acute variety of nitrosourea lung injury varies from 6 months to 3 years. There seems to be a synergistic effect with cyclophosphamide, radiation therapy, and, possibly, other chemotherapeutic agents. The clinical course is similar to that for bleomycin and cyclophosphamide. The outcome may be unpredictable and sometimes fatal. There have been fewer case reports of pulmonary toxicity with methyl-chloroethyl cyclohexyl nitrosourea and chloroethyl cyclohexyl nitrosourea. Fever is less commonly associated with this form of pulmo-



Fig. 3. Gemcitabine pulmonary toxicity occurred in this individual following treatment for transitional cell carcinoma. These bilateral infiltrates that are demonstrated by high-resolution CT scanning resolved after discontinuation of the agent.

nary toxicity than with most other chemotherapeutic drugs. Therapy usually consists of withholding the offending agent and institution of corticosteroids, which has variable, and often only transient, beneficial effects [47].

A long-term complication of BCNU toxicity is evidence of upper lobe pulmonary fibrosis many years after the completion of chemotherapy (Fig. 3). O'Driscoll and colleagues [48] followed 17 patients for up to 17 years; 12 of the 17 (71%) developed upper lobe fibrosis. The fibrosis is insidious in onset and seems to be intractably progressive. Corticosteroid therapy has not proven to be effective in delayed BCNU upper lobe fibrosis. Pneumothorax is another unusual complication that is almost exclusively associated with nitrosourea compounds [49]. This may be related to the upper lobe fibrobullous changes that are present in patients who have BCNU lung toxicity.

Novel and emerging chemotherapeutic agents

All trans retinoic acid

Tretinoin (All trans retinoic acid) has been used in acute promyelocytic leukemia where it induces differentiation of myeloid precursors and accelerates the maturation of leukemic cells, thereby promoting remission. It also has been used to reduce disseminated intravascular coagulation and hemorrhagic complications of promyelocytic leukemia. The drug is associated with several toxicities, including edema and fluid retention with pleuropericardial effusions that may evolve into a generalized capillary leak syndrome. In addition, multiple hemorrhagic complications have been described. In a series of 35 cases of promyelocytic leukemia that were treated with ATRA, nine patients developed respiratory distress [50]. Respiratory symptoms occurred between Day 2 and Day 21 of treatment with ATRA. Intravenous corticosteroid therapy seemed to be beneficial to patients who were affected with ATRA pulmonary syndrome. Based upon these observations, an additional study suggested that the incidence of ATRA-associated pulmonary syndrome can be reduced to roughly 10% with the use of preventative treatment with oral corticosteroids [51]. Autopsy examinations of lungs that were affected by ATRA revealed interstitial infiltration with maturing myeloid cells. The overall spectrum of the ATRA-associated pulmonary syndrome continues to evolve and includes the observations of myeloid cells and blasts in BAL, pulmonary leukostasis, nodular pulmonary infiltrates, noncardiogenic pulmonary edema, the adult respiratory distress

syndrome, Sweet's syndrome, and diffuse alveolar hemorrhage [52].

Gefitinib

Gefitinib (Iressa, ZD1839) is a selective tyrosine kinase inhibitor that is active downstream from the epidermal growth factor receptor. It is approved for patients who have advanced nonsmall cell lung cancer and failed to respond to platinum-based chemotherapy regimens. At least six cases of acute interstitial pneumonia have been associated with this agent; the overall incidence of gefitinib-associated interstitial lung disease may be in the range of 1% [53]. Diffuse ground glass opacities have been observed on CT imaging. Tissue examination in the available cases revealed diffuse alveolar damage. Although some patients respond to withdrawal of the agent and institution of corticosteroid therapy, others progress to fatal respiratory insufficiency. Hence, the clinician needs to remain mindful of this pulmonary complication of gefitinib therapy and discontinue the agent if symptoms and radiographic abnormalities are observed. Recently, a limited number of cases that showed pulmonary infiltration were reported in association with imatinib mesylate (Gleevec, ST1571), a novel tyrosine kinase inhibitor that is used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors [54].

