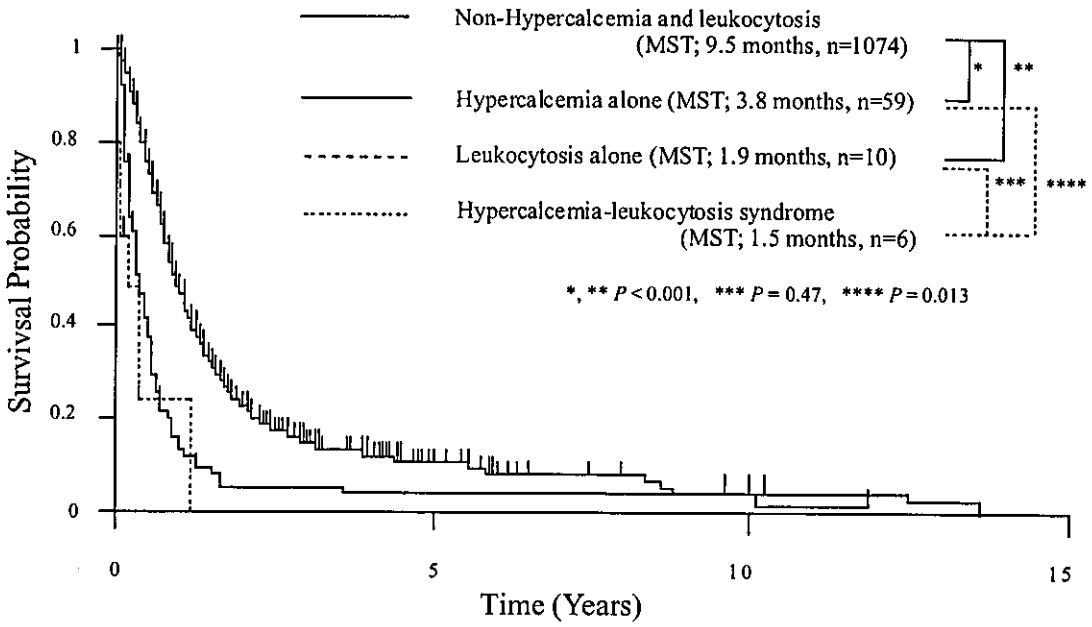

Fig. 1 Kaplan–Meier curve for overall survival in patients with hypercalcemia, leukocytosis or both.

blood mononuclear cells from normal human donors [16]. Increased osteoclastic bone resorption is one of the major causes of hypercalcemia [1]. Therefore, G-CSF secreted from cancer cells may cause not only leukocytosis but also hypercalcemia by promoting proliferation and differentiation of the common hematopoietic progenitors of granulocytes and osteoclasts. This might be one of the mechanisms by which leukocytosis and hypercalcemia develop concomitantly in some patients with lung cancer in the present study. Consistent with this notion, Asahi et al. have recently reported that a lung cancer cell line established from a squamous cell lung caner of a patient with hypercalcemia and leukocytosis produces both G-CSF and parathyroid hormone-related protein (PTH-rP) [6]. It has been widely-recognized that PTH-rP and G-CSF produced by cancer cells play a critical role in the pathophysiology of hypercalcemia and leukocytosis, respectively [17,18]. Thus, it seems likely that production of a factor in cancer cells which bipotently promotes the formation of granulocytes and osteoclasts leads to the simultaneous manifestation of hypercalcemia and leukocytosis.

5. Conclusion

In conclusion, our results demonstrate a significant correlation between the occurrence of hypercalcemia and leukocytosis and suggest that the hypercalcemia–leukocytosis syndrome is an independent clinical entity that indicates poorer outcome in lung cancer patients. These findings should deepen our understandings of the pathophysiology of hypercalcemia and leukocytosis and, more importantly, improve the management of cancer patients with these paraneoplastic syndromes.

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Preoperative concurrent chemoradiotherapy with cisplatin and docetaxel in patients with locally advanced non-small-cell lung cancer

H Katayama[1], H Ueoka*[,1], K Kiura[1], M Tabata[1], T Kozuki[1], M Tanimoto[1], T Fujiwara[2], N Tanaka[2], H Date[3], M Aoe[3], N Shimizu[3], M Takemoto[4] and Y Hiraki[4]

[1]Department of Internal Medicine II, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan; [2]Department of Surgery I, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan; [3]Department of Surgery II, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan; [4]Department of Radiology, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

The objective of this study was to assess the feasibility and effectiveness of an induction chemoradiotherapy regimen followed by surgery in patients with locally advanced non-small-cell lung cancer (LA-NSCLC). A total of 22 patients with LA-NSCLC were treated with induction chemoradiotherapy consisting of cisplatin (40 mg m^{-2}) and docetaxel (40 mg m^{-2}) given on days 1, 8, 29 and 36 plus concurrent thoracic irradiation at a dose of 40–60 Gy (2 Gy fraction^{-1} day^{-1}). Surgical resection was performed within 6 weeks after completion of induction therapy. Objective response to the induction therapy was obtained in 16 patients (73%). In all, 20 patients (91%) underwent surgery and complete resection was achieved in 19 patients (86%). Pathological downstaging and pathological complete response were obtained in 14 (64%) and five (23%) patients, respectively. With a median follow-up period of 32 months, the calculated 3-year overall and progression-free survival rates were 66 and 61%, respectively. It is noteworthy that the 3-year overall survival rate in 14 patients achieving pathological downstaging was extremely high (93%). Toxicity was manageable with standard approaches. No treatment-related deaths occurred. This combined modality treatment is feasible and highly effective in patients with LA-NSCLC. The results warrant further large-scale study to confirm the effectiveness of this regimen.
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Keywords: induction chemoradiotherapy; cisplatin; docetaxel; non-small-cell lung cancer

