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Original Paper

Weekly Docetaxel and Concomitant Boost Radiotherapy for Non-small Cell Lung Cancer. A Phase I/II Dose Escalation Trial

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In this phase I/II study, we investigated the radiosensitising effects of docetaxel in non-small cell lung cancer (NSCLC). 30 patients with stage IIIb (18 patients) and IV (12 patients) NSCLC were treated with 64 Gy of accelerated chest radiotherapy (5-week schedule using a concomitant boost technique) and docetaxel on a weekly basis. The docetaxel starting dose level was 20 mg/m^2/week and was escalated by 10 mg/m^2 increments in cohorts of 10 patients. Dose-limiting toxicity (grade 3 asthenia) was observed in 6 of 10 patients treated at the 40 mg/m^2/week dose level, enforcing a 50% dose reduction in 4 patients. Grade 3 neutropenia was observed in 5 of 30 patients (17%), 3 of which were treated at the high dose level. Peripheral neuropathy occurred in 3 (10%) patients. A significant decrease in the absolute lymphocyte count was observed in all patients; the nadir was reached on day 28 (mean ± standard deviation (S.D.) = 539 ± 363/ml) compared with pretreatment values (mean ± S.D. = 1842 ± 863/ml; $P = 0.002$). 6 out of 30 patients (20%) experienced grade 3 oesophagitis, resulting in a 1–2 week delay in overall treatment time. Complete response of the primary tumour was observed in 8 (27%) patients assessed 2 months after treatment. 4 of these patients had disease resistant to previous docetaxel-containing chemotherapy. A partial response occurred in 15 of 30 patients (50%) for an overall response rate of 77% (95% confidence interval (CI) 60–92%). Radiosensitisation with docetaxel is feasible and the recommended dose for further phase II studies is 30 mg/m^2/week. Further phase II studies are required to confirm the remarkably high response rate observed in the present trial.

Key words: docetaxel, radiotherapy, lung cancer
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INTRODUCTION

DOCETAXEL (TAXOTERE) is a novel semisynthetic agent of the taxoid class that acts by enhancing tubulin polymerisation and inhibiting microtubule depolymerisation [1, 2]. This leads to cell cycle arrest in the G2/M phase, known to be 2.5 times more sensitive to radiation than the G1/S phase [3]. The radiation sensitising effects of docetaxel have been confirmed *in vitro* and are probably related to the cell synchronisation effect [4]. Docetaxel has also shown remarkable response rates (23–33%) in phase II studies for advanced non-small-cell lung cancer (NSCLC).

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Recent studies have demonstrated that shorter high-dose radiotherapy schedules cause a statistically significant increase in local tumour control in NSCLC [5, 6]. The rationale for such an event is that 2–4 weeks after the beginning of fractionated radiotherapy, tumour clonogenic cells may enter a phase of rapid tumour repopulation [7]. Delivery of the total radiation dose within 3–5 weeks would, therefore, minimize the adverse impact of rapid tumour repopulation on radiotherapy efficacy. We make the assumption that agents able to block active cells in the radiosensitive G2/M cell cycle phase could also be important in abrogating the significance of this phenomenon. Thus, despite the acceleration of clonogenic cell proliferation, synchronising agents would block cells in the cell cycle sensitive phase and fractionated

radiotherapy would be more efficient in eradicating this important tumour cell component.

To determine whether docetaxel can safely be administered together with radiotherapy in NSCLC is, therefore, of particular interest. Administration of docetaxel on a weekly basis seems to be consistent with the rationale of cell cycle synchronisation. In this phase I/II study, we assessed the toxicity and response rate of escalated docetaxel weekly doses during the course of a relatively accelerated 5-week radiotherapy schedule for locally advanced NSCLC.