Irinotecan

Irinotecan, a semisynthetic camptothecin, has been used in some lung cancer trials and is prescribed for advanced colorectal cancer, either alone, or in combination with 5-fluorouracil. Early irinotecan registration studies in Japan documented a 1.8% incidence of pneumonitis [63,64]. In those reports, clinical features included fever, dyspnea, and reticulonodular infiltrates on chest radiography. Empiric corticosteroids have been recommended, but some patients progressed to fatal respiratory insufficiency. In subsequent United States trials, cough and dyspnea were described in roughly 20% of treated patients [65]; however, many of these patients had intrathoracic malignancies. Overall, the incidence of serious pulmonary toxicity related to irinotecan was much lower in the subsequent trials (approximately 0.4%) [65]. Nonetheless, cases of irinotecan-associated interstitial pneumonitis have been reported in the United States. Patients who have pre-existing pulmonary disease may be at particular risk.

Podophyllotoxins

Etoposide

Etoposide (VP-16) has been used widely in combination chemotherapy for small cell and nonsmall cell carcinoma of the lung. Despite its extensive use, only a few cases of etoposide-associated pulmonary toxicity have been reported [55]. Onset may occur after the first round of chemotherapy, although most of the associated cases occurred after prolonged treatment. Tissue examination reveals feature of alveolar edema, diffuse alveolar damage, and atypical type II pneumocytes. Withdrawal of the agent and corticosteroid therapy has been used with variable results.

Paclitaxel

Paclitaxel (Taxol) is one of the most potent chemotherapeutic agents in the treatment of breast, lung, and ovarian carcinomas and has experienced widespread use over the past 5 years. A limited number of case reports associated this agent with respiratory symptoms, including dyspnea, cough, wheezing and chest tightness [56]. Interstitial and reticulonodular infiltrates have been described on chest radiographic examination [57]. Cases of transient pulmonary infiltrates and suspected interstitial pneumonitis have been reported, although the true incidence of lung toxicity that is directly related to paclitaxel is not well understood. A prospective study of lung function in 33 patients who received paclitaxel with carboplatin (an agent with little evidence for direct lung toxicity) for nonthoracic malignancy revealed an isolated decrease in diffusing capacity without other clinical or radiographic evidence of pulmonary toxicity [58]. In other series of patients who had lung carcinoma, significant early and late pulmonary toxicity was noted in 10% and 68% of patients, respectively [59]. Attributing the toxicity directly to paclitaxel is clouded by the underlying thoracic neoplasm, as well as other cytotoxic agents that were used in these patients [60]. Nonetheless, clinicians should be aware of the potential for paclitaxel to impair pulmonary function.

Docetaxel

Docetaxel (Taxotere) is a new taxane derivative that has shown activity in the treatment of breast and nonsmall cell lung cancer. Occasional pulmonary toxicity, that presents as a hypersensitivity reaction, has been observed [61]. These cases responded rapidly to corticosteroid therapy. Recently, a small case series suggested that the combination of docetaxel

and gemcitabine has a particular propensity to induce severe pulmonary toxicity [62].

Immune modulatory agents

Interferons

IFNs have been used in a wide variety of malignant, idiopathic, infectious, and inflammatory conditions, including idiopathic pulmonary fibrosis. In particular, IFN- α and - β have been used in the treatment of hairy cell leukemia, myeloma, T-cell lymphoma, chronic myelogenous leukemia, malignant pleural effusions, melanoma, renal cell carcinoma, and Kaposi's sarcoma. IFN- γ has been included in investigative trials for mesothelioma and nonsmall cell lung carcinoma.

Administration of IFN compounds has been associated with a variety of pulmonary reactions. For example, IFN- α was associated with severe exacerbation of bronchospasm in patients who had pre-existing asthma [66]. In addition, a granulomatous reaction that was indistinguishable from sarcoidosis was described in association with IFN therapy [67]. These usually respond to reduction or withdrawal of the agent with or without the addition of corticosteroids. Noncaseating granulomas have been documented in the lung, lymph nodes, liver, and skin.

IFN-associated interstitial lung disease also has been described, occurring within weeks to months after initiation of IFN therapy [68]. Dyspnea and cough are observed and bilateral infiltrates are noted on chest radiography. A CD8 predominant lymphocytic response is found on BAL and a cellular interstitial pattern is present on histologic examination. IFN therapy was associated with a bronchiolitis obliterans organizing pneumonia in some biopsies [69]. Most affected patients respond to discontinuation of the IFN and addition of corticosteroid therapy. Recently, IFN- γ was used in idiopathic pulmonary fibrosis (IPF). Notably, a series reported 4 patients who had advanced IPF and developed acute hypoxemic respiratory failure during IFN- γ therapy [70]. This was not responsive to corticosteroid administration and was fatal in three cases. IFN- γ also was reported to be associated with a high incidence of severe radiation pneumonitis when used in multi-modality therapy for nonsmall cell lung carcinoma [71].