Since the majority of patients with locally advanced non-small-cell lung cancer (LA-NSCLC) develop distant metastases, the treatment outcomes of patients receiving surgery or radiotherapy alone are extremely poor. In previous reports, 5-year survival rates of LA-NSCLC patients undergoing locoregional treatment alone ranged from 5 to 15% (Pearson *et al*, 1982; Martini and Flehinger, 1987; Mountain, 1988; Shields, 1990; Cox *et al*, 1991). Therefore, a combined modality approach to control both local tumour and distant micrometastasis is required to improve the treatment outcome. A variety of multimodality therapies that include chemotherapy, surgery and/or radiotherapy have recently been assessed in clinical trials. Use of postoperative chemotherapy or radiotherapy has not shown an apparent survival benefit to date (The Lung Cancer Study Group, 1981; Pisters *et al*, 1994; Keller *et al*, 2000). Although Le Chevalier *et al* (2003) recently reported a statistically significant prolongation of survival in a large-scale randomised study of postoperative chemotherapy, the advantage was extremely limited. On the other hand, preoperative chemotherapy resulted in a definite survival advantage in a few randomised trials comparing preoperative chemotherapy plus surgery with surgery alone in LA-NSCLC patients (Rosell *et al*, 1994; Roth *et al*, 1994). Local recurrence rates in these trials were considerably high, however. For example, Rosell *et al* (1994) reported a local recurrence rate of 54% in patients who received preoperative mitomycin, ifosfamide and cisplatin. Similarly, in our previous study of preoperative cisplatin and irinotecan chemotherapy, the local recurrence rate was 33% overall and 50% in patients being treated for disease relapse (Date *et al*, 2002). Then, we considered that further prolongation of survival might be obtained by improvement of local control, adding concurrent thoracic irradiation to induction chemotherapy. In several recent reports, preoperative chemoradiotherapy in patients with LA-NSCLC was shown to be feasible and effective, although the new drugs developed in the 1990s such as irinotecan and docetaxel were not included (Albain *et al*, 1995; Choi *et al*, 1997; Eberhardt *et al*, 1998; Thomas *et al*, 1999). We have already confirmed the feasibility and effectiveness of concurrent chemoradiotherapy using cisplatin and docetaxel in patients with unresectable LA-NSCLC (Kiura *et al*, 2003), whereas a combination of cisplatin, irinotecan and concurrent thoracic irradiation has been reported to be toxic and unacceptable (Yokoyama *et al*, 1996). Based on these results, the present study was planned to assess the feasibility and effectiveness of this chemoradiotherapy as preoperative treatment in patients with LA-NSCLC.

*Correspondence: H Ueoka; E-mail: hueoka@md.okayama-u.ac.jp
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clinical

PATIENTS AND METHODS

Patient selection

Previously untreated patients with histologically confirmed stage IIIA or IIIB NSCLC, with measurable disease, were eligible for the study. In this study, a mediastinal lymph node $\geqslant 10$ mm along the short axis by CT scan was defined as a metastatic lymph node. The other inclusion criteria were age $\leqslant 75$ years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 (Oken *et al*, 1982), and adequate functional reserves of bone marrow (leucocyte count $>4000\,\mu l^{-1}$, platelet count $>100\,000\,\mu l^{-1}$), liver (serum bilirubin level $<1.5\,mg\,dl^{-1}$, aspartate aminotransferase and alanine aminotransferase levels (AST/ALT) <2 times the upper normal limit), kidney (serum creatinine level $<1.5\,mg\,dl^{-1}$, creatinine clearance $>60\,ml\,min^{-1}$) and lung (arterial oxygen pressure (PaO_2) >60 Torr). Patients with concomitant malignancies, supraclavicular lymph node involvement, or malignant pleural or pericardial effusion were excluded from the study. Written informed consent was obtained from all patients.

Evaluations

Staging procedures included medical history and physical examination, complete blood cell counts (CBC), standard blood chemistry profile, 24-h urine creatinine clearance (Ccr), electrocardiogram, chest radiography, computed tomography (CT) scans of the chest and upper abdomen, magnetic resonance imaging (MRI) of the brain, fibre optic bronchoscopy and radionuclide bone scan. Magnetic resonance imaging of the chest was required if mediastinal invasion was suspected.

During treatment, CBC was repeated two to three times a week, and blood chemistry tests, Ccr evaluations and chest radiograph were repeated at least once a week. Chest CT scans were repeated after each chemotherapy course. After completion of combined modality treatment, each patient was restaged with all tests used for the initial work-up, and followed monthly with chest radiographs. CT scans were repeated every 3 months.

Treatment plan

Chemotherapy was administered on days 1, 8, 29 and 36. Patients were premedicated with dexamethasone (8 mg) and granisetron (3 mg) or ondansetron (4 mg) immediately prior to cisplatin administration. Cisplatin $40\,mg\,m^{-2}$ diluted in 300 ml of physiological saline was given as a 1-h i.v. infusion, followed by docetaxel $40\,mg\,m^{-2}$ dissolved in 500 ml of physiological saline as a 1-h i.v. infusion. Patients then received hydration with 2000 ml of physiological saline. If leucocyte count was less than $3000\,\mu l^{-1}$ or platelet count less than $100\,000\,\mu l^{-1}$ on day 29, chemotherapy was postponed until recovery. No dose attenuations were planned for reductions in leucocyte or platelet counts on days 8 or 36. Radiotherapy was started on the first day of chemotherapy using a linear accelerator (6–10 MeV). A total radiation dose of 40 Gy was planned with conventional fractionation ($2\,Gy\,day^{-1}$). Dose escalation of radiotherapy was allowed for poorly responding tumours. The original volume included the site of primary tumour with a margin of 2 cm around the mass and the ipsilateral hilum, and the whole width of the mediastinum with a margin of 1 cm around the radiographically visible region of involvement extending inferiorly to 3 cm below the carina or 2 cm below the radiographically demonstrated tumour mass. The original volume was treated with an anterior–posterior parallel-opposed pair of portals at doses of 40 or 46 Gy. For poor responding patients, an additional 20 Gy dose was administered to the boost volume, including the sites of primary tumour and involved lymph nodes. The boost volume was treated with a pair of oblique fields to keep cumulative radiation dose to the spinal cord at less than 46 Gy.

