

Respiratory Failure in Cancer Patients: Non-Infectious Complications of Antineoplastic Agents for Solid Tumors

Bobbak Vahid* and Paul E. Marik

Thomas Jefferson University Hospital, Department of Pulmonary and Critical Care Medicine, Philadelphia, USA

Abstract: Chemotherapy-induced respiratory failure is being increasingly recognized as a cause of respiratory failure in the intensive care unit. The frequency of chemotherapy-induced respiratory failure is low, however with increasing number of patients receiving new chemotherapeutic agents more cases can be expected to be seen. Chemotherapy-induced respiratory failure can be due to bronchospasm and hypersensitivity reactions, pulmonary hemorrhage, interstitial pneumonitis, eosinophilic pneumonia, and non-cardiogenic pulmonary edema. Pulmonary and critical care physicians should be aware of the clinical presentation of chemotherapy-induced respiratory failure.

Keywords: Pulmonary toxicity, pneumonitis, respiratory failure, chemotherapy.

INTRODUCTION

Chemotherapy-induced respiratory failure is being increasingly recognized as a cause of respiratory failure in the intensive care unit. The frequency of chemotherapy-induced respiratory failure is low, but with increasing number of the patients receiving new chemotherapeutic agents more cases can be expected to be seen. Chemotherapy-induced respiratory failure can be due to bronchospasm and hypersensitivity reactions, pulmonary hemorrhage, interstitial pneumonitis, eosinophilic pneumonia, and non-cardiogenic pulmonary edema. Since more patients are being treated with new chemotherapeutic agents and regimens, associated acute respiratory failure can be expected to be increasingly recognized as a cause of acute respiratory distress syndrome (ARDS) in the intensive care unit. Clinicians should be aware of the clinical and radiographic presentation of chemotherapy-induced respiratory failure. Unfortunately, the diagnosis is complicated by an extensive differential diagnosis (pneumonia, cardiogenic pulmonary edema, etc). Physical examination, routine laboratory work-up, and radiographic findings are usually non-specific and do not allow for a definitive diagnosis. Bronchoscopy or open lung biopsy may be necessary in selected cases to establish the diagnosis. Chemotherapy-induced respiratory failure should be considered in all patients receiving chemotherapeutic agents. Cessation of the presumed culprit agent and treatment with systemic corticosteroids may result in resolution of respiratory failure [1, 2]. The major categories of chemotherapy induced respiratory failure are reviewed below.

INTERSTITIAL PNEUMONITIS

Several solid tumor antineoplastic agents are known to cause interstitial pneumonitis (Table 1). The incidence of chemotherapy-induced pneumonitis ranges roughly from 0.5% to 10% [3-37]. The combination of two or more agents may have synergistic effect and higher a frequency of pneumonitis can be expected. The risk factors for chemotherapy-induced pneumonitis are not well understood [5, 38]. Pre-

existing lung disease, smoking, and radiotherapy are possible risk factors [38, 39]. A high inspired oxygen concentration ($FiO_2 > 0.5$) may potentiate mitomycin-induced pneumonitis [21].

The clinical manifestations of chemotherapy-induced pneumonitis are nonspecific and include cough, fever, dyspnea, and hypoxemia. Rapid progression to respiratory failure and ARDS is not uncommon. The timing of clinical presentation is unpredictable. Most patients develop interstitial pneumonitis within 8 weeks after chemotherapy. Pre-medication with or concurrent treatment with corticosteroids may not prevent the development of interstitial pneumonitis. Leukocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein are common. Chest imaging may show diffuse or patchy ground-glass opacities or consolidations (Fig. 1). Unilateral pulmonary infiltrates do not exclude the diagnosis of drug-induced pneumonitis [1-38]. Bronchoscopy with bronchoalveolar lavage (BAL) plays an important role in the evaluation of patients with suspected chemotherapy-induced pneumonitis. BAL cell count may show a neutrophilia, lymphocytosis, or rarely eosinophilia. Bronchoscopy is also necessary to exclude infectious pneumonitis and pneumonia. The presence of malignant cell in BAL may suggest lymphangitic carcinomatosis. Elevated serum Krebs von den Lunge-6 (KL-6) levels have been reported in about 50% of patients with drug-induced pneumonitis. KL-6 is a mucin-like glycoprotein that is expressed by type II alveolar pneumocytes. Elevated levels of KL-6 however can also be seen in idiopathic interstitial pneumonitis, pneumonitis related to collagen vascular disease, hypersensitivity pneumonitis, radiation pneumonitis, viral pneumonia, pneumocystis pneumonia, and sarcoidosis [40-42]. 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.

