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A Prospective Study of Pulmonary Function in Patients Treated with Paclitaxel and Carboplatin

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BACKGROUND. Adverse effects of paclitaxel and carboplatin have been well described; however, pulmonary toxicity after patients receive this regimen has not been investigated extensively.

METHODS. To clarify this issue, 33 consecutive patients who were treated with paclitaxel and carboplatin underwent prospective evaluation of respiratory function, which included pulmonary symptoms, pulmonary function tests (PFTs), arterial blood gas levels, and radiographic studies. Assessment was performed before and after completion of chemotherapy in all patients. Patients with substantial declines in PFTs, defined as a decline $\geq$ 20 percent in forced expiratory volume in 1 second (FEV_1), total lung capacity (TLC), or diffusion capacity for carbon monoxide (DLCO), were reassessed 5 months later.

RESULTS. After chemotherapy, there were no significant changes in forced vital capacity (FVC; 111% $\pm$ 21% of the predicted value before chemotherapy vs. 111 $\pm$ 20% of the predicted value after chemotherapy), FEV_1 (108% $\pm$ 24% of the predicted value before chemotherapy vs. 107% $\pm$ 22% of the predicted value after chemotherapy), FEV_1/FVC ratio (79% $\pm$ 8% before chemotherapy vs. 78% $\pm$ 6% after chemotherapy), alveolar volume (VA; 95% $\pm$ 14% of the predicted value before chemotherapy vs. 96% $\pm$ 14% of the predicted value after chemotherapy), or TLC (96% $\pm$ 14% of the predicted value before chemotherapy vs. 97% $\pm$ 13% of the predicted value after chemotherapy). In contrast, there was a significant decline in DLCO (101% $\pm$ 20% of the predicted value before chemotherapy vs. 96 $\pm$ 21% of the predicted value after chemotherapy; $P < 0.05$). Arterial blood gas levels did not change after treatment. No patient had decreased FEV_1 or TLC levels by $\geq$ 20%, whereas 4 of 33 patients (12%) exhibited a substantial decline ($\geq$ 20%) in DLCO that persisted 5 months after treatment (DLCO at baseline, immediately after chemotherapy, and 5 months after the completion of chemotherapy, respectively: 99% $\pm$ 36% of the predicted value vs. 75% $\pm$ 28% of the predicted value vs. 74% $\pm$ 31% of the predicted value; $P < 0.05$). None of the 33 patients developed respiratory symptoms or had radiologic signs suggestive of lung toxicity. Among the various risk factors examined, baseline DLCO and FEV_1 levels were associated with changes in DLCO post-treatment.

CONCLUSIONS. This prospective analysis showed that the combination of paclitaxel with carboplatin induced an isolated decrease in DLCO level in the absence of clinical or radiologic evidence of toxicity. Further studies are needed to clarify whether this reduction in DLCO is predictive of subsequent pulmonary impairment. ***Cancer*** **2002;94:452–8.** © *2002 American Cancer Society.*

KEYWORDS: paclitaxel, carboplatin, adverse effects, lung toxicity, pulmonary function tests, diffusion capacity for carbon monoxide, respiratory symptoms, chest X-ray.

Paclitaxel is one of the most active chemotherapeutic agents for the treatment of several solid tumors, including ovarian, breast, and lung carcinoma.[1] Thus, many patients are being exposed to this drug.

Common adverse effects of paclitaxel include alopecia, bone marrow suppression, hypersensitivity reactions, and peripheral neuropathy.[2] A limited number of case reports or retrospective studies have indicated that treatment with paclitaxel was associated with a variety of respiratory symptoms, such as nonproductive cough, wheezing, shortness of breath, and chest tightness,[3–7] or with radiographic abnormalities, involving mainly interstitial infiltrates[4–7] and, rarely, bilateral nodules.[7] Interstitial infiltrates reported may reflect pneumonitis and have been described when paclitaxel was used as a single agent, especially when the drug was administered concurrently with irradiation.[8] In those studies, pulmonary function tests (PFTs) before and after treatment with paclitaxel were not made. The potential of paclitaxel to induce lung toxicity when it is administered alone or in combination with other drugs has not been investigated prospectively to date.