Following induction chemoradiotherapy, patients were evaluated for response based on a chest radiograph and CT scans. Patients without progressive disease were to have surgery within 6 weeks of completing induction therapy. The surgical procedure was determined on the basis of disease extent before induction treatment. Lobectomy was preferred; however, bilobectomy, sleeve resection, or pneumonectomy was performed in cases requiring those procedures because of primary tumour invasion. Resection with reconstruction of the chest wall was performed if necessary. The bronchial stump was covered with intercostal muscle pedicle.

Postoperative treatment was left to the physician's discretion. Usually, if apparent residual tumour was left or viable cells were found in the surgically resected specimens, further chemotherapy was given.

Response, survival and toxicity assessments

Response was assessed using ECOG criteria (Oken *et al*, 1982), with some modification, as follows: complete response (CR), disappearance of all tumour at the end of induction therapy; partial response (PR), a $\geqslant 50\%$ reduction in the sum of the products of two perpendicular dimensions of all measurable lesions; stable disease (SD), a $<50\%$ reduction and $<25\%$ increase in the sum of the products of two perpendicular dimensions of all measurable lesions; progressive disease (PD), a $\geqslant 25\%$ enlargement of tumour lesion or the appearance of any new lesions. Survival was assessed on an 'intent-to-treat' basis, with survival time defined as the period from initiation of chemoradiotherapy to death or the last follow-up evaluation. The survival curve was calculated by the Kaplan and Meier (1958) method. Toxicity was assessed by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (NCI-CTC version 2.0, 1998). Statistical analyses were performed using an SPSS Base System and Advanced Statistics Program (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between August 1998 and August 2001, 22 patients with stage IIIA or stage IIIB NSCLC were treated with this combined modality treatment. The baseline patient characteristics are listed in Table 1. Median age was 60 years and PS was 0 or 1 in all patients. In all, 18 patients had N2 disease, of whom nine had histologically proven N2 disease by mediastinoscopy or transbronchial needle aspiration biopsy. One patient had N3 disease in the contralateral mediastinal lymph node. Seven patients had T4 disease consisting of aortic invasion in three patients, pulmonary artery invasion in three, and mediastinal invasion in one, which were confirmed by enhanced chest MRI.

Induction therapy: response and toxicities

Out of 22 evaluable patients, 11 completed the planned chemoradiotherapy treatment. Chemotherapy dose was modified due to toxicity in 11 patients. Docetaxel dose was reduced on days 29 and 36 in four patients. Four patients did not receive chemotherapy on day 36 due to neutropenia in three patients and diarrhoea in one. In three patients, chemotherapy was omitted on both days 29 and 36 and only radiation therapy was accomplished, because of anaphylactic reaction to docetaxel, paralytic ileus and patient refusal in one patient each. The total radiation dose was 40 Gy in 10 patients, 46 Gy in nine and 60 Gy in three. Clinical response to induction therapy was PR in 16 patients (73%) and SD in six (27%). Toxicities experienced during induction therapy are listed in Table 2. Grades 3 and 4 leukopenia and neutropenia were each observed in 13 patients; however, no febrile neutropenia occurred. Nonhaematological toxicities were primarily gastrointestinal

Table 1 Patient characteristics

	No. of patients	
No. of patients evaluated	22	
Median age in years (range)	60	(30–73)
Sex		
Male	15	
Female	7	
ECOG PS		
0	11	
1	11	
Histology		
Adenocarcinoma	11	
Squamous cell carcinoma	11	
Stage of disease		
IIIA	14	
T1N2M0		3
T2N2M0		7
T3N2M0		4
IIIB	8	
T4N0M0		2
T4N1M0		1
T4N2M0		4
T3N3M0		1

ECOG = Eastern Corporative Oncology Group; PS = performance status.

Table 2 Toxicity of induction therapy ($n = 22$)

	Grade				
	1	2	3	4	% of toxicities ⩾grade 3
Leukopenia	2	6	10	3	59.1
Neutropenia	2	5	9	4	59.1
Anaemia	10	7	1	0	4.5
Thrombocytopenia	9	0	0	0	0
Nausea/vomiting	13	3	2	0	9.1
Diarrhoea	1	3	1	0	4.5
Constipation	0	0	0	1	4.5
Hepatic	8	2	0	0	0
Renal	3	0	0	0	0
Cardiac	0	0	0	1	4.5
Pulmonary	0	0	0	0	0
Oesophagitis	5	5	1	0	4.5
Allergy	0	0	0	1	4.5

Toxicity was assessed and graded using NCI common toxicity criteria (National Cancer Institute Common Toxicity Criteria, version 2.0, 1998).

effects, although three patients had serious effects including congestive heart failure with atrial fibrillation, paralytic ileus and anaphylactic reaction to docetaxel in one patient each.