PATIENTS AND METHODS

Recruitment criteria

30 patients with histologically confirmed NSCLC entered this phase I/II study. 18 patients had locally advanced stage IIIb disease. 12 had metastatic disease together with locally advanced disease and were referred for radiotherapy because of chest symptoms (haemoptysis, superior vena cava syndrome or chest wall invasion). Patients needed a performance status of equal to or less than 2 (WHO) as an entry requirement for the study. Written informed consent was obtained from all patients. Patients previously treated with radiotherapy to another chest site or chemotherapy (including paclitaxel or docetaxel) completed at least 2 months before recruitment were also eligible. Patients with a white blood cell count $< 2500/\mu l$ and a platelet count $< 120\,000/\mu l$ were excluded. Patients with haemoglobin < 10 g/ml were transfused until haemoglobin levels were raised > 11 g/ml. Pregnant women or patients with major heart, lung, liver, renal, psychiatric disease, or haematological malignancies were also excluded. Patients known to present severe allergic response to any drug or substance were excluded. Table 1 shows the patients' characteristics.

Pretreatment and treatment evaluation

Baseline studies included physical examination, chest radiography, whole blood count with differential and platelet count, complete biochemical profile, bone scan and computed tomography (CT) of the chest and upper abdomen. Whole blood cell count, serum urea and creatinine, and liver enzymes were analysed once a week during the radiotherapy period and for 4 weeks thereafter. Chest X-rays and electrocardiogram were performed every 2 weeks. Acute radiation toxicity was registered twice weekly, and radiotherapy delay was enforced in cases of grade 3 oesophagitis. The World Health Organization (WHO) scale was used to assess chemotherapy and acute radiation toxicity [8].

Table 1. *Patient and disease characteristics*

Number of patients	30
Age (years; mean, range)	65 (42–82)
Sex	
Male	30
Histology	
Squamous cell	19
Adenocarcinoma	8
Undifferentiated	3
Stage	
IIIb	18
IV	12
Radiotherapy field dimensions	
Large field	mean 272 cm^2 (range: 225–360 cm^2)
Boost	mean 52 cm^2 (range: 30–132 cm^2)
Previous chemotherapy	
None	12
Pretreated	18
Taxoid-based	8
Platinum-based	14
Doxorubicin-based	5

Response to treatment was assessed with a CT scan of the chest lesion on day 25 (to allow eventual modification of the radiotherapy fields) and 45–60 days after treatment completion. Duration of response was measured from the time the criteria for the objective response were first met, with the CT scan done every 2 months for the first 6 months and every 3–4 months (or earlier if necessary) thereafter. Complete response was defined as the disappearance of a measurable chest lesion within 2 months after treatment completion that lasted for at least 2 months after response documentation. A remnant scar on the CT scan measuring less than 5% of the initial tumour volume and with no signs of progression within 2 months after response documentation was considered a complete response. Similarly, partial and minimal response refers to a 50–95% and a 25–49% reduction in tumour size, respectively. Small reductions in tumour size (0–24%) that lasted at least 2 months after response documentation were considered stable disease. All other cases were considered progressive disease, irrespective of the initial response.

Radiotherapy schedule

Radiotherapy treatment planning was based on recent chest CT scans. Anteroposterior radiation portals encompassing the primary tumour and part of the mediastinum were used to deliver a daily dose of 1.6–1.8 Gy. The homolateral supraclavicular area was included in patients with an upper lobe mass. One or two oblique fields directed to the bulky tumour area were used to increase the tumour dose per fraction to 2.4 Gy. This additional dose was given immediately after the treatment of the two anteroposterior fields (concomitant boost technique) with no interfraction interval. Patients whose whole hemithorax was irradiated received 18 Gy with 1.2 Gy per fraction, with the concomitant boost technique applied afterwards. Patients received a normalised total dose calculated with time correction (for α/β ratio = 10 Gy) of 60–64 Gy [6, 9]. The planned overall treatment time was 5 weeks. The radiation dose delivered to the spinal cord (α/β ratio = 2 Gy) was less than 44 Gy.