To assess prospectively the effect of paclitaxel on pulmonary function, we designed a study that included patients who were treated with a combination of paclitaxel and carboplatin. PFTs (which have been recommended for the early detection of drug-associated pulmonary toxicity[9]), clinical history, respiratory symptoms, lung examination, arterial blood gas level, and radiographic studies were obtained before and after the completion of chemotherapy.

MATERIALS AND METHODS

Patients

Patients who were eligible for the study included those who were candidates for treatment with the combination of paclitaxel and carboplatin. Paclitaxel was administered intravenously over 3 hours at a dose of 175 mg/m^2, and carboplatin was administered intravenously over 1 hour at an area under the serum concentration-time curve dose of 6. A standard premedication regimen with ranitidine, dexamethasone, and diphenhydramine was used in all patients. Patients received four or six cycles of chemotherapy, depending on the extent of their disease. Exclusion criteria were primary lung carcinoma, metastatic disease in the thorax, prior chemotherapy or radiotherapy, recent (within 1 month) major surgery, presence of lung infection, and impaired performance status (Karnofsky performance status $< 80\%$). The study was approved by the Institutional Review Board, and all patients gave informed consent.

Clinical Assessment

At each scheduled appointment, a physical examination was performed, and the presence of respiratory symptoms, such as cough, phlegm, wheezing, or chest pain, were recorded. Dyspnea also was evaluated and was expressed on a scale of 1–4, with Grade 0 indicating no dyspnea, Grade 1 indicating mild dyspnea, Grade 2 indicating exertional dyspnea, Grade 3 indicating dyspnea at rest, and Grade 4 indicating dyspnea severe enough to require complete bed rest. If acute bronchitis or pneumonia was diagnosed, then PFTs were delayed until at least 10 days after recovery.

PFTs

PFTs were performed before chemotherapy (first measurement) and after the completion of chemotherapy (second measurement). They consisted of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), total lung capacity (TLC), and diffusion capacity for carbon monoxide (DLCO). All tests were performed with a Jaeger MasterScreen diffusion system (E. Jaeger, Wuerzburg, Germany). TLC was measured with the helium dilution method. Alveolar volume (VA) was measured to calculate DLCO by the single-breath technique. DLCO was corrected for actual hemoglobin concentration using the equation of Cotes.[10] Data on FVC, FEV_1, TLC, VA, and DLCO were expressed both in absolute values and as the percentage of the predicted value for each patient based on age, gender, and height, whereas the ratio of FEV_1 to FVC (FEV_1/FVC) was reported as an absolute percentage. Baseline PFTs were regarded as abnormal if the ratio of FEV_1/FVC was $< 75\%$ (obstruction), or if DLCO was $< 80\%$ of the predicted value after correction for anemia (isolated diffusion impairment),[11] or if TLC was $< 80\%$ of the predicted value (restriction).[12] Changes in the PFT values after chemotherapy were expressed as the differences between pretreatment and post-treatment values relative to the pretreatment values. Substantial declines in PFT values were defined as a reduction $\geq 20\%$ from baseline in FEV_1, TLC, or DLCO values, because this cut-off value has been used by numerous other studies;[9,13–15] in such patients, additional PFTs were performed 5 months after chemotherapy (third measurement).

Arterial Blood Gas Levels

On the same day that PFTs were performed, arterial blood gas levels were obtained from the radial artery before chemotherapy (baseline) and at the end of treatment in all patients. In those who exhibited a significant decline in PFT values, a third sample was obtained 5 months after the completion of all chemotherapy cycles. Blood samples were analyzed for PaO_2, $PaCO_2$, and pH by an automated, computerized gas analyzer (238 pH/Blood Gas Analyzer; Ciba Corning Diagnostics Ltd., Essex, United Kingdom).

Radiographic Evaluation

All patients had chest radiographs performed prior to and after chemotherapy as part of staging procedures. Those patients who demonstrated a post-treatment decline ≥ 20% in DLCO underwent a high-resolution computed tomographic (CT) scan of the thorax. Chest X-rays and CT scans were reviewed by a radiologist who was blinded to the results of the PFTs and to the clinical status of the patients. Radiographic evidence of toxicity was defined as the presence of new pulmonary interstitial or alveolar infiltrates on a chest X-ray or CT scan in the absence of infection or metastatic disease to the thorax.