Surgery and pathologic response

Two of 22 patients did not undergo surgical resection because of congestive heart failure ($n = 1$) and patient refusal ($n = 1$). For 20 patients who had surgery, the median time from the end of induction therapy to surgery was 37 days (range, 25–59 days). Surgical procedures included lobectomy in 16 patients, sleeve lobectomy in two and bilobectomy and pneumonectomy in one each. One patient who had contralateral mediastinal lymph node metastasis before beginning chemoradiotherapy underwent contralateral mediastinal lymph node resection (R3). In all, 19 patients had complete tumour resection with microscopically negative margins. In one patient, residual tumour remained microscopically at the resected margin after surgery. Pathological downstaging was obtained in 14 patients (64%) and pathological CR (no viable tumour cells in surgical specimens) was achieved in five of those 14 patients (23%), the latter five of whom were determined to have obtained PR by CT scan after induction therapy.

Postoperative treatment

Among 20 patients undergoing surgical resection, 12 received no postoperative chemotherapy or radiotherapy until disease progression. Six patients received postoperative chemotherapy consisting of cisplatin and docetaxel, of whom four had two treatment courses and two had one course because of toxicity (haemothorax and diarrhoea in one patient each). One patient whose tumour was not downstaged underwent further chemoradiotherapy comprising two courses of cisplatin and docetaxel with concurrent thoracic irradiation at a dose of 20 Gy. Another patient, whose tumour could not be completely resected, underwent bronchial artery infusion of cisplatin, mitomycin C and vindesine with concurrent thoracic irradiation at a dose of 20 Gy. Thus, two patients of 22 received a total radiation dose of 60 Gy.

Postoperative complications

The major postoperative complication was pulmonary toxicity. One patient receiving 60 Gy radiotherapy developed haemothorax during postoperative chemotherapy. He was successfully managed by thoracic tube drainage and was alive without recurrence at the time of this report. Two patients had massive pleural effusions and were successfully treated by tube drainage and pleural adhesion therapy. Six patients experienced radiation pneumonitis (grade 2 in four patients and grade 3 in two) and were treated with prednisolone. These toxicities were reversible.

Survival and pattern of relapse

At a median follow-up time of 32 months, seven of 22 patients have had disease relapse. Of those seven patients, six died of disease progression and one developed solitary brain metastasis and is still alive. Progression of local tumour was observed in only two of the six patients who died of cancer. The initial failure sites in the other four patients were supraclavicular lymph node, para-aortic lymph node, lung and lumbar spine in one patient each. A total of 15 patients are currently alive with no evidence of recurrent disease. The 3-year overall and progression-free survival rates were 66 and 61% in 22 enrolled patients (Figure 1), 68 and 63% in 20 patients who had surgical resection (Figure 2) and 93 and 74% in 14 patients who achieved downstaging of disease (Figure 3), respectively. Five patients achieving pathological CR are currently alive, although one has developed a solitary brain metastasis.

DISCUSSION

The objective of this study was to investigate the feasibility and effectiveness of an induction chemoradiotherapy regimen consisting of cisplatin, docetaxel and concurrent thoracic radiation followed by surgery in patients with LA-NSCLC. Results confirmed that this combined modality treatment was well tolerated. In other recent reports of induction chemoradiotherapy followed by surgery, the frequencies of treatment-related deaths were approximately 2% during induction therapy and between 4 and 7.5% after surgery (Albain *et al*, 1995; Choi *et al*, 1997; Eberhardt *et al*, 1998; Thomas *et al*, 1999). Therefore, it is notable that none of the

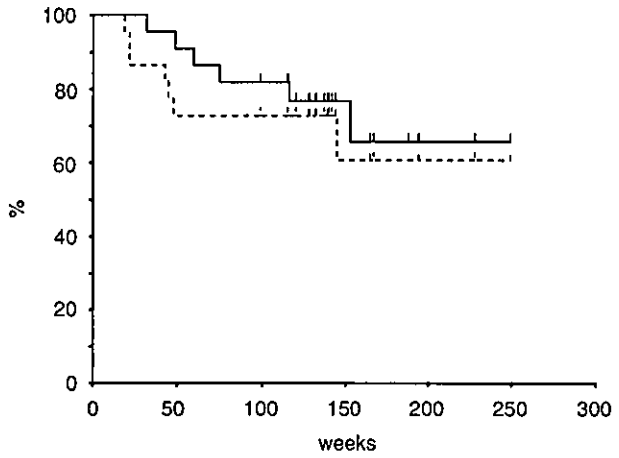

Figure 1 Overall and disease-free survival curves for 22 enrolled patients. Estimated 3-year survival and disease-free survival rates were 66 and 61%, respectively.

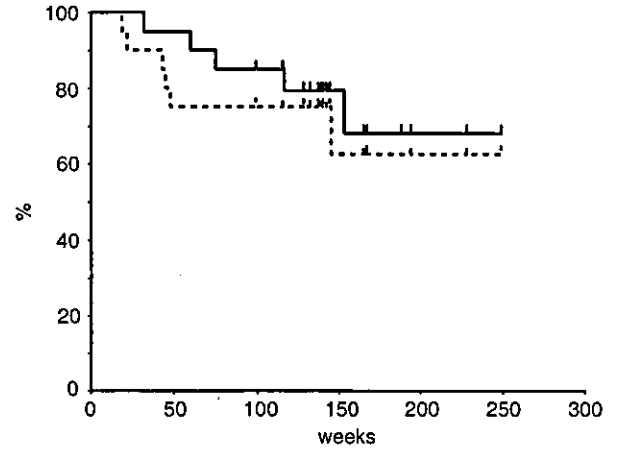

Figure 2 Overall and disease-free survival curves for 20 patients who underwent surgical resection. Estimated 3-year survival and disease-free survival rates were 68 and 63%, respectively.

