

Severe interstitial pneumonitis associated with the administration of taxanes

Shigeyuki Nagata · Naoyuki Ueda · Yasuhiro Yoshida · Hiroyuki Matsuda · Yoshihiko Maehara

Received: 11 September 2009 / Accepted: 26 February 2010 / Published online: 31 March 2010
© Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases 2010

Abstract Interstitial pneumonitis has sporadically been reported as a toxic effect of taxanes such as docetaxel and paclitaxel. This report describes 2 patients who developed interstitial pneumonitis after receiving chemotherapy including taxanes, and both cases grew serious enough to require respiratory support. The first case was a 57-year-old man with gastric cancer treated with docetaxel biweekly and S-1 for 2 weeks as adjuvant chemotherapy. After 4 courses of docetaxel, he presented acute dyspnea. The second case was a 66-year-old woman with breast cancer and postoperative pleural recurrence treated with weekly paclitaxel as fourth-line chemotherapy. She developed a dry cough, high fever, and dyspnea after 1 course of paclitaxel. In both cases, computed tomography (CT) showed extensive bilateral areas of ground-glass attenuation. They developed progressive interstitial infiltrates and respiratory failure that required mechanical ventilation. Taxane-induced interstitial pneumonitis was diagnosed to exclude other causes. From previous reports, intubation is associated with the survival of patients with taxane-induced interstitial pneumonitis. However, corticosteroid therapy was dramatically effective and resolved the interstitial pneumonitis in both our patients. Clinicians should be aware of this occasional complication during the course

of chemotherapy with taxanes and initiate treatment, including respiratory support, as soon as possible.

Keywords Taxane · Side effect · Interstitial pneumonitis · Chemotherapy · Corticosteroid

Introduction

The taxanes docetaxel (Taxotere, Aventis, Strasbourg France) and paclitaxel (Taxol, Bristol-Myers-Squibb, Princeton, NJ, USA), are antineoplastic agents widely used in the management of a range of malignant disorders. Pulmonary toxicity is a complication observed with several anticancer drugs, and interstitial pneumonitis (IP) related to the administration of taxanes occurs in <1% of cases [1–3]. This report presents the cases of 2 patients who developed acute, severe IP during chemotherapy including taxanes and who recovered with steroid pulse therapy and respiratory support.

Case report

Case 1

A 57-year-old man underwent a distal gastrectomy for gastric cancer (T4/N3/M0: stage IV) in January 2007. The patient was sequentially treated with docetaxel and S-1 (TS-1, Taiho, Tokyo, Japan) as adjuvant chemotherapy. Pretreatment chest radiography was normal, and no metastasis was seen on computed tomography (CT). His performance status was 1, and he had a history of smoking (30 cigarettes/day for 37 years). He was administered 35 mg/m² (53 mg/body) docetaxel for 90 min on days

S. Nagata · Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

S. Nagata · N. Ueda · Y. Yoshida · H. Matsuda
Department of Surgery, Nakabaru Hospital, Fukuoka, Japan

S. Nagata (✉)
Flat 5, Fitzroy Hall, 5 Shortlands Grove, Bromley,
Kent, London BR2 0LS, UK
e-mail: punchnagata@yahoo.co.jp

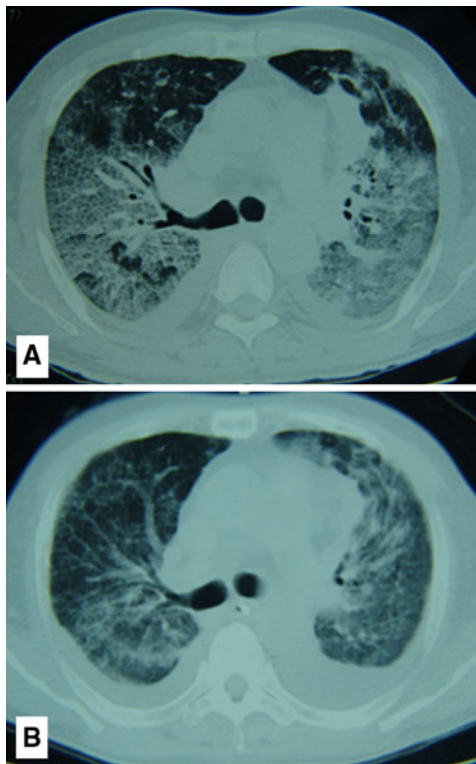


Fig. 1 Case 1. **a** Chest computed tomography (CT) on admission demonstrated mild pleural effusion and ground-glass opacity of the bilateral lungs, with focal consolidation and mild traction bronchiectasis. **b** Chest CT after extubation showed improvement in the interstitial infiltrate

1 and 15. He received 120 mg/body S-1 on days 1–14. The treatment cycle was repeated every 4 weeks from 15 February. The patient was premedicated with dexamethasone and ramosetron prior to docetaxel administration.