ORGANIZING PNEUMONIA

Organizing pneumonia (OP) is a well known manifestation of drug-induced lung disease. The clinical manifestations OP are similar to bacterial pneumonia, namely fever, cough, dyspnea, and consolidation of chest imaging. The

*Address correspondence to this author at the Thomas Jefferson University 834 Walnut Street Suite 650, Philadelphia, PA 19107, USA; Tel: 215 9556591; Fax: 215 9550830; E-mail: bobbak.vahid@mail.tju.edu

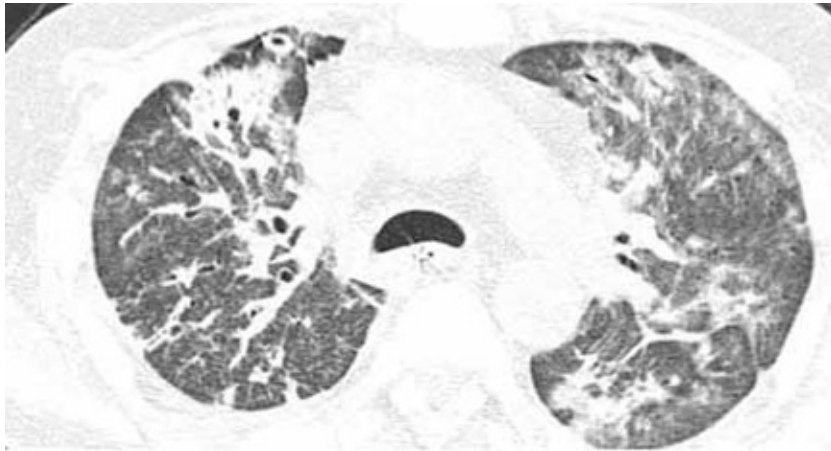


Fig. (1). A computed tomography scan of the chest showing bilateral diffuse pulmonary infiltrates in a patient with thalidomide-induced lung toxicity.

Table1. Classification and Agents Associated with Chemotherapy-Induced Respiratory Failure

| | |
|---------------------------------|---|
| Pneumonitis | Chlorozotocin Erlotinib Etoposide Everolimus Gefitinib Gemcitabine Ifosfamide Irinotecan Mitomycin-C Mitoxantrone Piritrexim Taxanes Temozolomide Temsirrolimus Thalidomide Topotecan Trastuzumab |
| Organizing pneumonia | Doxorubicin Thalidomide Teniposide Topotecan Trastuzumab |
| Non-cardiogenic pulmonary edema | Erlotinib Etoposide Irinotecan Gemcitabine Mitomycin-C Trastuzumab |
| Pulmonary Hemorrhage | Bevacizumab Gefitinib Gemcitabine Mitomycin-C |
| Severe Infusion Reaction | Etoposide Gemcitabine Oxaliplatin Matuzumab Mitomycin-C Taxanes Teniposide astuzumab |

lung biopsy shows polypoid intraluminal plugs of proliferating fibroblasts and myofibroblasts within alveolar ducts and interstitial infiltrates. Doxorubicin, thalidomide, teniposide, topotecan, and trastuzumab have been reported as a cause of OP. Cessation of culprit agent and systemic corticosteroids should result in rapid resolution of respiratory disease [43-46].