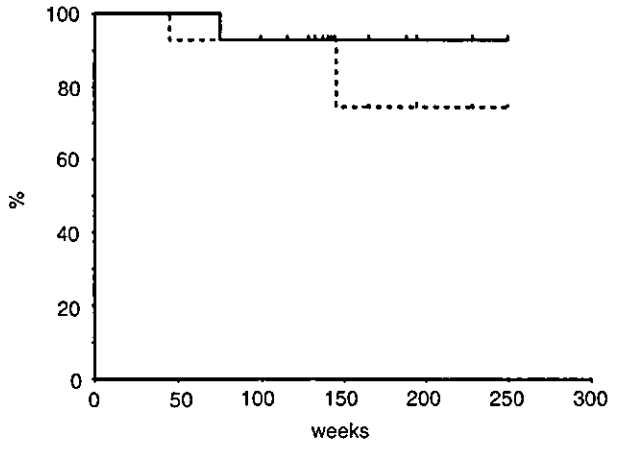

Figure 3 Overall and disease-free survival curves for 14 patients who achieved pathological downstaging of disease. Estimated 3-year survival and disease-free survival rates were 93 and 74%, respectively.

patients in the study reported herein experienced treatment-related deaths during induction therapy or after surgery. In the present study, the major toxicities of induction therapy, which included leukopenia, congestive heart failure, paralytic ileus and anaphylactic reaction to docetaxel, were manageable with standard approaches. The main postoperative toxicities were pulmonary complications such as haemothorax, massive pleural effusion and pneumonitis, which were also successfully managed by standard treatment.

Efficacy results after induction chemoradiotherapy were good, with 73% of patients responding and a 3-year survival rate of 66%. These findings are superior to those achieved in other studies in patients with LA-NSCLC. For example, 3-year survival rates of 27% for stage IIIA and 24% for stage IIIB patients were reported by Albain *et al*, 37% by Choi *et al* and 35% for stage IIIA and 26% for stage IIIB patients by Thomas *et al* (Albain *et al*, 1995; Choi *et al*, 1997; Thomas *et al*, 1999).

To improve local control, we adopted concurrent chemoradiotherapy as induction therapy. In the 1990s, a few randomised trials reported a survival advantage with induction chemotherapy followed by surgery, compared to surgery alone in patients with LA-NSCLC (Rosell *et al*, 1994; Roth *et al*, 1994). We also previously reported that induction chemotherapy with cisplatin and irinotecan was effective in 15 patients with LA-NSCLC, having pathologically confirmed mediastinal metastases (Date *et al*, 2002). The 3-year disease-free and overall survival rates were 24 and 40%, respectively, which were considered encouraging. However, pathological downstaging was obtained in only two patients (13%) and pathological CR in one (7%). Furthermore, initial disease relapse occurred at the local site in half of the patients who had disease relapse (Date *et al*, 2002). These results suggested that methods to achieve better local control were needed to improve the overall outcome for patients with LA-NSCLC.

Based on these findings, the study reported herein used induction chemoradiotherapy followed by surgery in attempts to improve the local tumour control. This approach resulted in downstaging of disease in 59% of the patients, which is similar to the result (67%) reported by Choi *et al* (Choi *et al*, 1997; Date *et al*, 2002), and significantly better than that in our previous study (13%, $P=0.007$). The pathological CR rate of 23% in the present study seemed to be improved in comparison with results of our previous study (7%, $P=0.40$) and Choi *et al* (10%), and comparable to those of Eberhardt *et al* (26%) and Thomas *et al* (18%) (Choi *et al*, 1997; Eberhardt *et al*, 1998; Thomas *et al*, 1999; Date *et al*, 2002). Moreover, local recurrence developed in only two (29%) of seven relapsed patients. Overall, these results indicate that considerably good local control can be achieved by using concurrent chemoradiotherapy as induction.

Several other factors may have contributed to the positive findings in this study. First, in an attempt to treat distant micrometastases, we used a two-drug combination of cisplatin plus docetaxel – one of the most active regimens for advanced NSCLC (Schiller *et al*, 2002). Cisplatin, the key drug in the treatment of NSCLC (Le Chevalier *et al*, 1999), has potent radiosensitising effects (DeWit, 1987), and docetaxel, a new active drug for NSCLC (Creane *et al*, 1999), also is a radiosensitising agent (Caffo, 2001). We thus considered that cisplatin plus docetaxel would be an excellent regimen to incorporate in concurrent chemoradiotherapy for LA-NSCLC. We previously reported that combined modality therapy using cisplatin and docetaxel with concurrent thoracic irradiation was feasible and effective in patients with unresectable LA-NSCLC (Kiura *et al*, 2003). The regimen achieved good control of local tumour and also of distant metastases. In previous studies of induction chemoradiotherapy, cisplatin-based regimens that included older agents such as etoposide, vinblastine, or vindesine were frequently used as induction chemotherapy (Albain *et al*, 1995; Choi *et al*, 1997; Eberhardt *et al*, 1998; Thomas *et al*, 1999). However, recent randomised trials showed cisplatin-based combi-

nations that incorporated newer drugs such as docetaxel, paclitaxel, and vinorelbine, which were more effective than older cisplatin-based regimens in patients with advanced NSCLC (Le Chevalier *et al*, 1994; Bonomi *et al*, 2000; Kubota *et al*, 2002). These findings thus support the use of a cisplatin plus docetaxel combination in chemoradiotherapy for LA-NSCLC.