Fourteen days after 4 courses of docetaxel, the patient was hospitalized with a dry cough and grade 1 dyspnea without fever. A physical examination revealed a mild diffuse fine crackle in the bilateral lungs, and a chest radiography revealed diffuse infiltrates throughout the lungs. Despite administration of empiric antibiotics, his respiratory condition rapidly worsened. Arterial blood gas demonstrated partial pressure of oxygen (pO_2) 60 mmHg, partial pressure of carbon dioxide (pCO_2) 29 mmHg, and oxygen saturation in arterial blood (SaO_2) 93% under O_2 7 L/min by mask 3 days after admission. Laboratory values were leukocyte count 19700/ μ l (normal range 3500–8500/ μ l), lactate dehydrogenase (LDH) 450 IU/L (normal range 119–229 U/L), KL-6 1945 U/ml (normal range, <500 U/ml), C-reactive protein (CRP) 6.3 mg/dl (normal range <0.3 mg/dl). Chest CT demonstrated mild pleural effusion and ground-glass opacity of the bilateral lungs, with focal consolidation and mild traction bronchiectasis, consistent with IP (Fig. 1a). Steroid pulse therapy [methylprednisolone

(mPSL)] 1 g daily for 3 days and gradually decreased thereafter was started 2 days after admission, and the patient was intubated and placed on mechanical ventilation 5 days after admission. Cultures obtained from sputum and pleural effusion were negative. Symptoms and laboratory data 16 days after admission (leukocyte count 4400/ μ l, LDH 288 IU/L, CRP 0.0 mg/dl, pO_2 107 mmHg, pCO_2 32.5 mmHg) improved. Radiographic findings steadily improved, and he was extubated that day (intubation time 11 days). He was subsequently treated with oral prednisolone for 2 months. At 15 days after extubation, CT showed improvement of the interstitial infiltrate (Fig. 1b). Thereafter, the patient was discharged (hospital stay 62 days) and finally died of peritonitis carcinomatosa 1 month after discharge.

Case 2

A 66-year-old woman underwent a modified radical mastectomy in August 2000 for hormone-receptor-negative breast cancer in the left breast (T1c/N0/M0: stage I). In July 2003, pleural recurrence was recognized and EC therapy (epirubicin 85 mg/body, cyclophosphamide 850 mg/body every 3 weeks) was introduced. Disease progression was observed after 11 cycles of EC therapy; thus, capecitabine (2400 mg/day; 3 weeks administration and 1 week rest) was administered for 2 years. After administration of capecitabine, 14 cycles of docetaxel (65 mg/body every 3 weeks) were completed; these treatments were ultimately ineffective. Then, paclitaxel combined with capecitabine was selected as the fourth-line chemotherapy agent. In July 2007, paclitaxel was administered at 80 mg/m² (110 mg/body) for 2 h on days 1, 8, and 15. Premedication with dexamethasone, diphenhydramine, famotidine, and ramosetron was administered prior to paclitaxel administration. Dexamethasone was administered after paclitaxel infusion. The chemotherapy course was scheduled to be repeated every 4 weeks and coadministered with capecitabine beginning at the second cycle. The patient's general condition was good prior to initiation of this regimen of chemotherapy. She had no history of smoking.

Ten days after the first round of paclitaxel, the patient presented with mild dry cough and high fever (38.7°C). Chest radiography showed no change in comparison with the previous one. Four days later, she developed moderate dry cough and progressive dyspnea. A physical examination revealed fine crackles in the bilateral lungs. An arterial blood gas was obtained from the patient on room air: pO_2 was 48 mmHg, pCO_2 36 mmHg, and SaO_2 86%. She was admitted immediately and treated with empiric antibiotic therapy. Laboratory values were leukocyte count 17020/ μ l, LDH 866 IU/L, CRP 26.5 mg/dl. Chest CT upon