Docetaxel administration and dose escalation

At 12 h and at 30 min before chemotherapy, patients received 32 mg orally (p.o.) and 125 mg intravenous (i.v.) bolus methylprednisolone, respectively. Ranitidine 300 mg p.o. was given daily throughout the 5-week treatment period. Docetaxel was diluted in 250 ml normal saline and infused within 20 min. Tropisetron (5 mg i.v.) was given as antiemetic treatment. Blood pressure was monitored and symptoms were assessed every 5 min during infusion and every 15 min for the following 1 h. No steroids were used thereafter if no allergic reaction occurred. Whenever an allergic reaction was observed, patients were given methylprednisolone (32 mg p.o.) 12 h after chemotherapy.

The docetaxel starting dose level was 20 mg/m^2/week and was escalated by 10 mg/m^2/week increments in every 10 patients. There was no interpatient escalation. Five weekly cycles of the drug were delivered during the 5-week course of radiotherapy. If grade 3/4 toxicity occurred, the dose was

reduced by 50% or chemotherapy was interrupted, depending on severity. The dose level of a cohort in which at least 40% of patients expressed grade 3/4 non-haematological toxicity was considered as the maximum tolerated dose level.

Phenotypic analysis of peripheral blood lymphocytes

The manufacturer's recommended volume of the appropriate monoclonal antibody was aliquotted in individual tubes and 100 µl of peripheral blood was added directly to each tube, vortexed, and incubated for 20 min at 4°C. After the addition of fluorescence-activated cell sorter lysing solution (Immunoprep Kit, Coulter, U.S.A.) samples were washed twice with phosphate buffered saline containing azide (0.1% v/v) and stored in phosphate buffered saline containing paraformaldehyde (1% v/v). Cells were either analysed directly or stored at 4°C overnight before analysis. The following monoclonal antibodies were used for phenotypic analysis: anti-CD3 (IOT3), anti-CD4 (IOT4), anti-CD8 (IOT8), anti-CD20 (IOT20), and anti-CD57 (IOT57). Irrelevant murine monoclonal antibodies of the IgG1, IgG2a and IgG2b subclasses, used to define background staining, were fluorescein isothiocyanate (FITC) coupled. All monoclonal antibodies were obtained from Immunotech (Lumigny, France). Flow cytometry was performed on the Elite scan apparatus (Coulter) equipped with Elite Software 4.1. After daily calibration, a total of 10 000 cells contained within the lymphocyte gate were analysed for each tube. A control sample obtained from normal blood donors was analysed concurrently with each experimental sample.

Statistical analysis

The statistical analysis and graph presentation of survival curves was performed using the GraphPad Prism 2.01 version package. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test was used to determine statistical differences between life tables. Haematological measurements were compared using the paired two-tailed *t*-test. P values < 0.05 were considered to be statistically significant.

RESULTS

Non-haematological docetaxel-related toxicity

Severe hypersensitivity reactions during or immediately after docetaxel infusion were rare. 2 of 30 patients experienced acute dorsal pain immediately after the beginning of infusion of the first cycle, leading to the interruption of the infusion. Methylprednisolone 250 mg i.v. was given immediately. Both patients received their treatment 10 min later with no further complications. Subsequent courses were not associated with a similar adverse event. One other patient experienced an asthma-like crisis during the third cycle and was successfully treated with oxygen and inhaled bronchodilators. 3 of 30 patients (10%) developed a mild skin rash in the few days after the first cycle and were treated with antihistamines. Hot flushes were observed in 8 of 30 patients (27%).

Steroid-related toxicity was minimal because the high dose of methylprednisolone was restricted to 1 day per week. 1 patient presented with steroid-related gastroplegia that rapidly regressed. 5 patients showed an increase in glucose levels to 250 mg%, but this was transient, lasting 1–2 days after steroid administration and no insulin was necessary.

Table 2 summarises the non-haematological dose-limiting toxicity. Docetaxel-related non-haematological toxicity was minimal in the 20 and 3 mg/m^2/week dose level cohorts. At these dose levels, grade 2 peripheral neuropathy was observed late in the course of treatment, after the third or fourth cycle, in 2 of 20 patients and regressed within 2–3 weeks after treatment completion. Mild (grade 1/2) asthenia, observed in 17 of 20 patients (85%), was never the cause of treatment interruption or delay. Grade 1 alopecia was observed in 15 of 20 (75%) patients, and grade 2 hypotension in 1 of 20 (5%).