A second factor to consider, regarding the positive results in this study, is that the administration of both cisplatin and docetaxel was fractionated, that is, given on days 1, 8, 29 and 36. This schedule increased the opportunities for simultaneous administration of chemotherapy and radiotherapy, and may thus have increased the radiosensitising effects of chemotherapy. Furthermore, fractionated drug administration may increase chemotherapy dose intensity. In the present study, the projected dose intensity of both cisplatin and docetaxel was 20 mg m^{-2} $week^{-1}$. In actuality, 18 mg m^{-2} $week^{-1}$ of cisplatin and 17 mg m^{-2} $week^{-1}$ of docetaxel was administered despite th use of concurrent thoracic irradiation. These doses are almost equal to those used for patients with advanced NSCLC, who are not receiving thoracic irradiation.

Third, although hyperfractionated radiotherapy has been the preferred approach in recent trials of preoperative chemoradiotherapy (Choi *et al*, 1997; Eberhardt *et al*, 1998; Thomas *et al*, 1999), results from a recent large-scale randomised trial in LA-NSCLC showed no superiority of hyperfractionation over standard fractionation (Curran *et al*, 2003). Thus, we used standard fractionation in the study reported herein, which allowed safe delivery of sufficient radiation doses, while avoiding severe radiation-induced oesophagitis or pneumonitis.

In conclusion, combined modality treatment consisting of induction therapy with cisplatin, docetaxel and concurrent thoracic irradiation followed by surgery is feasible and effective in patients with LA-NSCLC. A large-scale randomised trial is warranted to confirm these promising results.

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Long-term Effect of Gefitinib (ZD1839) on Squamous Cell Carcinoma of the Lung

TOSHIYUKI KOZUKI[1], KATSUYUKI KIURA[1], HIROSHI UEOKA[1], MASAHIRO TABATA[1], HIROSHI DATE[2], SHUJI HAMAZAKI[3], AKIHIRO BESSHO[4] and MITSUNE TANIMOTO[1]

[1]*Department of Internal Medicine II (Department of Hematology, Oncology and Respiratory Medicine),*
[2]*Department of Cancer and Thoracic Surgery and*
[3]*Department of Pathology, Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558;*
[4]*Department of Internal Medicine, National Shikoku Cancer Center Hospital,*
13 Horinouchi, Matsuyama 790-0007, Japan

Abstract. *This case report describes the effects of long-term treatment with the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib ('Iressa', ZD1839) on a patient with squamous cell carcinoma of the lung. Gefitinib is an orally active agent that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and host-dependent processes that promote tumor growth. A 62-year-old Japanese man with a history of heavy smoking was diagnosed with squamous cell carcinoma of the lung, clinical stage IIIB (T4N3M0), in August 2000. He received two cycles of cisplatin-based chemotherapy and subsequently underwent left upper lobectomy followed by thoracic radiotherapy. After these treatments, he underwent partial lobectomy and pneumonectomy because of disease recurrence. In June 2002, he started treatment with gefitinib 250 mg/day orally because of mediastinal lymph node recurrence and an elevated serum cytokeratin 19 fragment (CYFRA) level. As a result, the mediastinal lymph node markedly regressed and the serum CYFRA level became normalized. Although he experienced recurrence three times during the 18 months prior to treatment with gefitinib, recurrence has not been experienced in the 13 months since the start of gefitinib treatment, while tolerability has been acceptable.*

Correspondence to: Katsuyuki Kiura, Department of Internal Medicine II (Department of Hematology, Oncology and Respiratory Medicine), Okayama University Hospital, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. Tel: +81-86-235-7226, Fax: +81-86-232-8226, e-mail: kkiura@md.okayama-u.ac.jp

Key Words: NSCLC, squamous, EGFR, EGFR-TKI, gefitinib, ZD1839.

Case Report

The patient, a 62-year-old Japanese man who formerly smoked 30 cigarettes/day for 35 years, was admitted to our hospital on June 10, 2002.

Treatment history. In July 2000, the patient visited his local hospital because of back pain. A chest radiograph showed an abnormal shadow in the left upper lung and he was admitted to the hospital in August 2000. A biopsy specimen taken by fiberoptic bronchoscopy showed squamous cell carcinoma of the lung and a clinical stage of IIIB (T4N3M0) was diagnosed. He received two cycles of chemotherapy (cisplatin 80 mg/m^2 on day 1, mitomycin C 8 mg/m^2 on day 1, and vinorelbine 20 mg/m^2 on days 1 and 8) and achieved a partial response (PR). Following referral to the Department of Surgery II, Okayama University Hospital, Japan, on November 29, 2000, he underwent left upper lobectomy, followed by adjuvant radiotherapy at a dose of 2 Gy daily to a total dose of 50 Gy. The pathological stage went down to stage IIB (pT3N0M0). In July 2001, chest radiography showed a nodule in the left lower lung field. A transcutaneous biopsy specimen revealed recurrence of squamous cell carcinoma. On July 30, 2001 he received partial lower lobectomy with chest wall resection followed by oral uracil/tegafur (UFT) as adjuvant therapy. In February 2002, he noticed his left chest wall swelling. Chest computed tomographic (CT) scan revealed a mass in the remaining left lower lung with direct invasion to his left second to fourth ribs. White blood count (WBC) was 17,300/mm^3 and C-reactive protein (CRP) was elevated to 1.8 mg/dl (normal range, 0.0-0.3mg/dl). The serum cytokeratin 19 fragment (CYFRA) level was markedly elevated to 32.9 ng/ml (normal range, 0.0-2.8 ng/ml). He