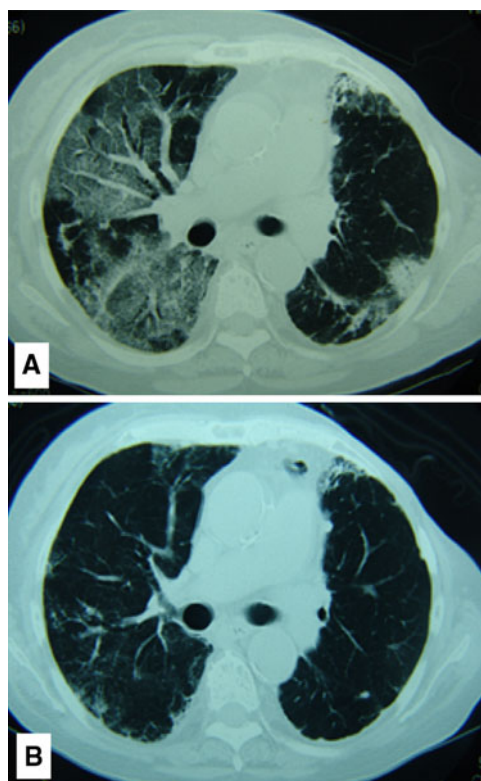


Fig. 2 Case 2. **a** Chest computed tomography (CT) on admission demonstrated ground-glass opacity of the bilateral lungs with mild traction bronchiectasis. **b** Chest CT at extubation showed improvement in the interstitial infiltrate

admission demonstrated ground-glass opacity of the bilateral lungs with mild traction bronchiectasis (Fig. 2a). She was intubated and placed on mechanical ventilation the following day. A drug-induced lymphocyte stimulation test (DLST) for paclitaxel was negative. However, steroid pulse therapy (same as case 1) was administered based on the diagnosis of paclitaxel-induced IP. Her symptoms and laboratory data improved 8 days after intubation (pO_2 94.9 mmHg, pCO_2 48.5 mmHg). Chest CT findings also improved (Fig. 2b). She was extubated the same day and was consequently treated with oral PSL for 2 months. She was discharged to her home (hospital stay 62 days). Subsequent S-1 chemotherapy was administered, and the patient was still alive at 18 months after discharge.

Discussion

The risk factors for developing pulmonary complications in association with drug therapy are total dose, patient age, history of smoking, prior or concurrent radiotherapy, oxygen therapy, other cytotoxic drug therapy, and preexisting pulmonary disease [1]. However, anticancer-drug-induced IP sometimes occurs, unrelated to the cumulative drug dose or

therapy duration of therapy. Although paclitaxel and docetaxel are similar in their mechanisms of action, their toxicities differ. Because paclitaxel is dissolved in cremophor, which is highly allergenic, hypersensitivity reactions may occur. The incidence of hypersensitivity reaction in association with docetaxel is thought to be smaller, and the number of case reports of docetaxel-induced IP is smaller than that of paclitaxel [4–18].

Observing the level of LDH and KL-6 is an effective method of diagnosing drug-induced IP. The level in the 2 cases presented here was increased at the onset. These values provide only a suggestion, not a definitive diagnosis. The clinical and radiographic features of drug-induced IP are nonspecific and similar to IP of other etiologies. The Japan Respiratory Society (JRS) guidelines for evaluation of drug-induced IP classify CT findings of drug-induced IP by their specific patterns [19]. This classification is convenient to allow clinicians to recognize disease morphology and predict prognosis. The diagnosis is finally made by exclusion. A bronchoalveolar lavage (BAL) or transbronchial lung biopsy (TBLB) is necessary to exclude other etiologies. BAL fluid from drug-induced IP reveals lymphocytic alveolitis, an increase in the number of total cells, an increased proportion of neutrophils and eosinophils, and a decreased CD4/CD8 ratio [4, 6, 10]. A TBLB from drug-induced IP reveals edema and swelling of the alveolar septum and interstitial and alveolar mononuclear cell infiltration with intraluminal organization and aggregation of alveolar macrophages [10, 11]. A drug provocation test is effective for diagnosing drug-induced IP [20]. The generation of drug-specific T cells can be confirmed in this test, suggesting that IP is caused by T-cell-mediated immune response. However, this test has low sensitivity (33.3% for anticancer drug), and it is difficult to determine whether the T cells identified by this test cause IP. Therefore, this test does not yield a definitive diagnosis.