Table 2. Non-haematological dose-limiting toxicity

Dose level (mg/m^2)	No. of patients	Toxicity (grade)								
		Asthenia			Oesophagitis			Hypotension		
		0/1	2	3	0/1	2	3	0/1	2	3
20	10	8	2	0	6	3	1	10	0	0
30	10	7	3	0	5	4	1	10	0	0
40	10	0	4	6	0	4	6	8	2	0

Pronounced asthenia and anorexia were the main side-effects observed in 10 patients treated with the 40 mg/m^2/week dose level. Grade 3 asthenia was the cause of treatment interruption in 1 of 10 patients and of 50% dose reduction in 3 of 10 patients. Asthenia started during the third or fourth week of treatment. 6 patients who completed the five cycles of the programmed dose experienced severe fatigue (grade 3), anorexia and weight loss (5–12 kg) that lasted for more than 4 weeks after treatment completion. This was the reason why no further dose escalation was considered. Grade 2 hypotension was observed in 1 of 10 patients (10%) concurrently with severe fatigue. One patient interrupted treatment because of diffuse dry skin desquamation observed an day 21. One patient had bilateral grade 2 leg oedema and 1 had grade 2 peripheral neutropathy. Grade 2 alopecia was observed in 6 of 10 patients.

No headache, arthralgia, myalgia, nausea, vomiting, diarrhoea, mucositis or nail disorders were observed at any of the three dose levels.

'In field' radiotherapy-related toxicity

Radiation-induced grade 3 oesophagitis that resulted in a 1–2 week treatment delay was observed in 6 of 30 patients (20%). However, delayed grade 3 oesophagitis that started immediately after treatment completion (week 6) was observed in another 4 patients treated with a 40 mg/m^2/week dose level. 5 of 20 (25%) and 8 of 10 patients of the 20–30 and 40 mg/m^2/week cohorts, respectively, complained of chest pain and a burning sensation that lasted up to 3 weeks after treatment completion. 2 patients (7%) presented with pneumothorax on weeks 6 and 7, respectively, and were successfully treated. 'In field' grade 2 early radiation skin toxicity was observed in 1 of 30 patients (3%). No patients developed neurological or heart-related late sequelae among the 8 patients who completed 8–12 months of follow-up. Moreover, localised pulmonary fibrosis was common, but was symptomatic in only 1 of the 8 patients.

Haematological toxicity

Haematological toxicity is shown in Table 3. Haemoglobin and neutrophil toxicity was minimal in all cohorts. Grade 3 neutropenia was observed in 2 of 20 patients (10%; 1 complicated with sepsis) treated with the 20 and 30 mg/m^2/week dose levels. 3 of 10 patients of the 40 mg/m^2/week cohort

Table 3. Haematological toxicity

Dose level/week (mg/m^2)	No. of patients	Toxicity (grade)										
		Haemoglobin			Neutrophils			Platelets			Lymphocytes	
		0/1	2	3	0/1	2	3	0/1	2	3	0–2	3–4
20	10	10	0	0	9	1	0	10	0	0	0	10
30	10	9	1	0	6	2	2	10	0	0	0	10
40	10	8	2	0	5	2	3	10	0	0	0	10

expressed grade 3 neutropenia (1 with sepsis). Patients with sepsis were successfully treated with antibiotics and human recombinant granulocyte colony-stimulating factor (5 μg/kg/day subcutaneously (s.c.)). Stable haemoglobin levels were maintained throughout the treatment at all dose levels, with a median reduction of 0.7 g/ml (nadir on week 4 or 5). 4 of 30 (13%) patients (all 4 with metastatic disease) were given red blood cell transfusions to maintain haemoglobin levels > 11 g/ml. No platelet toxicity was observed.

Severe lymphocytopenia was observed in all three cohorts. Starting from initial counts of 1842 ± 863 ml, lymphocyte counts were reduced to 539 ± 363 ml on day 28 ($P = 0.001$). 2 cases of interstitial pneumonia, but no cases of opportunistic pneumonia, were observed.

