

Infiltrative lung diseases: Complications of novel antineoplastic agents in patients with hematological malignancies

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Infiltrative lung disease is a well-known complication of antineoplastic agents in patients with hematological malignancies. Novel agents are constantly being added to available treatments. The present review discusses different pulmonary syndromes, pathogenesis and management of these novel agents.

Key Words: *Chemotherapy; Pneumonitis; Pulmonary toxicity; Respiratory failure*

Pulmonary involvement is a common and challenging condition in patients with hematological malignancies. Infiltrative lung diseases as a result of antineoplastic agent-associated pulmonary toxicity are being increasingly recognized as a cause of lung disease in patients with hematological malignancies. New agents are constantly being added to the list of available antineoplastic agents. Old medications with new indications (eg, thalidomide for multiple myeloma) may also cause pulmonary disease. Although pulmonary toxicity due to the older antineoplastic agents (bleomycin, busulfan, cyclophosphamide, methotrexate, melphalan, cytarabine and carmustatin) is well known, significant pulmonary toxicity may occur with the newer antineoplastic agents. The present article reviews the infiltrative lung diseases induced by novel antineoplastic agents in patients with hematological malignancies. Bone marrow transplantation and related pulmonary toxicities are not included. Various terms and definitions have been used in the literature to describe pulmonary complications of antineoplastic agents. To have a more unified understanding, we divided the antineoplastic agent-associated infiltrative lung diseases into eight groups based on clinical and pathological manifestations: nonspecific interstitial pneumonitis/fibrosis; organizing pneumonia (OP); desquamative interstitial pneumonia (DIP); eosinophilic pneumonia; granulomatous pneumonitis; noncardiogenic pulmonary edema (NCPE) and acute respiratory distress syndrome (ARDS); diffuse alveolar hemorrhage (DAH); and retinoic acid syndrome (Tables 1 and 2). Although the differentiation among these groups is arbitrary and the conditions may overlap, these definitions provide a useful framework for the present review. It is also important to

Les maladies pulmonaires infiltrantes : Les complications de nouveaux antinéoplasiques chez des patients atteints de tumeurs hématologiques malignes

La maladie pulmonaire infiltrante est une complication bien connue des antinéoplasiques chez les patients atteints de tumeurs hématologiques malignes. De nouveaux agents s'ajoutent constamment aux traitements disponibles. La présente analyse porte sur divers syndromes pulmonaires, différentes pathogénèses et diverses prises en charge de ces nouveaux agents.

emphasize that these patterns of lung injury for many antineoplastic agents have been described in limited case reports or small case series. On the other hand, patients with hematological malignancies often have multiple comorbidities and establishing a cause and effect relationship between specific agents and lung disease is sometimes a difficult task.

ANTINEOPLASTIC AGENT-ASSOCIATED INFILTRATIVE LUNG DISEASES

Nonspecific interstitial pneumonitis/fibrosis

Pneumonitis is an inflammatory condition of the lungs that is characterized by alveolitis and infiltration of the lung interstitium. The etiology of interstitial pneumonitis includes noninfectious (eg, idiopathic, medications, inhalational exposures, collagen-vascular disorders) and infectious (bacterial, viral or fungal pneumonia) causes. Antineoplastic agents are known to cause interstitial pneumonitis (Table 1). The clinical manifestations of antineoplastic-associated pneumonitis (ANAP) are nonspecific and include fever, dyspnea, chest pain, sputum production, hemoptysis, hypoxemia, leukocytosis and pulmonary infiltrates. Because pneumonia presents with a similar clinical picture, infectious causes should be excluded in patients in whom drug-induced pneumonitis is suspected. Patients with hematological malignancy are generally immunosuppressed and are therefore susceptible to opportunistic infections. Other conditions that mimic ANAP include cardiogenic pulmonary edema, aspiration pneumonitis, DAH, radiation pneumonitis and pulmonary infiltration of malignant cells (1). Patients with hematological malignancies receiving chemotherapy are exposed to variety of other medications with

