# Pulmonary toxicity and cancer treatment

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***Pulmonary toxicity is a serious potential complication of the use of cytotoxic drugs that can be debilitating and life threatening. Rapid recognition of this problem and its management are critical if morbidity is to be limited. This article discusses the mechanisms, common clinical features and risk factors for cytotoxic drug-induced pulmonary toxicity, and outlines general management principles.***

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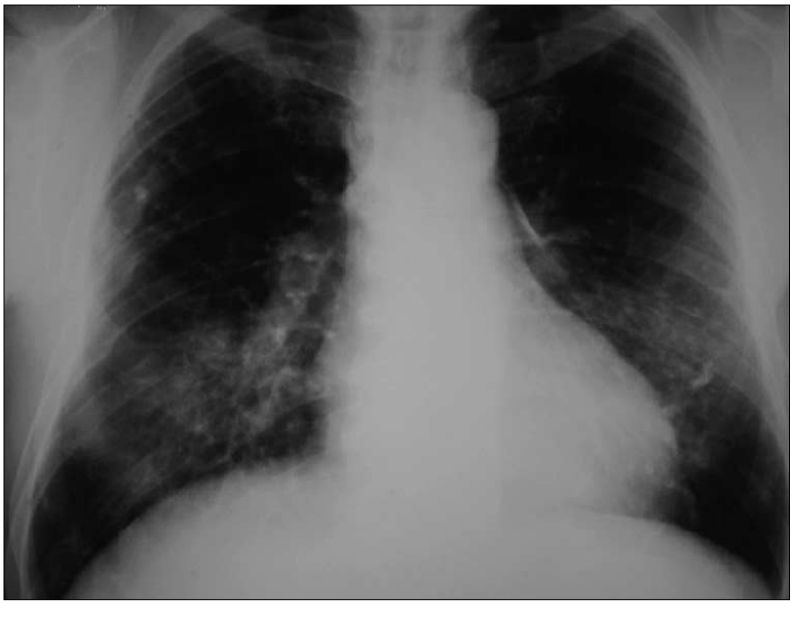
Cytotoxic drugs are the mainstay of treatment of metastatic solid tumours and haematological malignancies. They are associated with a common spectrum of adverse effects as detailed below.

## BLEOMYCIN-INDUCED INTERSTITIAL PNEUMONITIS

The alkylating agent bleomycin is a polypeptide antibiotic originally discovered in 1966 by Umezawa et al, and is used as part of standard therapy for treatment of germ cell tumours, often in combination with platinum and etoposide. Bleomycin has long been known to cause interstitial pneumonitis (BIP) (Rudders and Hensley, 1973) and this is the most thoroughly studied form of chemotherapy-induced lung toxicity. The incidence of BIP is 10%, with a fatality rate of between 1 and 2%.

***Figure 1. A chest radiograph from a patient with irinotecan-induced interstitial pneumonitis. A typical pattern of bilateral interstitial shadowing is seen.***



Two clinical forms of BIP have been described (Samuels et al, 1976). There is an early minimal form associated with exertional dyspnoea in up to 90% of patients, non-productive cough in 50–93% of patients and pyrexia in up to 80%, but physical examination and arterial oxygen saturations may be normal and radiographic features minimal. The late onset form is more severe with dyspnoea and low arterial oxygen saturation at rest, with prominent radiographic features.

Accumulation of the radionucleotide gallium-67 (Richman et al, 1975) has been shown to correlate with clinical severity, but is not used in routine clinical practice. There is anecdotal evidence that corticosteroids can reduce the degree of lung injury associated with BIP. Changes on chest X-ray can take up to 9 months to clear (*Figure 1*). Biopsy is commonly indicated and reveals a fibrosing alveolitis. BIP and pulmonary injury induced by other cytotoxic drugs arise from a combination of at least three key processes:

1. Oxidant injury and immune activation. Reactive oxygen species generated during activation of phagocytes lead to fatty acid oxidation, destabilization of cellular membranes and cell cytotoxicity. This is thought to result in the damage of pulmonary capillary endothelial cells and type I pneumocytes. Oxidant damage can directly initiate the inflammatory process.
2. Dysfunction of the matrix repair system. Chemotherapy-induced drug injury results in interstitial structural impairment as a result of excessive deposition of collagen by fibroblasts, and alteration of fibroblast proliferation.
3. Phagocyte proteolytic enzymes. Activated monocytes and neutrophils release proteolytic enzymes. Lung injury is associated

with promotion of reactive oxygen species-associated inhibition of proteolytic enzyme inhibitors. The disruption of homeostasis leads to lung damage as a result of unopposed action of these damaging proteolytic enzymes.