Figure 1 shows the mean absolute lymphocyte counts (assessed weekly for 8 weeks after the beginning of treatment) for the 30 lung cancer patients treated with docetaxel and radiotherapy; after treatment completion, a gradual increase in the absolute number of lymphocytes was observed, which was time-dependent. Moreover, phenotypic analysis of the peripheral blood lymphocytes from 10 patients (treated with the 30 and 40 mg/m^2/week dose levels) revealed that all lymphocyte subpopulations (CD3, CD4, CD8, CD20, and CD57) were significantly decreased on day 28 (Table 4).

Response

Table 5 shows the responses observed at the three dose levels. Complete response of the chest disease was observed in 8 of 30 (27%) patients and partial response in 15 (50%). The overall response rate was 77% (95% confidence interval (CI) 60–92%). One of the complete response patients had known refractory disease to taxoids. 5 and 10 patients with stage IIIb tumours showed a complete and partial response, respectively, for an overall response rate of 83%. The overall local (in radiotherapy field) response rate in stage IV cases was 67% (3 complete responses and 5 partial responses). Minimal response was seen in 4 (13%) patients and stable or progressive disease in 3 patients (10%). 7 of 30 patients had metastatic disease not previously exposed to docetaxel and none of these patients responded to treatment.

2 patients with stage IIIb disease who had responded to treatment died because of massive haemoptysis (1 week and 2 months after treatment completion, respectively). One of these patients showed necrotic tumour cavitation on CT scan. 3 stage IIIb patients died of local relapse (at 2, 4 and 6 months). 10 of 18 stage IIIb patients (55%) are alive with no evidence of local disease progression 3–15 months after treatment (Figure 2a). The median overall survival for stage IIIb was 7.5 months (Figure 2b).

3 of 12 treated patients (25%) with stage IV disease are alive with no evidence of local disease progression (3, 4 and 5

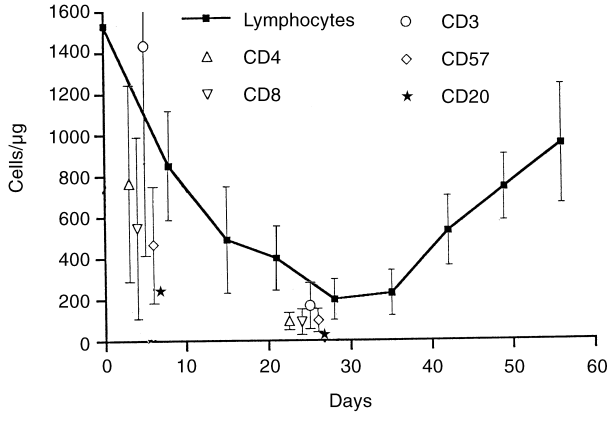

Figure 1. Total lymphocyte and lymphocyte subset analysis during and after docetaxel-based radiochemotherapy for non-small cell lung cancer.