Interleukin-2

IL-2 has been used, with or without lymphokine-activated killer cells, as an investigational agent for

treatment of certain malignancies [72–74]. More than 50% of the patients who were treated with IL-2 developed one or more pulmonary complications, including noncardiogenic pulmonary edema, the adult respiratory distress syndrome, bronchospasm, and cardiac dysfunction that led to cardiogenic pulmonary edema. In some individuals, a generalized capillary leak syndrome was described.

Tumor necrosis factor

TNF- α is a macrophage-derived cytokine that promotes inflammation and induces necrosis of certain neoplasms. TNF- α has been used as an investigational agent in treatment protocols for patients who have advanced malignancies [75,76]. In one series of 27 patients who were treated with TNF- α , pulmonary function studies showed a statistically significant decline in carbon monoxide diffusing capacity in all patients studied, beginning about 2 weeks after the initiation of therapy. The results of other tests of pulmonary function did not change significantly [76]. Associated respiratory impairment was noted in some individuals.

Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor

Although not chemotherapy agents, granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor receive wide application in the treatment of bone marrow suppression during chemotherapy, thereby enhancing the immune response of treated patients. Pulmonary infiltrates often occur during neutrophil recovery. Several case reports and small patient series proposed that GM-CSF and G-CSF may potentiate pulmonary toxicity of other chemotherapeutic agents [77]. It was also suggested that GM-CSF may induce a recall phenomenon of toxicity from other agents. These possibilities continue to be debated and require further observation.

Other chemotherapeutic agents

Procarbazine

Procarbazine has found use in treatment regimens for Hodgkin's disease and other lymphoproliferative disorders. Adverse pulmonary side effects that are related to procarbazine are fairly infrequent; only a few cases of probable procarbazine pneumonitis have been described [2,3]. These lung reactions may

be cytotoxic in nature. In other patients, toxicity was related to a rapid-onset hypersensitivity reaction that was associated with eosinophilia that declined after the drug was discontinued.

Zinostatin

Zinostatin has been associated with a few reports of pulmonary toxicity that usually occurred in patients who received the drug for prolonged periods of time [3]. This agent has been associated with the unique drug reaction of hypertrophy of the pulmonary vasculature which may be related to be a direct cytotoxic effect of the drug on the pulmonary endothelium.

Vinblastine

Vinblastine, a vinca plant alkaloid, is one of the oldest chemotherapeutic agents that is still commonly use. Vinblastine is included in a wide variety of chemotherapeutic regimens for hematologic and solid malignancies. Traditionally, vinblastine was believed to have little, if any, pulmonary toxicity. Reports associated vinblastine with pulmonary complications when it is combined with other agents, particularly mitomycin C. This combination was complicated by bronchospasm, interstitial pneumonitis, and a noncardiac pulmonary edema [78,79].

Summary

The lung has significant susceptibility to injury from a variety of chemotherapeutic agents. The clinician must be familiar with classic chemotherapeutic agents with well-described pulmonary toxicities and must also be vigilant about a host of new agents that may exert adverse effects on lung function. The diagnosis of chemotherapy-associated lung disease remains an exclusionary process, particularly with respect to considering usual and atypical infections, as well as recurrence of the underlying neoplastic process in these immune compromised patients. In many instances, chemotherapy-associated lung disease may respond to withdrawal of the offending agent and to the judicious application of corticosteroid therapy.

References

- [1] Massin F, Fur A, Reybet-Degat O, et al. Busulfan-induced pneumopathy. *Rev Mal Respir* 1987;4:3–10.