NON-CARDIOGENIC PULMONARY EDEMA

Non-cardiogenic pulmonary edema (NCPE), acute lung injury, and ARDS are described after presumed chemotherapy-induced lung injury. The mechanisms of lung injury are not well understood. Systemic release of cytokines (gemcitabine), direct injury to the alveolar epithelium (etoposide, mitomycin, irinotecan), hypersensitivity reactions (etoposide, mitomycin) and impairment of alveolar repair by type II pneumocytes (erlotinib, trastuzumab) are suggested [9, 20, 38, 39, 47]. Elevated BAL neutrophils and diffuse alveolar damage with fibrin membrane formation may be found [32, 47-50]. Supportive care is mainstay of treatment. The role of corticosteroids is not clear.

PULMONARY HEMORRHAGE

Diffuse alveolar hemorrhage (DAH) is characterized by bloody BAL return and the presence of hemosiderin-laden macrophages in BAL. The clinical presentation is nonspecific and includes fever, dyspnea, and hemoptysis. Drug-induced DAH has been described with gefitinib, gemcitabine, and mitomycin-C [7, 38, 51]. Pulmonary hemorrhage and hemoptysis has been reported in 2.3% of patients with non-squamous non-small cell lung cancer treated with bevacizumab. In these patients pulmonary hemorrhage may lead to respiratory failure and fatalities. Pulmonary hemorrhage associated with bevacizumab is more common in patients with squamous cell carcinoma and has been reported in 31% of patients [52-54]. Diffuse alveolar hemorrhage as a manifestation of mitomycin-C induced hemolytic-uremic-like syndrome is rare [51].

INFUSION REACTIONS

Bronchospasm and hypersensitivity reaction (angioedema, rash, urticaria, hypotension, arthralgia, nausea, vomiting, hypotension or hypertension) during infusion or shortly

thereafter (within minutes) are potentially fatal complications of several chemotherapeutic agents (Table 1). These infusion reactions are usually self limited (less than 24 hours). Premedication with anti-histamines and corticosteroids may prevent infusion-related reactions. The incidence of infusion-related reactions is usually higher than the incidence of interstitial pneumonitis. Oxaliplatin infusion-related reactions occur with frequency of 1.3%. Patients become symptomatic within 5 to 50 minutes after starting oxaliplatin infusion. Hypertensive crisis resulting in change in mental status is particularly common with oxaliplatin infusion-related reactions [55]. Mitomycin-infusion results in bronchospasm in about 5% patients [47]. Hypersensitivity reaction to teniposide has been reported in 3.6% to 6.5% of patients. Clinical manifestations develop within first 10 to 20 minutes of teniposide infusion. It is interesting to note that in patients with leukemia, infusion reactions tend to occur after completion of the infusion. The timing of infusion-related reactions are unpredictable and may occur during the first or subsequent treatment cycles [56]. Monoclonal antibodies may also cause hypersensitivity reactions. Bronchospasm related to matuzumab has been reported in 5% of patients and less than 1% of matuzumab infusions. Infusion-related symptoms due to trastuzumab can be seen in 15% of the patients. Severe episodes of hypotension, bronchospasm and hypoxemia leading to death are rare [57, 58].

DIAGNOSIS

The diagnosis of chemotherapy-induced respiratory failure is complicated. Pneumonia, cardiogenic pulmonary edema, aspiration, lymphangitic carcinomatosis, radiation pneumonitis and adult respiratory distress syndrome secondary to sepsis should be excluded before considering the diagnosis of chemotherapy-induced respiratory failure. Blood culture, serum serology, echocardiogram, and bronchoscopy are important to exclude infections (bacterial, viral, fungal), heart failure, and lymphangitic carcinomatosis. Open lung biopsy in selected cases can be helpful to exclude alternative diagnoses and establishing the diagnosis of pneumonitis.