Data Analysis and Presentation

Data were stored and analyzed with the Sigmastat statistical software package (Jandel Corporation, San Rafael, CA). All variables entered in the analyses were expressed as the mean ± standard deviation. P values < 0.05 were considered statistically significant. Paired t tests were performed to analyze changes in PFT values and arterial blood gas levels after chemotherapy in the entire group of patients. Repeated-measures analyses of variance were used to assess changes in the above-mentioned variables over time in those patients who underwent follow-up. To isolate which groups differed from the others, a multiple comparison procedure was used (Student–Newman–Keuls method). Factors of possible importance for a change in DLCO post-treatment, such as age, gender, smoking habits, baseline PFT levels (FVC, FEV_1, FEV_1/FVC ratio, TLC, and DLCO), PaO_2, and cumulative dose of paclitaxel, were entered into a multiple linear regression model, and nonsignificant variables were deleted by backward elimination (deletion criterion; $P > 0.05$).

RESULTS

Thirty-three patients were entered in this study, and their characteristics are listed in Table 1. Most patients were treated for bladder carcinoma (45%), and the majority of patients (58%) received a total of four cycles with a combination of paclitaxel and carboplatin. Chemotherapy was administered either as adjuvant treatment or for metastatic disease. Hemoglobin concentration before chemotherapy was 12.1 g/dL ± 1.5 g/dL and dropped to 11.7 g/dL ± 1.6 g/dL after the completion of all chemotherapy cycles ($P = 0.06$). The mean total dose of paclitaxel administered was 1437 mg ± 272 mg (range, 960–2040 mg).

Before chemotherapy, the mean FVC, FEV_1, FEV_1/FVC, TLC, and DLCO levels were within normal ranges (Table 2). However, some patients had the following pulmonary function abnormalities: Nine patients (27%) had an obstructive pattern, and, of these, only two patients had moderate-to-severe obstruction (FEV_1, 58% and 47% of the predicted value, respectively). Six patients (18%) had an isolated but mild impairment in diffusion capacity (abnormal DLCO ranging from 60% to 77% of the predicted value), and four patients (12%) had mild restrictive ventilatory defects (abnormal TLC ranging from 70% to 79% of the pre-

TABLE 1
Patient Characteristics ($N = 33$ Patients)

Characteristic	No.
Age (yrs)	61 ± 11[a]
Gender	
Female	20
Male	13
Height (cm)	162 ± 10[a]
Weight (kg)	72 ± 13[a]
Smoking habits	
Current, exsmokers	18
Nonsmokers	15
Type of neoplasm	
Bladder	15
Ovarian	12
Endometrial	4
Cervical	2
No. of chemotherapy cycles	
Four	19
Six	14

[a] Values shown are the mean ± standard deviation.

TABLE 2
Pulmonary Function Tests and Arterial Blood Gases at Baseline and After Chemotherapy with Paclitaxel and Carboplatin in All Patients ($N = 33$ Patients)[a]

Variable	Baseline	After chemotherapy	P value
FVC (L)	3.4 ± 0.8	3.4 ± 0.8	NS
FVC (% pred)	111 ± 21	111 ± 20	NS
FEV_1 (L)	2.6 ± 0.7	2.6 ± 0.7	NS
FEV_1 (% pred)	108 ± 24	107 ± 22	NS
FEV_1/FVC (%)	79 ± 8	78 ± 6	NS
TLC (L)	5.1 ± 1.0	5.2 ± 1.0	NS
TLC (% pred)	96 ± 14	97 ± 13	NS
DLCO (mmol/min/kPa)	7.87 ± 1.89	7.45 ± 2.01	< 0.05
DLCO (% pred)	101 ± 20	96 ± 21	< 0.05
VA (L)	4.85 ± 1.04	4.99 ± 1.09	NS
VA (% pred)	95 ± 14	96 ± 14	NS
PaO_2 (mmHg)	85 ± 10	85 ± 9	NS
$PaCO_2$ (mmHg)	39 ± 3	39 ± 4	NS
pH	7.39 ± 0.03	7.40 ± 0.03	NS

FVC: forced vital capacity; % pred: percent of the predicted; FEV_1: forced expiratory volume in 1 second; FEV_1/FVC: forced expiratory volume in 1 second to forced vital capacity ratio; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide; VA: alveolar volume; NS: nonsignificant.
[a] Values shown are the mean ± standard deviation.