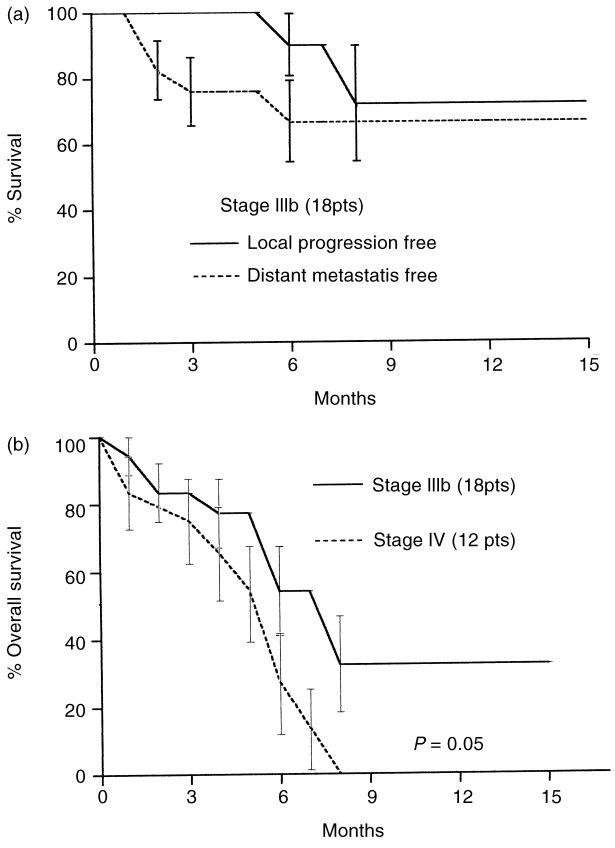

Figure 2. (a) Local progression-free and distant metastasis-free survival; and (b) overall survival stratified for stage, for 30 stage IIIb non-small cell lung cancer patients treated with docetaxel-based radiochemotherapy.

Table 4. *Analysis of lymphocyte subsets*

Lymphocytes	Day 0 (mean ± S.D.)	Day 28 (mean ± S.D.)	*P* value
Total	1842 ± 863*	539 ± 363	0.002
CD3	1423 ± 824	334 ± 231	0.002
CD4	798 ± 422	197 ± 137	0.001
CD20	110 ± 54	22 ± 8	0.0003
CD57	168 ± 230	134 ± 62	0.002

S.D., standard deviation. *Results are expressed as the mean value ± S.D. of the observed absolute individual numbers of cells/ml.

months after treatment). 9 patients died of distant metastases 1–7 months after treatment completion, although no patients had local disease progression confirmed by CT scan. The median survival for all stage IV patients was 5.5 months (Figure 2b), which was significantly lower than that for stage IIIb patients ($P = 0.05$). Figure 3 shows the resolution of large masses seen even before completion of treatment.

DISCUSSION

Locally advanced inoperable NSCLC is a major therapeutic problem because radiotherapy results are disappointing, with 5-year survival less than 10%. The value of chemotherapy combined with radiotherapy remains controversial. Three of five randomised studies have shown no survival advantage of chemoradiotherapy over radiotherapy alone [10–14]. In a recent study, we showed that 45% of patients with locally advanced disease treated with radiotherapy alone will die from local relapse with no evidence of distant metastases [15]. Moreover, short schedules of high-dose radiotherapy delivered within less than 5 weeks substantially improved the overall and local disease-free survival [5, 6]. An additional treatment that would increase the local control rate without increasing toxicity would therefore result in further benefit.

In the present study, we established a well-tolerated docetaxel scheme that could be administered concurrently with radiotherapy in patients with NSCLC. Weekly doses of up to 30 mg/m^2 were well tolerated with minimal haematological toxicity and without severe asthenia, which was observed in higher doses. This regimen, which delivers a total dose of 90 mg/m^2 within 3 weeks, is in accordance with a previous phase I study of docetaxel given on days 1 and 8 every 3 weeks where the maximum tolerated dose was 100 mg/m^2 [16]. The radiation-induced acute toxicity, although higher than expected from conventional radiotherapy alone, was similar to that reported by accelerated regimens [17]. It mainly concerned oesophagitis, which was the cause of 1–2 week treatment delay in 20% of patients. However, severe oesophagitis was more frequent in the high dose level (40 mg/m^2/week) and was dose-limiting at this dose level. Reduction of the radiation dose intensity delivered to the oesophagus, whenever possible, is strongly recommended to avoid treatment delay and protect patients' quality of life during treatment.

The other dose-limiting toxicity associated with docetaxel administration was grade 3 fatigue, which was observed in 4 of 10 patients treated with the high (40 mg/m^2/week) dose level. Asthenia resulted in treatment refusal in 1 patient and docetaxel dose reduction in 3 other patients. Moreover, asthenia was observed after the third or fourth week of treatment, suggesting that it is cumulative. Administration of vitamins and antidepressants did not prove to be of any help; the patients recovered from this toxicity 3–4 weeks post-treatment.