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TABLE 1
Agents associated with antineoplastic agent-associated pneumonitis

Agent	Class	Indications	Incidence	Clinical course
Anagrelide	Platelet-reducing agent	Essential thrombocytosis; polycythemia vera	0.70%	Pulmonary fibrosis after one year. Respiratory failure is rare, steroid therapy is effective
Anthracyclines	Cytotoxic antibiotics	Leukemia; lymphoma; multiple myeloma	Rare	Usually reported with concurrent use of other antineoplastic agents (bleomycin, vincristine, cyclophosphamide, chlorambucil). Steroid responsive
Azacitidine	Demethylating agent	Myelodysplastic syndrome	<5%	Respiratory failure is rare.
Bortezomib	Proteasome inhibitor	Multiple myeloma	15.2%	Pneumonitis usually occurs four to 12 days after the first cycle, High incidence has been reported in Japanese patients. Previous auto-stem cell transplant may be a risk factor. Steroids may reduce the risk of pneumonitis
Cladribine	Purine analogue	Hairy cell leukemia	Rare	Pneumonitis has been reported seven to 10 days after therapy. Steroid responsive
Dasatinib	Tyrosine kinase inhibitor	Chronic myelogenous leukemia	Rare	Steroid responsive
Fludarabine	Purine analogue	Non-Hodgkin's lymphoma; chronic lymphocytic leukemia	1.8% to 8.6%	Pneumonitis occurs days to weeks after therapy. Pneumonitis may occur after the first or subsequent therapies. Steroids are effective
Imatinib	Tyrosine kinase inhibitor	Chronic myelogenous leukemia	0.2% to 1.3%	Pneumonitis develops after first week of therapy and up to 9.5 months after treatment with imatinib
Interferon-alpha	Interferon	Chronic myelogenous leukemia; hairy cell leukemia; non-Hodgkin's lymphoma	1.5%	Subacute to chronic pneumonitis
Lenalidomide	Thalidomide derivative	Multiple myeloma; myelodysplastic syndrome	6%	Hypersensitivity-like pneumonitis with lymphocytic alveolitis
Procarbazine	Alkylating agent	Hodgkin's lymphoma	Rare	Procarbazine-induced pneumonitis is usually seen in association with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) Pneumonitis usually occurs during or after (five to seven days) the second or third cycle of procarbazine. Steroids are effective
Rituximab	Monoclonal antibody	B-cell malignancies	Rare	Pulmonary fibrosis is rare. Pneumonitis is usually seen in association with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
Thalidomide	Thalidomide	Multiple myeloma	Rare	Pulmonary fibrosis is rare
Tositumomab	Monoclonal antibody plus iodine-131	B-cell malignancies	Rare	Interstitial pneumonitis and severe hemorrhagic pneumonitis resulting in respiratory failure has been reported in patients
Trofosfamide	Alkylating agent	Lymphoma	Rare	Trofosfamide is metabolized to ifosfamide and to a lesser degree cyclophosphamide, which are known to have pulmonary toxic effects

potential pulmonary toxicity (eg, granulocyte-colony stimulating factor, amphotericin B and acyclovir) (2-5). Pulmonary disease due to these medications should be considered in the differential diagnosis. Because clinical, imaging and laboratory findings of ANAP are nonspecific and any of the above-mentioned conditions can mimic ANAP, ANAP is a diagnosis by exclusion (1).