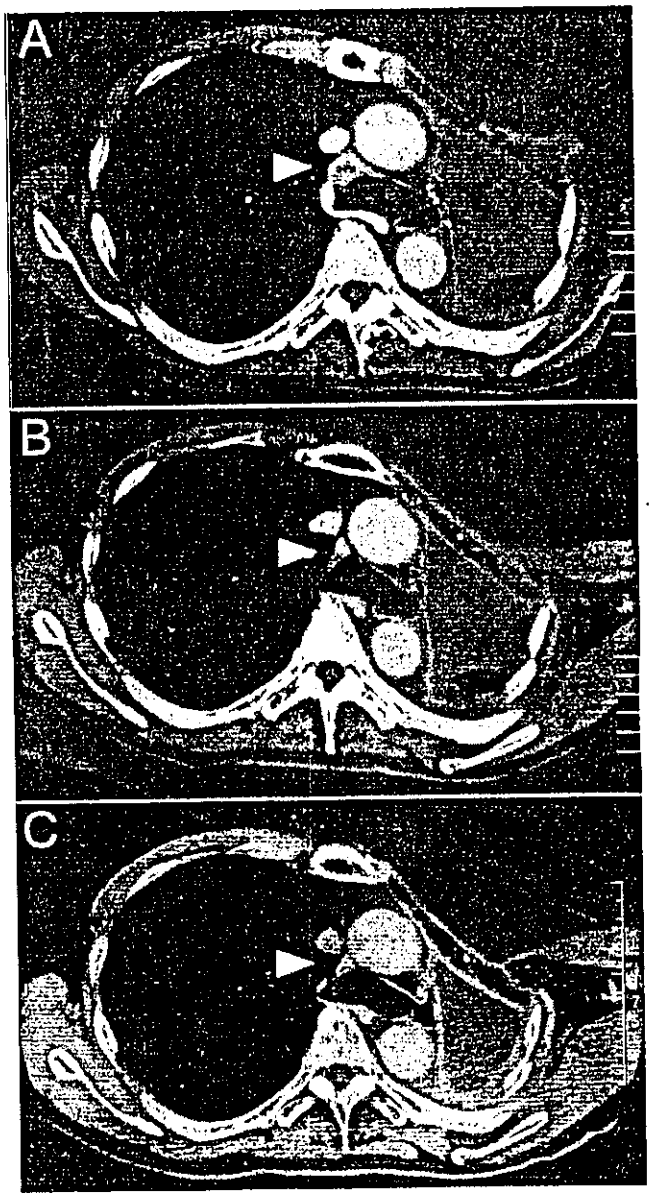

Figure 1. *Contrast-enhanced chest CT scans before and after gefitinib treatment. Before gefitinib treatment (a) single mediastinal lymph node (21 x 16 mm, white arrowhead) was detected. Twenty-eight days (b) and 12 months (c) after gefitinib treatment, the mediastinal lymph node was markedly regressed.*

underwent left pneumonectomy with chest wall reconstruction on March 18, 2002. After pneumonectomy, the serum CYFRA level and WBC returned to normal.

Patient status before gefitinib treatment. On June 10, 2002 the patient was admitted to our hospital following contrast-enhanced CT scans of the chest showing a single mediastinal lymph node swelling (21 x 16 mm) (Figure 1), which was not detected in the chest CT scan of April 2002. He applied for inclusion in a compassionate use program of gefitinib. He had felt anterior chest pain possibly due to operation and had a performance status (PS) of 1. On physical examination, he had tenderness at the site of his operation scar on the left anterior chest and breathing was not audible on the left side of the lung. The WBC was elevated to 14,100/mm^3 and platelet count and CRP were slightly elevated. The serum CYFRA level was again elevated, to 3.8 ng/ml, although carcinoembryonic antigen and squamous cell carcinoma-related antigen were within the normal range. There were no other metastatic lesions of lung, abdomen, brain or bone. We concluded that he had progressive disease, because of a single mediastinal lymph node swelling supported by elevation of the serum CYFRA level.

In histological assessments of the first and the third operation specimens (Figure 2), a majority of the cells did not show a uniform differentiation, but cells with stratification and keratinization were detected in a focal area (white arrowhead in Figure 2) and the patient was diagnosed with poorly-differentiated squamous cell carcinoma of the lung.

Gefitinib treatment. The patient began treatment with gefitinib 250 mg/day orally on June 12, 2002. On July 9, 2002, marked mediastinal lymph node regression was noted, as shown in Figure 1b and the serum CYFRA level and WBC returned to within the normal range. Adverse events were grade 1 (National Cancer Institute common toxicity criteria version 2.0) acne-like rash and diarrhea, and grade 2 liver dysfunction. Skin rash and diarrhea were mild and transient. Grade 1 liver dysfunction was assessed on September 5, 2002 and gefitinib was continued for a further 3 weeks, when grade 2 liver dysfunction occurred. Gefitinib was interrupted for 14 days until complete liver recovery. However, liver dysfunction occurred again on readministration of gefitinib. Therefore, after a further interruption of 14 days, the patient resumed gefitinib 250 mg once daily for 14 consecutive days followed by 14 days off, according to a schedule used in a phase I trial (1). Using this schedule, liver dysfunction has not occurred since January 2003. Contrast-enhanced CT scan of the chest on June 12, 2003 did not detect regrowth of a mediastinal lymph node (Figure 1c). The serum CYFRA level remained within the normal limit for more than 12 months (ongoing at the time of reporting), at which time the patient remains in full-time employment. He continues to take gefitinib 250 mg/day, with no additional treatment and visits our hospital once a month.