- [2] Limper AH, Rosenow III EC. Drug-induced pulmonary disease. In: Murray JF, Nadel J, editors. *Textbook of respiratory medicine*. Philadelphia: W.B. Saunders Company, Inc.; 2000. p. 1971–94.
- [3] Rosenow III EC, Limper AH. Drug induced pulmonary disease. *Semin Respir Infect* 1995;10:86–95.
- [4] Myers JL. Pathology of drug-induced lung disease. In: Katzenstein AL, Askin F, editors. *Surgical pathology of non-neoplastic lung disease*. 2nd edition. Philadelphia: W.B. Saunders; 1990. p. 97–127.
- [5] Rosenow III EC. Chemotherapeutic drug-induced pulmonary disease. *Semin Respir Med* 1980;2:89–96.
- [6] Aronchick JM, Gefter WB. Drug-induced pulmonary disease: an update. *J Thor Imag* 1991;6:19–29.
- [7] Snyder LS, Hertz MI. Cytotoxic drug-induced lung injury. *Semin Respir Infect* 1988;3:217–28.
- [8] Lehne G, Lote K. Pulmonary toxicity of cytotoxic and immunosuppressive agents. *Acta Oncol (Madr)* 1990; 29:113–24.
- [9] Twohig KJ, Matthay RA. Pulmonary effects of cytotoxic agents other than bleomycin. *Clin Chest Med* 1990;11:31–54.
- [10] Brooks Jr BJ, Seifter EJ, Walsh TE, et al. Pulmonary toxicity with combined modality therapy for limited stage small cell lung cancer. *J Clin Oncol* 1986;4: 200–9.
- [11] Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. *Semin Oncol* 1982;9:34–51.
- [12] Klein DS, Wilds PR. Pulmonary toxicity of antineoplastic agents: anaesthetic and postoperative implications. *Ann Anesth Soc J* 1983;30:399–405.
- [13] Carson CW, Cannon GW, Egger MJ, et al. Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum* 1987;16:186–95.
- [14] Gispen JG, Alarcon GS, Johnson JJ, et al. Toxicity of methotrexate in rheumatoid arthritis. *J Rheumatol* 1987;14:73–9.
- [15] Limper AH. Drug induced lung disease: new developments. In: Braunwald E, editor. *Harrison's online*. New York: The MacGraw Hill Companies; 2000. Available at: <http://harrisons.accessmedicine.com>. Accessed on 9 January 2004.
- [16] Jules-Elysee K, White DA. Bleomycin-induced pulmonary toxicity. *Clin Chest Med* 1990;11:1–20.
- [17] Heard B, Cooke R. Busulphan lung. *Thorax* 1968;23: 187–93.
- [18] Wolkowicz J, Sturgeon MB, Rawji M, et al. Bleomycin-induced pulmonary function abnormalities. *Chest* 1992;101:97–101.
- [19] Bellamy EA, Husband JE, Blaquiére RM, et al. Bleomycin-related lung damage: CT evidence. *Radiology* 1985;156:155–8.
- [20] Mills P, Husband J. Computed tomography of pulmonary bleomycin toxicity. *Semin Ultrasound CT MR* 1990;11:417–22.
- [21] Ingrassia III TS, Ryu JH, Trastek VF, et al. Oxygen-exacerbated bleomycin pulmonary toxicity. *Mayo Clin Proc* 1991;66:173–8.