**Risk factors for BIP**

BIP is related to the duration of therapy (Holoye et al, 1976), prior radiotherapy (Samuels et al, 1976), age, bolus *vs* continuous infusion, dose >450 units (Parvinen et al, 1983), and cigarette smoking (Senan et al, 1992). Renal dysfunction has been suggested to be a risk factor for BIP (Dalgleish et al, 1984; van Barneveld et al, 1984; Kawai et al, 1998). Furthermore, co-administration of cisplatin also increases the risk of BIP. Oxygen therapy can increase lung injury caused by bleomycin, as a result of exacerbation of free radical damage (Ingrassia et al, 1991). Some studies have suggested exacerbation of BIP by granulocyte colony stimulating factor (G-CSF) (Matthews, 1993; Yokose et al, 1998) but this is a contentious area as other studies have failed to demonstrate an association of G-CSF with BIP (Saxman et al, 1997).

## GEMCITABINE-ASSOCIATED PULMONARY TOXICITY

Gemcitabine, a pyrimidine analogue of deoxycytidine, is widely used in the treatment of both haematological and solid malignancies including non-small cell lung, pancreatic and ovarian cancers. Estimated worldwide use in 2002 was 217 400 patients. Gemcitabine is associated an uncommon but serious interstitial pneumonitis that has been associated with fatality, and which develops rapidly within 72 hours. The incidence has been estimated at between 0.02% and 0.06% (Roychowdhury et al, 2002). In a series of three cases, typical radiological features on computed tomography (CT) were bilateral ground glass opacities, thickened septal lines and bilateral septal lines (Boiselle et al, 2000). Gemcitabine-induced lung damage is typically reversible with steroids if recognized early (Joerger et al, 2002).

Gemcitabine is commonly prescribed in a platinum-based doublet for the treatment of non-small cell lung cancer; platinum resistance may be common, and there is currently interest in exploring the efficacy of non-platinum containing combinations in this malignancy. Use of a combination of docetaxel and gemcitabine has been explored in a weekly schedule, but is associated with significant pulmonary toxicity (Dunsford et al, 1999).

Pulmonary toxicity associated with administration of docetaxel and thalidomide in treatment of hormone-refractory prostate cancer has been observed (Behrens et al, 2003). Four presentations associated with lung injury are:

- Interstitial pneumonitis
- Dyspnoea without objective pathological findings
- Pulmonary embolus
- Pleural effusion.

## OTHER CYTOTOXIC DRUGS AND PULMONARY TOXICITY

Irinotecan is a topoisomerase 1 inhibitor used extensively for the treatment of metastatic colon cancer, which has been linked to pulmonary toxicity (Madarnas et al, 2000). In early clinical studies in Japan, progressive deterioration followed by death was typical, with no response to corticosteroids. Dyspnoea and cough have been described in 20% of patients in American studies with irinotecan (Madarnas et al, 2000). Pre-existing pulmonary dysfunction may predispose to irinotecan-induced lung injury.

Procarbazine has been used in cytotoxic drug combinations with particularly high activity in the treatment of Hodgkin's disease. However, the lung damage arising from procarbazine is often severe and irreversible (Mahmood and Mudad, 2002). Fludarabine has also been associated with pulmonary toxicity, occuring with an incidence of 8.6% (Helman et al, 2002). Fludarabine-induced interstitial pneumonitis is corticosteroid responsive (Helman et al, 2002; Mahmood and Mudad, 2002; Stoica et al, 2002).

Bischloronitrosourea (BCNU, carmustine) is used commonly in the treatment of CNS malignancies, and is associated with pulmonary toxicity manifesting as dyspnoea, resting hypoxia, and non-specific pulmonary fibrosis on transbronchial biopsy. BCNU-induced lung injury occurs in between 20 and 30% of patients, and is dose related. At doses of greater than 1500 mg/m$^2$, the incidence is 50%. BCNU-induced lung injury responds to corticosteroids; in one case report, cessation of steroids led to relapse of pneumonitis (Richter et al, 1979). Pulmonary toxicity has been also been described with other agents including busulfan, methotrexate, raltitrexed and etoposide.