TABLE 3
Frequency Distribution of Decreases in Lung Function Indices After Chemotherapy with Paclitaxel and Carboplatin

	No.		
% Decrease	FEV_1	TLC	DLCO
0–10	20	14	8
11–19	3	1	10
≥ 20	0	0	4

FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide.

TABLE 4
Factors Contributing to a Change in Diffusion Capacity for Carbon Monoxide After Therapy with Paclitaxel and Carboplatin

Variable	Regression coefficient	Standard error	*P* value
DLCO (mmol/min/kPa)	−0.37	0.11	0.002
FEV_1 (L)	+1.22	0.28	0.0002

DLCO: diffusion capacity for carbon monoxide; FEV_1: forced expiratory volume in 1 second.

dicted value). The mean PaO_2 and $PaCO_2$ levels before chemotherapy were within normal limits; however, in two patients, the PaO_2 levels were 67 mm Hg and 64 mm Hg, respectively, and another two patients had mild hypercapnia ($PaCO_2$, 45 mm Hg and 46 mm Hg, respectively).

After the completion of chemotherapy, no significant changes in mean values of airflow, lung volume parameters, or arterial blood gas levels were found. In contrast, DLCO levels decreased significantly (Table 2). The frequency distribution of decreases in lung function parameters after treatment in the entire group of patients is outlined in Table 3. Several patients had a decrease in FEV_1 or TLC after therapy, but none of them met the criteria for substantial declines in these two indices. In contrast, 4 of 33 patients (12%) showed a decline ≥ 20% in DLCO levels. The final multiple-regression analysis showed that the change in DLCO levels after therapy with paclitaxel and carboplatin was associated with higher baseline DLCO levels and lower pretreatment FEV_1 levels, whereas it was unrelated to age, gender, smoking history, cumulative dose of paclitaxel, or PaO_2 or to any other PFT values (Table 4).

At baseline, no patient had respiratory symptoms at rest or during exercise, and, in particular, smokers with an obstructive ventilatory defect on PFTs did not show a clinical pattern of chronic bronchitis. During chemotherapy and after completion of all cycles, none of the patients developed clinical or radiologic signs of acute or chronic respiratory toxicity.

Regarding the four patients with substantial (≥ 20%) declines in DLCO levels, their clinical characteristics and individual PFTs at baseline, immediately after chemotherapy, and at 5 months after chemotherapy are shown in Table 5. Two patients were smokers (Patients 1 and 4), and the other two patients had never smoked (Patients 2 and 3). Considering the four patients as a group, it was noted that the decline in DLCO levels persisted for 5 months after chemotherapy (DLCO at baseline, immediately after chemotherapy, and at 5 months after the completion of chemotherapy, respectively: 99% ± 36% of the predicted value vs. 75% ± 28% of the predicted value vs. 74% ± 31% of the predicted value; $P < 0.05$), whereas VA levels (89% ± 14% of the predicted value vs. 86% ± 11% of the predicted value vs. 83% ± 15% of the predicted value; $P = 0.13$) and PaO_2 levels (73 mm Hg ± 8 mm Hg vs. 76 mm Hg ± 6 mm Hg vs. 69 mm Hg ± 15 mm Hg; $P = 0.56$) did not change over the same period. With regard to radiographic findings, in two patients, high-resolution CT scans of the thorax were normal (Patients 1 and 3); in contrast, one patient (Patient 2) had cystic bronchiectasis in both lower lobes, and another patient (Patient 4) had an apical shadow in the right lung that was compatible with old tuberculosis. Of the four patients, only one (Patient 4) was complaining of symptoms: He had Grade 2 dyspnea, which probably was explicable on the basis of his underlying lung disease, i.e., prior tuberculosis and severe airflow obstruction evident on PFTs (baseline FEV_1, 47% of the predicted value; FEV_1/FVC ratio, 54%).