Another potentially important side-effect is the severe lymphocytopenia observed at all dose levels. In a previous study of paclitaxel chemoradiotherapy for lung cancer, Reckzeh and colleagues [18] observed a similar effect on lymphocyte counts which resulted in interstitial pneumonia outside the radiation field in 7 of 15 patients. Phenotypic analysis of lymphocyte subsets revealed that T ($CD4^+$ and $CD8^+$), B ($CD20^+$) and NK ($CD58^+$) cells are equally affected during the weekly administration of the docetaxel–radiotherapy combination. This finding strongly suggests that the regimen results in non-specific inhibition of lymphopoiesis. Whether lymphocytopenia is directly related to docetaxel or to its combination with corticosteroids or radiotherapy or both cannot be answered from the present study. However, a similar decrease in the absolute number of $CD4^+$ cells was also observed in patients with NSCLC treated with docetaxel–cisplatin or docetaxel–vinorelbine combination (not shown). Therefore, this $CD4^+$ lymphocytopenia is probably related to the docetaxel administration rather than to radiotherapy.

The onset of asthenia and loss of appetite occurred in the third week, together with the appearance of a severe drop in lymphocyte count. The mechanisms of the appearance of asthenia during cytotoxic treatment are unknown. Further studies are needed to determine whether immunological mechanisms may contribute to the appearance of fatigue.

In spite of the low absolute number of $CD4^+$ cells, no case of opportunistic infection was observed in this group of 30 patients; on the contrary, symptomatic interstitial pneumonia, which was successfully treated with antibiotics, was detected in only 2 of 30 patients (6.6%). This is in overt contrast to the findings of Reckzeh and colleagues, in which many of their patients developed interstitial pneumonia.

Docetaxel has shown substantial activity against NSCLC [19–21]. In previous phase II studies of first-line treatment

Table 5. *Response of the primary tumour*

	Complete response	Partial response	Minimal response	Stable or progressive disease	Response rate (%)
Dose level (mg/m^2/week)					
20 ($n = 10$)	3	4	3	0	70
30 ($n = 10$)	4	5	0	1	90
40 ($n = 10$)	1	6	1	2	80
Stage					
IIIb ($n = 18$)	5	10	2	1	83
IV ($n = 12$)	3	5	2	2	67
Total	8	15	4	3	77

with docetaxel combined with cisplatin or vinorelbine, we confirmed a 48 and 36% response rate, respectively [22, 23]. The overall response rate of 77% with 27% complete responses observed in the present study is encouraging, as most patients had disease unresponsive to chemotherapy. A dramatic resolution of large masses was seen even before treatment completion (Figure 3), showing an important activity of the regimen in a subset of tumours. One complete response and three partial responses were observed in patients previously treated with taxoid-based chemotherapy. Additional comparative studies in stage III patients are needed to fully demonstrate this beneficial effect of docetaxel.

The high response rate and the unexpected early complete response (before the completion of 35 Gy) observed in 3 of 30 cases (10%) may be relevant to the recently reported activity of taxanes on apoptosis-related proteins. Taxanes induce phosphorylation of the anti-apoptotic protein bcl-2 [24]. Moreover, a p53-independent taxane-inducible apoptosis pathway has been suggested [25] and, indeed *p53* mutations in NSCLC seem not to affect the sensitivity to