MANAGEMENT

The mainstay of drug-induced pneumonitis is the cessation of the presumed culprit agent. There are no data to guide corticosteroids treatment in chemotherapy-induced pneumonitis. Methyl-prednisolone 1 gm a day for 3 days in patients with respiratory failure can be used. Lower doses of corticosteroids (methyl-prednisolone 60 mg every 6hours) may be used in less severe cases of pneumonitis [1, 2]. We taper the corticosteroids based on clinical response and improvement in oxygenation.

REFERENCES

- [1] Higenbottam T, Kuwano K, Nemery B, *et al.* Understanding the mechanism of drug-associated interstitial lung disease. *Br J Cancer* 2004; 91(Suppl 2): S31-S37.
- [2] Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer* 2004; 91(Suppl 2): S18-S23.
- [3] Sordillo EM, Sordillo PP, Stover D, *et al.* Chlorozotocin(DCNU)-induced pulmonary toxicity. *Cancer Clin Trials* 1981; 4: 397-399.
- [4] Leimgruber K, Negro R, Baier S, *et al.* Fatal interstitial pneumonitis associated with docetaxel administration in a patient with hormone-refractory prostate cancer. *Tumori* 2006; 92: 542-544.
- [5] Kouroussis C, Mavroudis D, Kakolyris S, *et al.* High incidence of pulmonary toxicity of weekly docetaxel and gemcitabine in patients with non-small cell lung cancer: results of a dose-finding study. *Lung Cancer* 2004; 44: 363-368.
- [6] Inoue A, Saijo Y, Maemondo M *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; 361: 137-139.
- [7] Ohyanagi F, Ando Y, Nagashima F *et al.* Acute gefitinib-induced pneumonitis. *Int J Clin Oncol* 2004; 9: 406-409.
- [8] Sumpter K, Harper-Wynne C, O'Brien M *et al.* Severe acute interstitial pneumonia and gefitinib. *Lung Cancer* 2004; 43: 367-368.
- [9] Gupta N, Ahmed I, Steinberg H, *et al.* Gemcitabine-induced pulmonary toxicity. *Am J Clin Oncol* 2002; 25: 96-100.
- [10] Roychowdhury DF, Cassidy CA, Peterson P, *et al.* A report on serious pulmonary toxicity associated with gemcitabine-based therapy. *Investigational New Drugs* 2002; 20: 311-315.
- [11] Baker WJ, Fistel SJ, Jones RV, *et al.* Interstitial pneumonitis associated with ifosfamide therapy. *Cancer* 1990; 65: 2217-2221.
- [12] Chen YM, Shih JF, Lee CS, *et al.* Phase II study of docetaxel and ifosfamide combination chemotherapy in non-small-cell lung cancer patients failing previous chemotherapy with or without paclitaxel. *Lung cancer* 2003; 39: 209-214.
- [13] Tammaro KA, Baldwin PD, Lundberg AS. Interstitial lung disease following erlotinib (Tarceva) in a patient who previously tolerated gefitinib (Iressa). *J Oncol Pharm Pract* 2005; 11: 127-130.