DISCUSSION

We demonstrated that patients who were treated with the combination of paclitaxel and carboplatin developed a significant but clinically silent decrease in DLCO. Among the risk factors evaluated, baseline DLCO and FEV_1 levels seemed to be determinants that influenced the trend of DLCO after this treatment.

The administration of paclitaxel has been associated with various adverse effects,[2] and, with regard to pulmonary toxicity, pneumonitis has been described mostly in a number of retrospective studies or case reports. Khan et al.[6] retrospectively studied 239 patients with various malignancies who were treated with paclitaxel, etoposide, and cyclophosphamide with or without thoracic irradiation. Those authors demonstrated that bilateral pneumonitis associated with dry cough and dyspnea occurred in 3 of 239 patients (1%). Pulmonary infiltrates and symptoms were evident within 6 hours after the drug infusion, and the radiologic signs resolved in 24–96 hours,

TABLE 5
Clinical Characteristics and Pulmonary Function Tests at Baseline, After, and at 5 Months Following Chemotherapy with Paclitaxel and Carboplatin in Patients with a Substantial Decline in Diffusion Capacity for Carbon Monoxide (N = 4 Patients)

			FVC (% pred)			FEV_1 (% pred)			FEV_1/FVC (%)			TLC (% pred)			VA (% pred)			DLCO (% pred)		
Patient	Gender	Age (yrs)	Bsl	After	Five mos	Bsl	After	Five mos	Bsl	After	Five mos	Bsl	After	Five mos	Bsl	After	Five mos	Bsl	After	Five mos
1	M	73	115	103	108	107	101	100	71	75	71	102	93	96	101	91	94	132	102	110
2	F	54	67	70	62	58	58	50	74	71	68	81	78	65	79	77	64	77	51	49
3	F	66	127	115	112	122	107	107	79	77	79	105	101	96	103	99	94	126	96	91
4	M	75	66	60	55	47	49	42	54	62	57	79	81	79	76	78	77	60	48	47

FVC: forced vital capacity; % pred: percent of the predicted; FEV_1: forced expiratory volume in 1 second; FEV_1/FVC: forced expiratory volume in 1 second to forced vital capacity ratio; TLC: total lung capacity; VA: alveolar volume; DLCO: diffusion capacity for carbon monoxide; Bsl: baseline; After: immediately after chemotherapy; Five mos: 5 months after chemotherapy; M: male; F: female.

whereas symptoms responded to parenteral corticosteroid therapy. Similarly, Ayoub and coworkers[7] reviewed the records of 122 patients with lymphoma who were treated with single-agent paclitaxel. Those authors found that, of six patients with abnormal radiologic findings, only 1 patient (< 1%) had histologic findings suggestive of nonspecific idiopathic pneumonitis, and that neoplasms along with infections accounted for the chest X-ray abnormalities observed in the remaining patients. Ramanathan et al.[5] reported three patients who developed transient pulmonary infiltrates 2–14 days after the administration of paclitaxel and carboplatin that resolved completely in all patients. Three additional case reports have described pneumonitis in another three patients.[4,16,17] Although the exact pathophysiology explaining pneumonitis is unclear, a delayed type hypersensitivity reaction involving both immunologic mechanisms (mainly T-lymphocytes) and nonimmunologic mechanisms has been postulated.[6,16] Alternatively, it has been proposed that paclitaxel, especially when combined with radiation, may lead to protracted lymphocytopenia, resulting in an immunodeficiency state, thus causing opportunistic infections that account, at least in part, for the interstitial infiltrates observed on chest X-rays.[8] Except for pneumonitis, the administration of paclitaxel also has been associated in a percentage of treated patients with other pulmonary side effects, such as dyspnea, chest tightness, or bronchospasm,[3,4] which probably also are components of a delayed hypersensitivity reaction. Whether the active drug itself[18]or the cremophor EL (polyoxyethylated castor oil) vehicle[19] used in the formulation of paclitaxel is the inciting agent remains to be determined. Regardless of the mechanisms involved in lung toxicity, all of these reports suggest that pulmonary dysfunction does occur to some degree after treatment with paclitaxel and that its outcome generally is favorable.