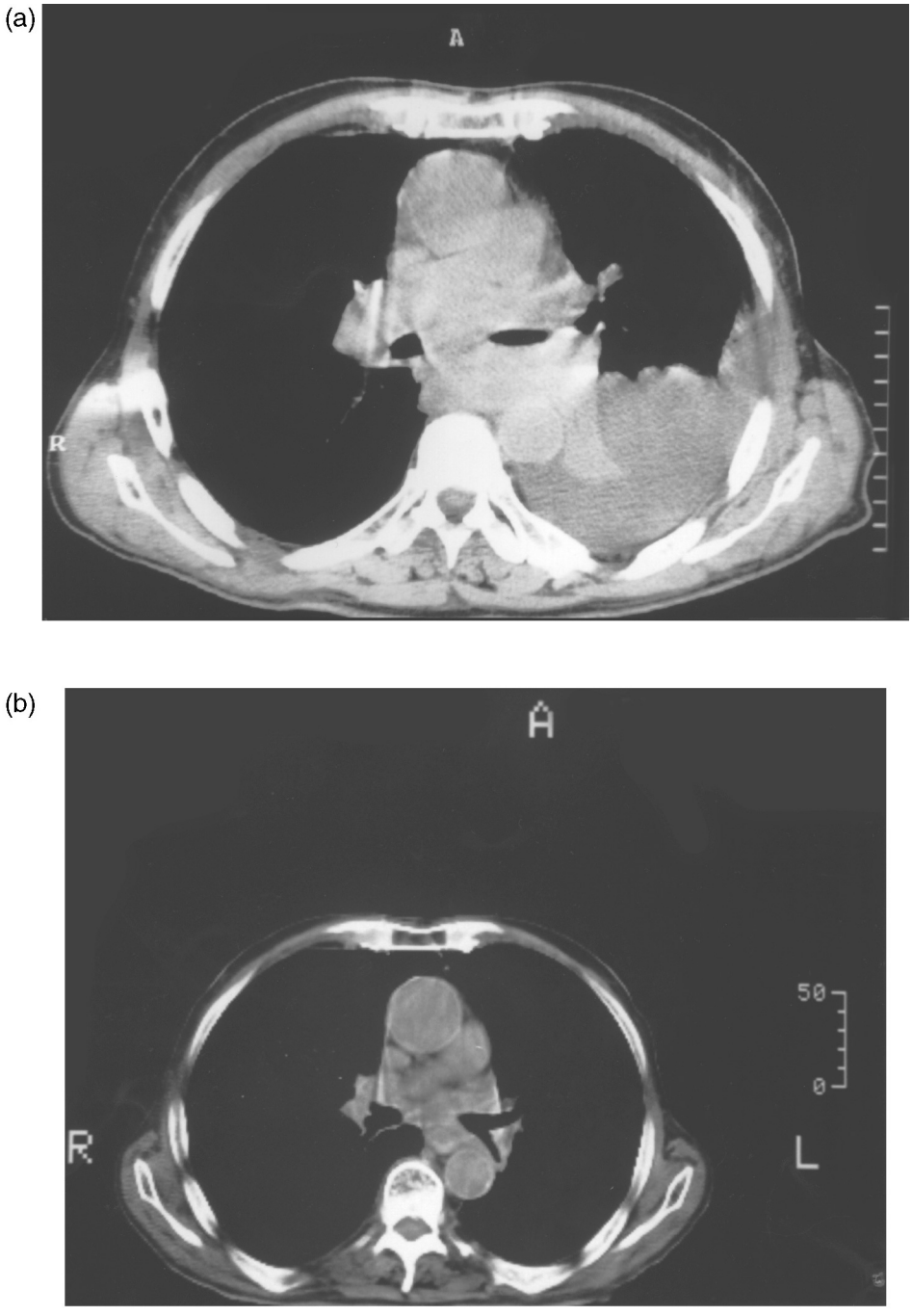

Figure 3. (a) Patient with locally advanced high-grade squamous cell lung carcinoma before treatment and after 24 Gy of radiotherapy (18 Gy delivered to the whole hemithorax) together with docetaxel (30 mg/m^2/weekly); (b) complete response documented 4 weeks after the beginning of treatment. Bars on (a) and (b) represent 10 cm and 5 cm respectively of actual length.

radiotherapy [26]. Since radiation kills cancer cells by apoptosis induction, the combined radiation and taxane therapy may become a unique model to investigate novel approaches in radiosensitisation based on apoptosis modulation.

We conclude that docetaxel-sensitised radiotherapy is feasible and this treatment option looks promising for stage IIIb NSCLC, as the high response rate (even after low radiation doses), the patterns of failure and overall survival (approximately 65% local and distant progression-free survival 15 months after treatment) were far beyond expectations [27]. Because 20 mg/m^2/week was as effective as higher dose levels, a twice-weekly regimen (i.e. 15–20 mg/m^2 twice a week) that could better induce cell synchronisation would be a challenging regimen to test.

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