- [14] Herbst R S, prager D, Hermann R, *et al.* TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005; 23: 5892-5899.
- [15] Shepherd F A, Rodrigues Pereira J, Ciuleanu T, *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353: 123-132.
- [16] Vahid b, Esmaili A. Erlotinib-associated acute pneumonitis: Report of two cases. *Canadian Respir J* 2007; 14: 167-170.
- [17] Ohnishi K, Sakai F, Kudoh S, *et al.* Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib. *Leukemia* 2006; 20: 1162-1164.
- [18] Lin JT, Yeh KT, Fang HY, *et al.* Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; 47: 1693-1695.
- [19] Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; 79: 80-81.
- [20] Michielin O, Udry E, Periard D, *et al.* Irinotecan-induced interstitial pneumonia. *Lancet Oncol* 2004; 5: 322-324.
- [21] Orwoll ES, Kiessling PJ, Patterson JR. Interstitial pneumonia from mitomycin. *Ann Intern Med* 1978; 89: 352-355.
- [22] Linette DC, McGee KH, McFarland JA. Mitomycin-induced pulmonary toxicity: Case report and review of the literature. *Ann Pharmacother* 1992; 26: 481-484.
- [23] Tomlinson J, Tighe M, Johnson S, *et al.* Interstitial pneumonitis following mitozantrone, chlorambucil and prednisolon (MCP) chemotherapy. *Clin Oncol* 1999; 11: 184-186.
- [24] Pasetto LM, Monfardini S. Is acute dyspnea related to oxaliplatin administration? *World J Gastroenterol* 2006; 12: 5907-5908.
- [25] Yague XH, Soy E, Merino BQ, *et al.* Interstitial pneumonitis after oxaliplatin treatment in colorectal cancer. *Clin Transl Oncol* 2005; 7: 515-517.
- [26] Roth BJ, Manola J, Dreicer R, *et al.* Piritrexim in advanced, refractory carcinoma of the urothelium (E3896): A phase II trial of the Eastern Cooperative Oncology Group. *Invest New Drugs* 2002; 20: 425-429.
- [27] de Wit R, Verweij J, Slingerland R, *et al.* Piritrexim-induced pulmonary toxicity. *Am J Clin Oncol* 1993; 16: 146-148.
- [28] Shitara K, Ishii E, Kondo M, *et al.* Suspected paclitaxel-induced pneumonitis. *Gastric Cancer* 2006; 9: 325-328.
- [29] Suzuki N, Hiraki A, Takigawa N, *et al.* Severe interstitial pneumonia induced by paclitaxel in a patient with adenocarcinoma of the lung. *Acta Med Okayama* 2006; 60: 295-298.
- [30] Abrey LE, Oslon JD, Raizer JJ, *et al.* A phase II trial of temozolomide for patients with recurrent or progressive brain metastasis. *J Neuro-oncol* 2001; 53: 259-265.
- [31] Brandwein JM, Yang L, Schimmer AD, *et al.* A phase II study of temozolomide therapy for poor-risk patients aged ≥60 years with acute myeloid leukemia: low levels of MGMT predict for response. *Leukemia* 2007; 21: 821-824.