The effects of paclitaxel on PFTs have not been well described. The only available study that addressed this issue was the report by Robert and coworkers.[20] Those authors studied patients with advanced nonsmall lung carcinoma who were treated with paclitaxel, cisplatin, and radiation. Lung toxicity was determined in general on the basis of symptoms and radiologic data in all patients. In 27 of 43 patients, however, evaluation also included PFTs. It was found that 5–6 months after treatment, FVC levels and especially DLCO levels decreased significantly. No correlation was found between changes in pulmonary function indices and the incidence of acute or late pulmonary toxicity.

To clarify further the magnitude of alterations in pulmonary function as a result of therapy with paclitaxel, we prospectively evaluated a group of patients with various malignancies. We excluded those patients with primary or metastatic lung carcinoma to avoid confusion from compromise in PFT values by the tumor itself. Although paclitaxel is used frequently in the treatment of several tumors, its administration as a single agent is limited. Thus, we decided to assess patients who received a combination of paclitaxel and carboplatin for two reasons: First, this combination is used increasingly in patients with a broad range of tumor types[21]; second, and of paramount importance for the purpose of our study, it is well known that, although carboplatin can cause hypersensitivity reactions (which, nonetheless, are distinguishable easily from the reactions noted after the administration of paclitaxel[22]), carboplatin lacks pulmonary toxicity,[2,3,21,22] even if it used in conjunction with radiation.[23] Contrary to most previous studies, our investigation examined the possibility of paclitaxel-induced lung toxicity on the basis of respiratory symptoms, radiologic findings, and arterial blood gas levels and particularly on the basis of PFTs. We found that our patients as a group had a significant drop in DLCO levels (5%) after treatment with paclitaxel and carbo-

platin and that, in 12% of patients, the decline in DLCO levels was ≥ 20%, whereas the other lung function indices studied were unaffected. Both VA and FVC levels remained unaffected by treatment, suggesting that the decline in DLCO level was not due to an inadequate patient effort during performance of the maneuvers. Of more importance, no changes in arterial blood gas levels were noted, no new infiltrates on chest radiographs or CT scans occurred, and no respiratory symptoms were experienced. The DLCO level is the most sensitive measurement for drug-induced lung toxicity, and it has been suggested that a reduction ≥ 20% from the baseline DLCO level should be a warning that toxic effects have occurred.[9] The interpretation of an asymptomatic decline in DLCO level remains controversial and obscure: One study reported an asymptomatic patient with a normal chest radiograph but a reduced DLCO level and fibrosis on lung biopsy, suggesting the high sensitivity of this test.[24] Conversely, the DLCO level may be decreased in patients without pulmonary signs or symptoms or an abnormal chest radiograph, and these same patients may never develop other evidence of pulmonary disease.[25] It is noteworthy that the decline in DLCO levels in our patients who were reevaluated 5 months after the completion of treatment still was present. It is not clear whether slowly progressive interstitial lung disease will develop later in some of patients with asymptomatic pulmonary dysfunction, and long-term follow-up is continuing. In addition, it should be considered that, in these particular patients, standard deviation intervals were wide; consequently, a larger patients group may have been necessary to draw firmer conclusions. It is logical, however, to avoid further treatment with paclitaxel-containing regimens in such patients.

Multiple regression analysis in this study indicated that, among the various potential contributors to the observed drop in DLCO level, baseline FEV_1 and DLCO levels were significant predictors. It may be hypothesized that some degree of airflow obstruction sensitizes the lung for cytotoxic injury. The predisposition of patients with higher baseline DLCO levels to exhibit greater changes in DLCO is not surprising, because a similar finding was reported previously in patients with Hodgkin disease who were treated with bleomycin and/or irradiation.[26]

In conclusion, patients who received paclitaxel and carboplatin did not suffer pulmonary-related mortality or complications but developed an asymptomatic fall in their DLCO level. Longer follow-up is needed to assess the evolution of pulmonary function tests and to determine whether this abnormality will improve or progress to clinically evident lung disease.