- [22] Goldiner PL, Carlon GC, Cvitkovic E, et al. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. *BMJ* 1978;1:1664–7.
- [23] Van Barneveld RWC, Sleijfer DT, VanDerMark TW, et al. Natural course of bleomycin-induced pneumonitis. A follow-up study. *Am Rev Respir Dis* 1987;135:48–51.
- [24] Santrach PJ, Askin FB, Wells RJ, et al. Nodular form of bleomycin-related pulmonary injury in patients with osteogenic sarcoma. *Cancer* 1989;64:806–11.
- [25] Cohen MB, Austin JH, Smith-Vaniz A, et al. Nodular bleomycin toxicity. *Am J Clin Pathol* 1989;92:101–4.
- [26] Verweij J, van Zanten T, Souren T, et al. Prospective study on the dose relationship of mitomycin C-induced interstitial pneumonitis. *Cancer* 1987;60:756–61.
- [27] Linette DC, McGee KH, McFarland JA. Mitomycin-induced pulmonary toxicity: case report and review of the literature. *Ann Pharmacother* 1992;26:481–4.
- [28] Sheldon R, Slaughter D. A syndrome of microangiopathic hemolytic anemia, renal impairment, and pulmonary edema in chemotherapy-treated patients with adenocarcinoma. *Cancer* 1986;58:1428–36.
- [29] Fernandez HF, Tran HT, Albrecht F, et al. Evaluation of safety and pharmacokinetics of administering intravenous busulfan in a twice-daily or daily schedule to patients with advanced hematologic malignant disease undergoing stem cell transplantation. *Biol Blood Marrow Transplant* 2002;8:486–92.
- [30] Bedrossian CWM, Luna MA, Conklin RH, et al. Alveolar proteinosis as a consequence of immunosuppression. *Hum Pathol* 1980;11:527–35.
- [31] Aymard JP, Gyger M, Lavalley R, et al. A case of pulmonary alveolar proteinosis complicating chronic myelogenous leukemia. *Cancer* 1984;53:954–6.
- [32] Watanabe K, Sueishi K, Tanaka K, et al. Pulmonary alveolar proteinosis and disseminated atypical mycobacteriosis in a patient with busulfan lung. *Acta Pathol Jpn* 1990;40:63–6.
- [33] Morgan M, Dodds A, Atkinson K, et al. The toxicity of busulphan and cyclophosphamide as the preparative regimen for bone marrow transplantation. *Br J Haematol* 1991;77:529–34.
- [34] Malik SW, Myers JL, DeRemee RA, et al. Lung toxicity with cyclophosphamide use: two distinct patterns. *Am J Respir Crit Care Med* 1996;154:1851–6.
- [35] Hasan FM, Mark EJ. A 28-year-old man with increasing dyspnea, dry cough, and fever after chemotherapy for lymphoma. *N Engl J Med* 1990;323:737–47.
- [36] Hilliquin P, Renoux M, Perrot S, et al. Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. *Br J Rheumatol* 1996;35:441–5.
- [37] Cooper Jr JAD, White DA, Matthey RA. Drug-induced pulmonary disease: Part 1: Cytotoxic drugs. Part 2. Noncytotoxic drugs. *Am Rev Respir Dis* 1986;33:488–505.
- [38] Andersson BS, Luna MA, Yee C, et al. Fatal pulmonary failure complicating high-dose cytosine arabinoside therapy in acute leukemia. *Cancer* 1990;65:1079–84.
- [39] Jehn J, Göldel N, Rienmauller R, et al. Noncardiogenic pulmonary edema complicating intermediate and high-dose Ara C treatment for relapsed acute leukemia. *Med Oncol Tumor Pharmacother* 1988;5:41–7.
- [40] Joerger M, Gunz A, Speich R, et al. Gemcitabine-related pulmonary toxicity. *Swiss Med Wkly* 2002;132:17–20.
- [41] Nelson R, Tarasoff P. Dyspnea with gemcitabine is commonly seen, often disease related, transient, and rarely severe. *Eur J Cancer* 1995;31:197–8.
- [42] Gupta N, Ahmed I, Steinberg H, et al. Gemcitabine-induced pulmonary toxicity: case report and review of the literature. *Am J Clin Oncol* 2002;25:96–100.
- [43] Rosado MF, Kett DH, Schein RM, et al. Severe pulmonary toxicity in a patient treated with gemcitabine. *Am J Clin Oncol* 2002;25:31–3.
- [44] Helman Jr DL, Byrd JC, Ales NC, et al. Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002;122:785–90.
- [45] Massin F, Coudert B, Foucher P, et al. Nitrosourea-induced lung diseases. *Rev Malad Respir* 1992;9:575–82.
- [46] Parish JM, Muhm JR, Leslie KO. Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003;78:630–4.
- [47] Weinstein AS, Diener-West M, Nelson DF, et al. Pulmonary toxicity of carmustine in patients treated for malignant glioma. *Cancer Treat Rep* 1986;70:943–6.
- [48] O'Driscoll BR, Hasleton PS, Taylor PM, et al. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990;323:378–82.
- [49] Durant JR, Norgard MJ, Murad TM, et al. Pulmonary toxicity associated with bischloroethyl nitrosourea (BCNU). *Ann Intern Med* 1979;90:191–4.
- [50] Frankel SR, Eardley A, Lauwers G, et al. The “retinoic acid syndrome” in acute promyelocytic leukemia. *Ann Intern Med* 1992;117:292–6.
- [51] Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-trans retinoic acid treatment of acute promyelocytic leukemia. *Leukemia* 1995;9:774–8.
- [52] Nicolls MR, Terada LS, Tuder RM, et al. Diffuse alveolar hemorrhage with underlying pulmonary capillaritis in the retinoic acid syndrome. *Am J Respir Crit Care Med* 1998;158:1302–5.
- [53] Cohen MH, Williams GA, Sridhara R, et al. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. *Oncologist* 2003;8:303–6.
- [54] Rosado MF, Donna E, Ahn YS. Challenging problems in advanced malignancy: imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003;21:3171–3.
- [55] Gurjal A, An T, Valdivieso M, et al. Etoposide-induced pulmonary toxicity. *Lung Canc* 1999;26:109–12.