The mechanism of drug-induced lung injury is poorly understood, but there are thought to be 2 types: the allergic type and the cell-mediated cytotoxic type [1, 3]. They are designated to be type I and type IV hypersensitivity reactions to the drug, respectively. Type I appears to be due to basophilic histamine release and mediated by immunoglobulin (Ig)E. This response induces acute dyspnea, bronchospasm, hypotension, and an erythematous rash (a serious reaction occurs within a few minutes after administration), develops in as many as 30% of cases, and diminishes to 1–3% with steroid premedication. Type IV, T-cell-mediated tissue injury, presents as an acute–subacute clinical course (from a few hours to 2 weeks) of bilateral pulmonary infiltrates and is usually transient. The response to steroids is poorly characterized. Paclitaxel can induce a cell-mediated immunologic reaction with pulmonary sequestration of activated specific lymphocytes, because some cases show a positive

Table 1 Previous reports of taxane-induced pneumonitis

Drug	Case number	Mean age (years)	Sex (M/F)	Diagnosis				Smoking			Intubation		Steroid pulse		Outcome		References
				LC	BC	GC	Others	Yes	No	NP	Yes	No	Yes	No	Recover	Death	
Docetaxel	12	66.3 (44–75)	8/4	8	2		2	0	10	8	4	4	8	6	6	[4–7]	
Paclitaxel	19	62.8 (44–79)	10/9	9	6	4	10	4	5	3	16	10	9	12	7	[8–18]	

LC lung cancer, BC breast cancer, GC gastric cancer, NP not précised

leukocyte migration test [10]. Mechanisms of action based on a hypersensitivity to docetaxel and paclitaxel are supported by pathology studies on TBLB [7, 11]. In many previous reports of taxane-induced IP, infiltrates and symptoms promptly resolve with oxygen therapy or corticosteroid therapy only and without ventilation support [4–12]. The patients in this report presented pulmonary injury with diffuse interstitial infiltrates, rapid progression, and poor response to broad-spectrum antibiotics therapy. The patient in case 1, who had not previously received radiation, oxygen inhalation, or other cytotoxic therapy, developed severe respiratory symptoms with hypoxia 14 days after receiving the 4 cycles of docetaxel (cumulative dosage 424 mg) and S-1. CT findings were compatible with the acute IP-like pattern described in the JRS guidelines [19]. The patient in case 2, who received no previous radiation or oxygen inhalation but was administered other cytotoxic therapy for a long duration, presented severe respiratory symptoms with hypoxia and pulmonary infiltrates 10 days after receiving the last dose of paclitaxel (cumulative dosage 330 mg). CT findings were compatible with an acute hypersensitivity pneumonia-like pattern described in the JRS guidelines [19]. The half-life of docetaxel and paclitaxel are 11.1 and 8.5 h, respectively, which suggest that the blood concentration of the respective drugs was sufficient low at the time of onset. No BAL or TBLB was obtained from the two patients because of the life-threatening pneumonitis and respiratory failure. The patient in case 2 had a malignant recurrence in the left lung, but the main lesion of IP was in the right lung; therefore, the recurrence was unlikely to have caused the IP. After excluding other resultant factors, including the possibility of IP induced by other drugs, connective lung disease, or an unusual infection such as cytomegalovirus (CMV), *Pneumocystis carinii*, or legionella, taxane-induced IP was diagnosed in both cases. In case 2, the DLST for paclitaxel was negative, and steroid therapy was effective in resolving her condition. These findings may suggest that the etiology of the IP in case 2 was a type I reaction. The patient in case 1 received docetaxel combined with S-1 for gastric cancer, and the causative agent was unclear. S-1 is a novel oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on a biochemical modulation of 5-fluorouracil (5-FU) and is widely used as a single agent or in

combination therapies for gastric cancer patients in Japan. S-1-induced interstitial pneumonitis is very rare. Patients receiving combination therapies with taxanes and other agents have a higher risk of drug-induced pneumonitis [3].

Previous case reports are summarized in Table 1 [4–18]. Intubation is associated with survival ($p = 0.0033$); 35.4% of cases require respiratory ventilation. The total mortality rate is 42%, but the mortality rate in intubated cases is very high (81.8%). Therefore, pneumonitis requiring intubation is likely to be more fatal. The survival rate in patients receiving steroid pulse therapy is low (50%). It is unclear whether the pneumonitis in the fatal cases was resistant to steroid therapy or induction of pulse therapy was too late. However, steroid pulse therapy is not the complete answer for IP treatment.