The incidence of ANAP varies considerably and has been reported in 0.1% to 15% of treated patients in various phase II or phase III trials (Table 1) (6-57). Concurrent use of steroids does not necessarily prevent the development of ANAP, and severe cases of ANAP have been described with thalidomide, lenalidomide, rituximab, bortezomib and anthracyclines. Clinical symptoms range from mild dry cough and dyspnea on exertion to rapidly progressive disease and respiratory failure. Fever is a common finding. Skin rash and wheezing are less common, and when present, suggest a hypersensitivity reaction. Nonspecific systemic markers of inflammation including leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, and elevated C-reactive

protein are common. Peripheral eosinophilia and abnormal liver transaminases are uncommon and suggest a hypersensitivity reaction (6-57). Common computed tomography scan patterns are diffuse or patchy ground-glass opacities, diffuse reticular and reticulonodular pattern, focal or patchy consolidation, and multiple pulmonary nodules. Bronchoscopy is helpful in evaluation of patients with suspected ANAP. Bronchoalveolar lavage (BAL) and protected microbiology brush can be used to evaluate for infections. BAL cytology may also show viral cytopathic effects. Hypercellular BAL with neutrophilia or lymphocytosis is a common finding. Lung biopsy either by transbronchial technique or video-assisted thoracic surgery can be extremely helpful to demonstrate the presence of pneumonitis and exclude alternative diagnoses. Pathology findings include nonspecific pneumonitis, acute or chronic inflammatory interstitial infiltrates, fibrosis, vasculitis and scattered organizing pneumonia (6-57). ANAP is diagnosed when clinical and radiographic manifestations are compatible with ANAP and other potential causes are excluded.

The mainstay of management of ANAP is the cessation of the culprit agent. Corticosteroid treatment is guided by anecdotal data. Methylprednisolone 1 g/day for three days in patients with respiratory failure has been used. Lower doses of corticosteroids (methylprednisolone 60 mg every 6 h) may be considered in less severe cases of pneumonitis. Corticosteroid taper based on clinical response and improvement in oxygenation is a reasonable strategy (58). Other measures, including empirical treatment for infections until the culture results are available and maintaining euvolemic status, are also important in ANAP management.

OP

OP is a pathological diagnosis characterized by polypoid intraluminal plugs of proliferating fibroblasts and myofibroblasts within alveolar ducts and interstitial infiltrates. OP is a well-known type of drug-induced lung disease. OP presents clinically with fever, cough, dyspnea and pulmonary infiltrates on chest imaging. Exclusion of infection and lung biopsy are necessary for definitive diagnosis. Anthracyclines, cladribine, interferon-alpha, rituximab and thalidomide have been associated with OP. Cessation of culprit agent and systemic corticosteroids should result in rapid resolution of respiratory disease (21,59-66).

DIP

DIP is a less common form of lung pathology. DIP is mostly seen in smokers with idiopathic interstitial pneumonitis. DIP is characterized by uniform filling of distal airspaces by numerous pigmented alveolar macrophages. Multinucleated cells, eosinophils and lymphocytes are also present. The macrophages have abundant cytoplasm with finely granular dusty brown pigment. DIP-like pathology has been described with cladribine, interferon-alpha and rituximab. Lung biopsy is necessary for diagnosis. Cessation of culprit agent and systemic corticosteroids are mainstays of therapy (21,67).

Eosinophilic pneumonia

Eosinophilic pneumonia is characterized by fever, bilateral infiltrates on chest radiograph, hypoxemia and alveolar eosinophilia. Chest auscultation may reveal bibasilar/diffuse crackles or transient wheezing. Interstitial infiltrates on chest imaging usually progress to extensive alveolar and interstitial infiltrates. Leukocytosis with neutrophilia or eosinophilia is common. Cladribine, fludarabine and interferon-alpha can rarely cause eosinophilic pneumonia. Eosinophilic pneumonia is steroid responsive (68-71).

Granulomatous pneumonitis

Granulomatous pneumonitis is seen in hypersensitivity-like pneumonitis and sarcoidosis. Loose non-necrotizing granulomas are described in hypersensitivity-like pneumonitis induced by fludarabine, rituximab and trofosamide (22,24,26,34,37-41). Sarcoid-like disease is an uncommon complication of interferon therapy. Mediastinal lymphadenopathy, pulmonary infiltrate and noncaseating granulomas similar to sarcoidosis may develop after interferon therapy. Interferon-induced sarcoidosis tends to resolve after cessation of interferon therapy (72-75).