- [56] Shannon VR, Price KJ. Pulmonary complications of cancer therapy. *Anesth Clin N Amer* 1998;16:563–86.
- [57] Ramanathan RK, Reddy VV, Holbert JM, et al. Pulmonary infiltrates following administration of paclitaxel. *Chest* 1996;110:289–92.
- [58] Dimopoulou I, Galani G, Dafni U, et al. A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. *Cancer* 2002;94:452–8.
- [59] Robert F, Spencer SA, Childs HA, et al. Concurrent chemo-radiation therapy with cisplatin and paclitaxel for locally advanced non-small cell lung cancer: long-term follow-up of a phase I trial. *Lung Cancer* 2002; 37:189–99.
- [60] 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. *Sem Radiation Oncol* 1999;9:136–47.
- [61] Etienne B, Perol M, Nesme P, et al. Acute diffuse interstitial pneumopathy following docetaxel. *Rev Malad Respir* 1998;15:199–203.
- [62] Dunsford ML, Mead GM, Bateman AC, et al. Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. *Ann Oncol* 1999;18: 943–1007.
- [63] Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a derivative of camptothecin, for previously untreated non small cell lung cancer. *J Clin Oncol* 1992;10:16–20.
- [64] Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. *J Clin Oncol* 1992;10:1225–9.
- [65] Madarnas Y, Webster P, Shorter AM, et al. Irinotecan-associated pulmonary toxicity. *Anticancer Drugs* 2000; 11:709–13.
- [66] Bini EJ, Weinshel EH. Severe exacerbation of asthma: a new side effect of interferon-alpha in patients with asthma and chronic hepatitis C. *Mayo Clin Proc* 1999; 74:367–70.
- [67] Rubinowitz AN, Naidich DP, Alinsonorin C. Interferon-induced sarcoidosis. *J Comp Assist Tomogr* 2003;27: 279–83.
- [68] Kumar KS, Russo MW, Boreczuk AC, et al. Significant pulmonary toxicity associated with interferon and ribavirin therapy for hepatitis C. *Am J Gastro* 2002;97: 2432–40.
- [69] Patel M, Ezzat W, Pauw KL, et al. Bronchiolitis obliterans organizing pneumonia in a patient with chronic myelogenous leukemia developing after initiation of interferon and cytosine arabinoside. *Eur J Haematol* 2001;67:318–21.
- [70] Honore I, Nunes H, Groussard O, et al. Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;167:953–7.
- [71] Shaw EG, Deming RL, Creagan ET, et al. Pilot study of human recombinant interferon gamma and accelerated hyperfractionated thoracic radiation therapy in patients with unresectable stage IIIA/B nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys* 1995;31: 827–31.
- [72] Lazarus DS, Kurnick JT, Kradin RL. Alterations in pulmonary function in cancer patients receiving adoptive immunotherapy with tumor-infiltrating lymphocytes and interleukin-2. *Am Rev Respir Dis* 1990; 141:193–8.
- [73] Saxon RR, Klein JS, Bar MH, et al. Pathogenesis of pulmonary edema during interleukin-2 therapy: correlation of chest radiographic and clinical findings in 54 patients. *AJR* 1991;156:281–5.
- [74] Conant EF, Fox KR, Miller WT. Pulmonary edema as a complication of interleukin-2 therapy. *AJR* 1989; 152:749–52.
- [75] Hocking DC, Phillips PG, Ferro TJ, et al. Mechanisms of pulmonary edema induced by tumor necrosis factor-alpha. *Circ Res* 1990;67:68–77.
- [76] Kuei JH, Tashkin DP, Figlin RA. Pulmonary toxicity of recombinant human tumor necrosis factor. *Chest* 1989; 96:334–8.
- [77] Vial T, Descoates J. Clinical toxicity of cytokines used as hematopoietic growth factors. *Drug Saf* 1995; 13:371–406.
- [78] Rao SX, Ramaswamy G, Levin M, et al. Fatal acute respiratory failure after vinblastine-mitomycin therapy in lung carcinoma. *Arch Intern Med* 1985;145: 1905–7.
- [79] Hoelzer KL, Harrison BR, Luedke SW, et al. Vinblastine-associated pulmonary toxicity in patients receiving combination therapy with mitomycin and cisplatin. *Drug Intell Clin Pharm* 1986;20:287–9.