- [32] Vahid B, Mehrotra A. Trastuzumab (Herceptin)-associated lung injury. *Respirology* 2006; 11: 655-658.
- [33] Zimmerman MS, Ruckdeschel JC, Hussain M. Chemotherapy-Induced Interstitial Pneumonitis During Treatment of Small Cell Anaplastic Lung Cancer. *J Clin Oncol* 1984; 2: 396-405.
- [34] Atkins MB, Hidalgo M, Stadler WM, *et al.* Randomized phase II study of multiple dose levels of CCI-779, a novel Mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004; 22: 909-918.
- [35] Rothenburger M, Teerling E, Bruch C, *et al.* Calcineurin inhibitor-free immunosuppression using Everolimus (Certican) in maintenance heart transplant recipients: 6 months' follow-up. *J Heart Lung Transplant* 2007; 26: 250-257.
- [36] Iguchi T, Sakoda M, Chen CK, *et al.* Interstitial pneumonia during treatment with thalidomide in a patient with multiple myeloma. *Rinsho Ketsueki* 2004; 45: 1064-1066.
- [37] Onozawa M, Hashino S, Sogabe S, *et al.* Side effects and good effects from new chemotherapeutic agents. Case 2. Thalidomide-induced interstitial pneumonitis. *J Clin Oncol* 2005; 23: 2425-2426.
- [38] Barlési F, Villani P, Doddoli C, *et al.* Gemcitabine-induced severe pulmonary toxicity. *Fundam Clin Pharmacol* 2004; 18: 85-91.
- [39] Takano T, Ohe Y, Kusumoto M, *et al.* Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer* 2004; 45: 93-104.
- [40] Kobayashi J, Kitamura S. KL-6: a serum marker for interstitial pneumonia. *Chest* 1995; 108: 311-315.
- [41] Ohnishi H, Yokoyama A, Yasuhara Y, *et al.* Circulating KL-6 levels in patients with drug induced pneumonitis. *Thorax* 2003; 58: 872-875.
- [42] Kobayashi J, Kitamura S. Serum KL-6 for the evaluation of active pneumonitis in pulmonary sarcoidosis. *Chest* 1996; 109: 1276-1282.
- [43] Tsao YT, Dai MS, Chang H, *et al.* Bronchiolitis obliterans organizing pneumonia presenting as hemoptysis in a patient of Hodgkin's lymphoma undergoing chemotherapy. *J Med Sci* 2006; 26: 115-118.
- [44] Jacobs C, Slade M, Lavery B. Doxorubicin and BOOP. A possible near fatal association. *Clin Oncol* 2002; 14: 262.
- [45] Radzikowska E, Szczepulska E, Chabowski M, Bestry I. Organising pneumonia caused by trastuzumab (herceptin) therapy for breast cancer. *Eur Respir J* 2003; 21: 552-555.
- [46] Edgerton CC, Gilman M, Roth BJ. Topotecan-induced bronchiolitis. *South Med J* 2007; 97: 699-701.
- [47] Okuno SH, Frytak S. Mitomycin lung toxicity. Acute and chronic phase. *Am J Clin Oncol* 1997; 20: 282-284.
- [48] Marruchella A, Fiorenzano G, Merizzi A, *et al.* Diffuse alveolar damage in a patient treated with gemcitabine. *Eur Respir J* 1998; 11: 504-506.
- [49] Maitland ML, Wilcox R, Hogarth DK, *et al.* Diffuse alveolar damage after a single dose of topotecan in a patient with pulmonary fibrosis and small cell cancer. *Lung Cancer* 2006; 54: 243-245.
- [50] Okamoto I, Fujii K, Matsumoto M, *et al.* Diffuse alveolar damage after ZD 1839 therapy in a patient with non-small cell lung cancer. *Lung Cancer* 2003; 40: 339-342.
- [51] Torra R, Poch E, Torras A, *et al.* Pulmonary hemorrhage as a clinical manifestation of hemolytic-uremic syndrome associated with mitomycin C therapy. *Chemotherapy* 1993; 39: 453-456.
- [52] Johnson DH, Fehrenbacher L, Novotny WF, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; 22: 2184-2191.
- [53] Sandler A, Gray R, Perry MC, *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355: 2542-2550.
- [54] Herbst RS, Sandler AB. Non-small cell lung cancer and antiangiogenic therapy: what can be expected of bevacizumab? *Oncologist* 2004; 9 (Suppl 1): 19-26.
- [55] Lee MY, Yang MH, Liu JH, *et al.* Severe anaphylactic reactions in patients receiving oxaliplatin therapy: a rare but potentially fatal complication. *Support Cancer Care* 2007; 15: 89-93.
- [56] O'Dwyer PJ, King SA, Fortner CL, *et al.* Hypersensitivity Reactions to Teniposide (VM-26): An Analysis. *J Clin Oncol* 1986; 8: 1262-1269.
- [57] Kollmannsberger C, Schttenhelm M, Honecker F, *et al.* A phase I study of the humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody EMD 72000 (Matuzumab) in combination with paclitaxel in patients with EGFR-positive advanced non-small-cell lung cancer (NSCLC). *Ann Oncol* 2006; 17: 1007-1013.
- [58] Tripathy D, Slamon DJ, Cobleigh M, *et al.* Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 2004; 22: 1063-1070.