NCPE and ARDS

NCPE is a nonspecific term that is used to describe pulmonary edema not associated with heart failure. NCPE is caused by fluid retention and increased capillary leak caused by cytokine

TABLE 2
Agents associated with infiltrative lung diseases

Organizing pneumonia
Anthracyclines
Cladribine
Interferon-alpha
Rituximab
Thalidomide
Desquamative interstitial pneumonia
Cladribine
Interferon-alpha
Rituximab
Eosinophilic pneumonia
Cladribine
Fludarabine
Interferon-alpha
Granulomatous pneumonitis
Fludarabine
Interferon-alpha
Rituximab
Trofosamide
Noncardiogenic pulmonary edema/acute respiratory distress syndrome
All-trans retinoic acid
Alemtuzumab
Arsenic trioxide
Cladribine
Cyclosporine
Dasatinib
Decitabine
Gemtuzumab
Imatinib
Interferon-alpha
Pentostatin
Diffuse alveolar hemorrhage
All-trans retinoic acid
Gemtuzumab
Rituximab
Retinoic acid syndrome
All-trans retinoic acid
Arsenic trioxide

release. Pathology shows dilated lymphatic channels, alveolar septal edema, peribronchial edema, pleural effusion, pericardial effusion and occasionally ascites. Hydration with 5% dextrose that is commonly performed before and after administration of some antineoplastic agents (eg, pentostatin) may contribute to formation of pulmonary edema. Pentostatin is a potent adenosine deaminase inhibitor used in the treatment of hairy cell leukemia. Fatal pulmonary edema and respiratory distress have been observed after pentostatin therapy especially in combination with fludarabine, carmustatin, etoposide, rituximab and high-dose cyclophosphamide (76-80). Decitabine is a new demethylating agent indicated in the management of patients with myelodysplastic syndrome. In a phase III trial (81), an increased incidence of pulmonary edema was reported (6% versus 0% in the placebo group). Imatinib results in fluid retention and pulmonary edema. Imatinib inhibits platelet-derived growth factor, which regulates fluid absorption in the intestines (51). Dasatinib is associated with pulmonary edema in approximately 4% of treated patients. Fluid retention may also lead to pleural

effusion, pericardial effusion and ascites (47). The role of steroids in the management of NCPE is unknown. Supportive care and diuresis are the main therapeutic strategies.

ARDS as a severe type of NCPE has also been described as a potential complication of antineoplastic agents. Two types can be distinguished: lung injury and severe interstitial pneumonitis, and respiratory failure as a manifestation of infusion-related reactions. Cyclosporine (82), all-trans retinoic acid (ATRA) (83), arsenic trioxide (84) and bortezomib (10) are associated with lung injury and diffuse alveolar damage that may present clinically as ARDS. Cyclosporine is used in the treatment of T-cell large granular lymphocyte leukemia. A high concentration of cyclosporine in pulmonary circulation after administration through a central line has been associated with development of lung injury and ARDS (82,85-87). Severe pneumonitis resulting in ARDS can be seen with anagrelide (9), azacytidine (17), cladribine (21), interferon-alpha (18), procarbazine (33), rituximab (37) and tositumomab (19,20). Infusion-related reactions occur during or shortly after infusion of some antineoplastic agents (eg, monoclonal antibodies, anthracyclines). Clinical manifestations include fever, cough, dyspnea, wheezing, skin rash, vomiting and hypotension. Alemtuzumab and gemtuzumab ozogamicin infusion-related reactions may also be complicated by pulmonary infiltrates and ARDS (88-90). Alemtuzumab is an anti-CD52 monoclonal antibody and is indicated in the treatment of chronic lymphocytic leukemia. Gemtuzumab ozogamicin is an anti-CD33 monoclonal antibody conjugated to a modified antitumour antibiotic, calicheamicin. This agent is active against CD33-positive acute myelogenous leukemia. Infusion-related reactions due to cytokine release are common (33%). Severe cases of ARDS have been described within a day of the gemtuzumab ozogamicin 2 h infusion. Leukocyte counts above $60 \times 10^9/L$ has been observed in these patients. Reduction of peripheral blasts to below $30 \times 10^9/L$ with hydroxyurea or leukopheresis before gemtuzumab ozogamicin infusion may prevent this potentially fatal pulmonary complication (91,92).