## HYPERSENSITIVITY REACTIONS AND DRUG-INDUCED PULMONARY OEDEMA

Hypersensitivity reactions to chemotherapy have been described. Offending drugs include methotrexate, nitrofurantoin, bleomycin,

cyclophosphamide and sulfonamide. The drug reaction is idiosyncratic, i.e. independent of dose. Peripheral eosinophilia is found in up to 40%, and high resolution CT scan shows patchy ground glass changes, and occasionally consolidation. Mitomycin and cyclophosphamide have been linked to pulmonary injury, and mediate non-cardiogenic pulmonary oedema.

### KEY POINTS

- Chemotherapy-induced pulmonary toxicity is a potentially life-threatening complication that is caused by a wide range of cytotoxic drugs.
- Lung toxicity is commonly a dose-related interstitial pneumonitis, but can present with idiosyncratic hypersensitivity reactions, or pulmonary oedema.
- Interstitial pneumonitis may be suspected in any patient with dyspnoea, reduced oxygen saturation, and diffuse interstitial shadowing on chest X-ray, and abnormal gas transfer on pulmonary function testing.
- Biopsy may be required to confirm suspected chemotherapy-induced interstitial pneumonitis.
- Corticosteroids may be effective in reversing chemotherapy-induced interstitial pneumonitis in several instances.
- Early recognition of drug-induced pulmonary toxicity is vital to avert fatality or severe long-term pulmonary damage.

## NOVEL ANTICANCER AGENTS AND PULMONARY TOXICITY

Gefitinib is a low molecular weight epidermal growth factor receptor targeting tyrosine kinase that exhibits anticancer activity in non-small cell lung cancer. There have been reports of interstitial pneumonitis associated with its use, although this is uncommon; the predominant symptoms being diarrhoea and rash (Rabinowits et al, 2003). However, in two large randomized trials, interstitial lung disease occurred no more frequently with gefitinib than placebo (Giaccone et al, 2004; Herbst et al, 2004). Pulmonary toxicity has also been linked to the anti-CD20 monoclonal antibody rituximab, used in the treatment of follicular non-Hodgkin's lymphoma.

## GENERAL PRINCIPLES OF MANAGEMENT OF CHEMOTHERAPY-INDUCED LUNG INJURY

Cytotoxic drug-induced pulmonary toxicity may be suspected if dyspnoea occurs in conjunction with clinical or radiological evidence of interstitial lung disease, following commencement of chemotherapy. Radiographic features of interstitial pneumonitis are typical, and may include bilateral interstitial shadowing (symmetrical or asymmetrical) and septal lines. CT is more sensitive than chest X-ray in diagnosing pulmonary toxicity (38% *vs* 15% by chest X-ray). Early stage lung injury is typically associated with ground glass changes, whereas features of coarse reticular opacities and consolidation dominate in more advanced cases. Suspicion should lead to immediate withdrawal of the offending drug and initiation of an early investigation to establish a diagnosis. The carbon dioxide diffusing capacity (DLCO) is also a sensitive marker for pulmonary damage.

The differential diagnosis includes infections with organisms including *Pneumocystis* spp. and fungi as the patients are usually immunosuppressed by the chemotherapy and perhaps by the underlying disease. Bronchoscopy with broncho-alveolar lavage and transbronchial biopsy, and occasionally video-assisted thoracoscopic lung biopsy may be needed to distinguish between the various possibilities. Non-specific histological features of a fibrosing alveolitis are typically seen on lung biopsy in drug-induced toxicity although a wide variety of other features may occur. Corticosteroids are a useful intervention that may delay or limit the pulmonary damage. Gamma-interferon has been shown to reduce lung injury in patients with steroid-refractory interstitial pneumonitis (Suratt et al, 2003).

## CONCLUSIONS

Pulmonary toxicity can occur in association with several cytotoxic drugs as a result of their narrow therapeutic index, and should be considered where decreased lung function occurs following administration. Early diagnosis is essential to prevent irreversible and severe lung damage, or avert fatality. **HM**

*Conflict of interest: none.*


Behrens RJ, Gulley JL, Dahut WL (2003) Pulmonary toxicity during prostate cancer treatment with docetaxel and thalidomide. *Am J Ther* **10:** 228–32

Boiselle PM, Morrin MM, Huberman MS (2000) Gemcitabine pulmonary toxicity: CT features. *J Comput Assist Tomogr* **24:** 977–80

Dalgleish AG, Woods RL, Levi JA (1984) Bleomycin pulmonary toxicity: its relationship to renal dysfunction. *Med Pediatr Oncol* **12:** 313–17