Both patients received chemotherapy including taxanes presented with high fever, dry cough, dyspnea, and diffuse lung infiltrates. The symptoms developed acutely over 1–2 days, rapidly progressed despite empiric antibiotic therapies, and culminated in respiratory failure requiring mechanical ventilation. Taxane-induced IP was diagnosed by excluding the other possible etiologies and considering the clinical course. Both patients responded to high-dose corticosteroids and neither died of pneumonitis. We thus conclude that IP is often encountered in patients receiving chemotherapy including taxanes, and it also may be life threatening. It may produce a wide variety of clinicopathological findings. As taxanes are used and their adverse effects recognized, clinicians should be aware of the possibility of pulmonary toxicity and begin the appropriate treatment as soon as possible.

Conflict of interest statement The authors declare they have no competing interests.

References

- Cooper JAD, White DA, Matthey RA. Drug-induced pulmonary disease. Part 1: cytotoxic drugs. *Am Rev Respir Dis*. 1986;133: 321–40.
- Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med*. 1995;332:1004–14.

3. Grande C, Villanueva MJ, Huidobro G, Casal J. Docetaxel-induced interstitial pneumonitis following non-small-cell lung cancer treatment. *Clin Transl Oncol*. 2007;9:578–81.
4. Merad M, Cesne AL, Baldeyrou P, Mesurolle B, Chevalier TL. Docetaxel and interstitial pulmonary injury. *Ann Oncol*. 1997;8:191–4.
5. Etienne B, Perol M, Nesme P, Vuillermoz S, Robinet G, Guerin JC. Pneumopathie interstitielle diffuse aiguë sous docetaxel (Taxotere). A propos de 2 observations. *Rev Mal Respir*. 1998;15:199–203.
6. Wang GS, Yang KY, Perng RP. Life-threatening hypersensitivity pneumonitis induced by docetaxel (taxotere). *Br J Cancer*. 2001;85:1247–50.
7. Read WL, Mortimer JE, Picus J. Severe interstitial pneumonitis associated with docetaxel administration. *Cancer*. 2002;94:847–53.
8. Ramanathan RK, Reddy VV, Holbert LM, Belani CP. Pulmonary infiltrates following administration of paclitaxel. *Chest*. 1996;110:289–92.
9. Khan A, McNally D, Tutschka PJ, Bilgrami S. Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother*. 1997;31:1471–4.
10. Fujimori K, Yokoyama A, Kurita Y, Uno K, Saijo N. Paclitaxel-induced cell-mediated hypersensitivity pneumonitis. Diagnosis using leukocyte migration test, bronchoalveolar lavage and transbronchial lung biopsy. *Oncology*. 1998;55:340–4.
11. Wong P, Leung AN, Berry GJ, Atkins KA, Montoya JG, Ruoss SJ, et al. Paclitaxel-induced hypersensitivity pneumonitis: radiographic and CT findings. *Am J Roentgenol*. 2001;176:718–20.
12. Goldberg HL, Vannice SB. Pneumonitis related to treatment with paclitaxel. *J Clin Oncol*. 1995;13:534–5.
13. Shitara K, Ishii E, Kondo M, Sakata Y. Suspected paclitaxel-induced pneumonitis. *Gastric Cancer*. 2006;9:325–8.
14. Nakakubo Y, Naoe K, Okushiba T, Matsumura Y, Watanabe F, Kawamura T. A case of paclitaxel-induced acute bilateral pneumonitis in advanced breast cancer. *J Jpn Clin Surg*. 2003;64:823–36.
15. Taniguchi N, Shinagawa N, Kinoshita I, Nasuhara Y, Yamazaki K, Yamaguchi E, et al. A case of paclitaxel-induced pneumonitis. *J Jpn Resp Soc*. 2004;42:158–63.
16. Hasegawa K, Maruyama M, Ebuchi M, Sakoma T. A case of paclitaxel-induced acute bilateral pneumonitis in advanced gastric cancer. *Jpn J Cancer*. 2005;51:447–53.
17. Uto N, Niimi M, Osako T, Yokoyama H. Two case reports of pneumonitis induced by the weekly administration of paclitaxel. *Jpn J Pharmacol*. 2005;41:1395–7.
18. Noguchi T, Ueno M, Udagawa H, Ehara K, Mine S, Kinoshita Y, et al. A case of recurrent gastric cancer followed by fatal interstitial pneumonitis after paclitaxel administration. *Jpn J Gastroenterol Surg*. 2006;39:1487–92.
19. American Thoracic Society, European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2002;165:277–304.
20. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy*. 2004;59:809–20.