REFERENCES

1. Crown J, O'Leary M. The taxanes: an update. *Lancet* 2000; 355:1176–8.
2. Lowenthal RL, Eaton K. Toxicity of chemotherapy. *Hematol Oncol Clin North Am* 1996;10:967–90.
3. Shannon VR, Price KJ. Pulmonary complications of cancer therapy. *Anesthesiol Clin North Am* 1998;16:563–86.
4. Goldberg HL, Vannice SB. Pneumonitis related to treatment with paclitaxel [letter]. *J Clin Oncol* 1995;13:534–5.
5. Ramanathan RK, Reddy VV, Holbert JM, Belani CP. Pulmonary infiltrates following administration of paclitaxel. *Chest* 1996;110:289–92.
6. Khan A, McNally D, Tutschka PJ, Bilgrami S. Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother* 1997;31:1471–4.
7. Ayoub JP, North L, Greer J, Cabanillas F, Younes A. Pulmonary changes in patients with lymphoma who receive paclitaxel [letter]. *J Clin Oncol* 1997;15:2476.
8. Reckzeh B, Merte H, Pfluger KH, Pfab R, Wolf M, Havemann K. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. *J Clin Oncol* 1996;14: 1071–6.
9. Cooper JAD, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: cytotoxic drugs. *Am Rev Respir Dis* 1986;133:321–40.
10. American Thoracic Society. Single-breath carbon monoxide diffusion capacity (transfer factor). Recommendations for a standard technique—1995 update. *Am J Respir Crit Care Med* 1995;152:2185–98.
11. American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis* 1986;133:1205–9.
12. Hughes JMB. Presentation of pulmonary function test to the clinician. In Hughes JMB, Pride NB, editors. Lung function tests. Physiological principles and clinical applications. London: W. B. Saunders, 1999:287–95.
13. Ulrik CS, Backer V, Aldershvile J, Pietersen AH. Serial pulmonary function tests in patients treated with low-dose amiodarone. *Am Heart J* 1992;123:1550–4.
14. Castro M, Veeder MH, Mailliard JA, Tazelaar HD, Jett JR. A prospective study of pulmonary function in patients receiving mitomycin. *Chest* 1996;109:939–44.
15. Cottin V, Tebib J, Massonnet B, Souquet PJ, Bernard JP. Pulmonary function in patients receiving long-term low-dose methotrexate. *Chest* 1996;109:933–8.
16. 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.
17. Schweitzer VG, Juillard GJ, Bajada CL, Parker RG. Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. *Cancer* 1995;76:1069–72.
18. Essayan DM, Kagey-Sobotka A, Colarusso PJ, Lichtenstein LM, Ozols RF, King ED. Successful parenteral desensitization to paclitaxel. *J Allergy Clin Immunol* 1996;97:42–6.
19. Lorenz W, Reimann HJ, Schmal A, Dormann P, Schwarz B, Neugebauer E, Doenicke A. Histamine release in dogs by cremophor E1 and its derivatives: oxethylated oleic acid is the most effective constituent. *Agents Actions* 1977;7:63–7.

20. Robert F, Childs HA, Spencer SA, Redden DT, Hawkins MM. 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. *Semin Radiat Oncol* 1999;9(2 Suppl 1):136–47.
21. Judson I, Kelland LR. New developments and approaches in the platinum arena. *Drugs* 2000;59(Suppl 4):29–36.
22. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141–5.
23. Groen HJM, Van der Mark TW, Van der Leest AHD, de Vries EGE, Mulder NH. Pulmonary function changes in lung-cancer patients treated with radiation with or without carboplatin. *Am J Respir Crit Care Med* 1995;152: 2044–8.
24. Comis RL, Kuppinger MS, Ginsberg SJ, Crooke ST, Gilbert R, Auchincloss JH, et al. Role of single-breath carbon monoxide diffusing capacity in monitoring the pulmonary effects of bleomycin in germ cell tumor patients. *Cancer Res* 1979;39:5076–80.
25. Pascual RS, Mosher MB, Sikand RS, De Conti RC, Bouhuys A. Effects of bleomycin on pulmonary function in man. *Am Rev Respir Dis* 1973;108:211–7.
26. Horning SJ, Adhikari A, Rizk N, Hoppe RT, Olshen RA. Effect of treatment for Hodgkin's disease on pulmonary function: results of a prospective study. *J Clin Oncol* 1994; 12:297–305.