Dunsford ML, Mead GM, Bateman AC, Cook T, Tung K (1999) Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. *Ann Oncol* **10:** 943–7

Giaccone G, Herbst RS, Manegold C et al (2004) Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. *J Clin Oncol* **22:** 777–84

Helman DL Jr, Byrd JC, Ales NC, Shorr AF (2002) Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* **122:** 785–90

Herbst RS, Giaccone G, Schiller JH et al (2004) Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. *J Clin Oncol* **22:** 785–94

Holoye PY, Jenkins DE, Greenberg SD (1976) Pulmonary toxicity in long-term administration of BCNU. *Cancer Treat Rep* **60:** 1691–4

Ingrassia TS 3rd, Ryu JH, Trastek VF, Rosenow EC 3rd (1991) Oxygen-exacerbated bleomycin pulmonary toxicity. *Mayo Clin Proc* **66:** 173–8

Joerger M, Gunz A, Speich R, Pestalozzi BC (2002) Gemcitabine-related pulmonary toxicity. *Swiss Med Wkly* **132:** 17–20

Kawai K, Hinotsu S, Tomobe M, Akaza H (1998) Serum creatinine level during chemotherapy for testicular cancer as a possible predictor of bleomycin-induced pulmonary toxicity. *Jpn J Clin Oncol* **28:** 546–50

Madarnas Y, Webster P, Shorter AM, Bjarnason GA (2000) Irinotecan-associated pulmonary toxicity. *Anticancer Drugs* **11:** 709–13

Mahmood T, Mudad R (2002) Pulmonary toxicity secondary to procarbazine. *Am J Clin Oncol* **25:** 187–8

Matthews JH (1993) Pulmonary toxicity of ABVD chemotherapy and G-CSF in Hodgkin's disease: possible synergy. *Lancet* **342:** 988

Parvinen LM, Kilkku P, Makinen E, Liukko P, Gronroos M (1983) Factors affecting the pulmonary toxicity of bleomycin. *Acta Radiol Oncol* **22:** 417–21

Rabinowits G, Herchenhorn D, Rabinowits M, Weatge D, Torres W (2003) Fatal pulmonary toxicity in a patient treated with gefitinib for non-small cell lung cancer after previous hemolytic-uremic syndrome due to gemcitabine. *Anticancer Drugs* **14:** 665–8

Richman SD, Levenson SM, Bunn PA, Flinn GS, Johnston GS, DeVita VT (1975) 67Ga accumulation in pulmonary lesions associated with bleomycin toxicity. *Cancer* **36:** 1966–72

Richter J, Hastedt R, Dalton JF, Marshall D, Raymond LW, (1979) Pulmonary toxicity of bischloronitrosourea: report of a case with transient response to corticosteroid therapy. *Cancer* **43:** 1607–12

Roychowdhury DF, Cassidy CA, Peterson P, Arning M (2002) A report on serious pulmonary toxicity associated with gemcitabine-based therapy. *Invest New Drugs* **20:** 311–15

Rudders RA, Hensley GT (1973) Bleomycin pulmonary toxicity. *Chest* **63:** 627–8

Samuels ML, Johnson DE, Holoye PY, Lanzotti VJ (1976) Large-dose bleomycin therapy and pulmonary toxicity. A possible role of prior radiotherapy. *JAMA* **235:** 1117–20

Saxman SB, Nichols CR, Einhorn LH (1997) Pulmonary toxicity in patients with advanced-stage germ cell tumors receiving bleomycin with and without granulocyte colony stimulating factor. *Chest* **111:** 657–60

Senan S, Paul J, Thomson N, Kaye SB (1992) Cigarette smoking is a risk factor for bleomycin-induced pulmonary toxicity. *Eur J Cancer* **28A:** 2084

Stoica GS, Greenberg HE, Rossoff LJ (2002) Corticosteroid responsive fludarabine pulmonary toxicity. *Am J Clin Oncol* **25:** 340–1

Suratt BT, Lynch DA, Cool CD, Jones RB, Brown KK, (2003) Interferon-gamma for delayed pulmonary toxicity syndrome resistant to steroids. *Bone Marrow Transplant* **31:** 939–41

van Barneveld PW, Sleijfer DT, van der Mark TW et al (1984) Influence of platinum-induced renal toxicity on bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. *Oncology* **41:** 4–7

Yokose N, Ogata K, Tamura H et al (1998) Pulmonary toxicity after granulocyte colony-stimulating factor-combined chemotherapy for non-Hodgkin's lymphoma. *Br J Cancer* **77:** 2286–90