DAH

DAH is characterized by hemorrhagic BAL return and presence of hemosiderin-laden macrophages in BAL. The clinical presentations are nonspecific and include fever, dyspnea and hemoptysis. ATRA, gemtuzumab and rituximab rarely induce DAH. High-dose steroids are used in the treatment of drug-induced DAH (93-94).

Retinoic acid syndrome

ATRA and arsenic trioxide are effective therapies for acute promyelocytic leukemia (APL). Retinoic acid syndrome occurs two to 21 days after ATRA induction therapy in approximately 25% of patients. Fever, weight gain, generalized edema, respiratory distress, alveolar hemorrhage, renal failure, pericardial effusion, pleural effusions, cervical lymphadenopathy, intermittent hypotension, thromboembolism and intracranial hemorrhage are common clinical manifestations. A syndrome identical to retinoic acid syndrome occurs in approximately 30% of APL patients treated with arsenic trioxide. Retinoic acid syndrome occurs only during induction therapy. Retinoic acid syndrome has not been observed in postremission arsenic trioxide or ATRA therapies. Mortality for ATRA- and arsenic trioxide-induced retinoic acid syndrome are 4.5% and 1.4%, respectively (95-104).

Chest imaging shows diffuse infiltrates, peripheral small nodules, consolidations or pulmonary edema. Pulmonary pathological findings include alveolar hemorrhage, pulmonary capillaritis, intra-alveolar myeloid cell infiltration, alveolar septal edema, diffuse alveolar damage and fibrinous exudates. ATRA and arsenic trioxide induce differentiation of APL cells to more mature cells in vitro and in vivo. This differentiation is thought to contribute to leukocytosis seen after initiation of the therapy. High peripheral leukocyte count was suggested as a possible risk factor for development of retinoic acid syndrome. This pharmacological cell differentiation may induce production and release of granulocyte-macrophage colony stimulating factor and cytokines like interleukin-1, tumour necrosis factor-alpha, interleukin-6 and interleukin-8. These cytokines have been suggested to contribute to pulmonary toxicity in retinoic acid syndrome. Prior corticosteroid therapy (eg, prednisone 30 mg) may reduce the risk for retinoic acid syndrome. Systemic corticosteroids such as dexamethasone are the mainstay of therapy (95-104).

OTHER PULMONARY TOXICITIES

Bronchospasm during or shortly after administration of alemtuzumab (88), anthracyclines (16), gemtuzumab (92), interferon-alpha (29), L-asparaginase (105), nelarabine (76) and rituximab (106) can occur. Pleural effusion can also occur as a pulmonary complication of antineoplastic agents and has been reported with all-trans retinoic acid (95-104), clofarabine (17), dasatinib (47), imatinib (107), interferon-alpha (29) and nelarabine (76). Because granulocyte and granulocyte-macrophage colony stimulating factors are used commonly in cancer patients on chemotherapy, granulocyte and granulocyte-macrophage colony stimulating factors-induced lung toxicity should be considered as part of the differential diagnosis. Acute interstitial pneumonitis and NCPE have been associated with use of granulocyte and granulocyte-macrophage colony stimulating factors mainly in patients with non-Hodgkin's lymphoma (108-110).

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