Discussion

This is the first case report to describe the long-term effects of gefitinib on a patient with squamous cell carcinoma of the lung. This patient initially received cisplatin-based

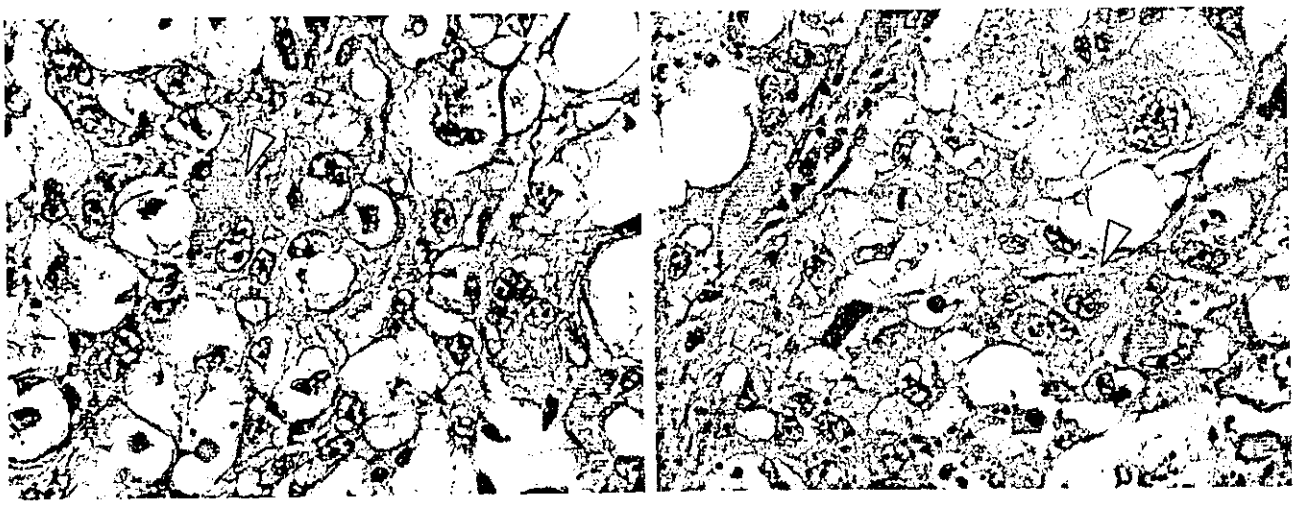

Figure 2. *(a) Specimen from the first operation on November 29, 2000 and (b) specimen from the third operation on March 18, 2002 (hematoxylin and eosin, magnification x340).*

chemotherapy and radiotherapy and underwent surgery three times in 18 months. After gefitinib treatment, recurrence has not been experienced, with acceptable toxicities for 13 months. In this case, gefitinib is working well as the last defensive line.

The two phase II trials showed higher efficacy rates for gefitinib in female patients, patients with good PS and patients with adenocarcinoma (2,3). Nevertheless, both trials support the use of gefitinib in squamous cell carcinoma of the lung: 3/43 patients (7%) in IDEAL 1 and 2/32 patients (6%) in IDEAL 2 with squamous cell carcinoma achieved a PR (2-4). In addition, Ruckdeschel *et al.* reported one PR (7%) among 15 patients with squamous cell carcinoma of the lung (5). Between August 2001 and April 2003, 12/89 (14%) of patients with NSCLC treated with gefitinib in our hospital and the National Shikoku Cancer Center Hospital were diagnosed with squamous cell carcinoma of the lung and 3/12 patients (25%; 95% confidence interval [CI], 9%-43%) with squamous cell carcinoma achieved a PR, including the patient described. Therefore, a relatively small, but significant, population of patients with squamous cell carcinoma of the lung is clearly sensitive to gefitinib. In gefitinib, patients with squamous cell carcinoma may therefore have a valuable additional treatment option other than palliative care, since response rates of carboplatin against chemotherapy-naïve NSCLC patients and docetaxel against refractory NSCLC patients are 9% and 7%, respectively (6, 7).

Tumor burdens were small in two of the three cases of PR we have seen. Of these, the case we describe showed a single mediastinal node recurrence, while a second case, a 59-year-old Japanese woman who smoked 25 cigarettes/day for 39 years, presented with regrowth of primary lung tumor and pulmonary metastasis (new lesions) after cisplatin and docetaxel with concurrent thoracic radiotherapy. The second case has also continued in PR for 10 months, although gefitinib treatment was interrupted transiently because of grade 2 skin rash. The third case, a 67-year-old Japanese man who formerly smoked 20 cigarettes/day for 44 years, revealed total opacification of the left lung after thoracic radiotherapy, five cycles of paclitaxel and carboplatin and two cycles of gemcitabine. At a very advanced stage, under oxygen supplement, he received gefitinib treatment, at which the bulky mass markedly regressed and atelectasis of the left lung disappeared. The duration of response was 4 months. We have previously reported a dramatic effect of gefitinib for a female patient with adenocarcinoma and poor PS (8); our current report shows that a relatively good response rate and long duration of response can also be seen in cases with small tumor burden and good PS.

A strong correlation between smoking history and the effect of gefitinib has been reported (9) and the efficacy of gefitinib might be linked to the etiology of disease in smokers *versus* never-smokers. Gene mutation in lung cancers is more frequent in smokers than non-smokers (10). Therefore in smokers, cancer cells may escape growth control at a high rate, including *via* pathways that are independent of EGFR signaling. Nevertheless, the PRs we have described have been in patients who were heavy smokers.

We have established two cell lines derived from a patient with squamous cell carcinoma of the lung both before and after cisplatin-based chemotherapy (11). Interestingly, EBC-2/R cells, isolated after cisplatin-based chemotherapy, are

8.6-fold more sensitive to gefitinib than EBC-2 cells isolated before chemotherapy (12). We are investigating the mechanistic causes behind this increased sensitivity in a cisplatin-resistant cell line derived from squamous cell carcinoma of the lung.

Since the introduction of gefitinib to Japan in July 2002, there have been reports of patients who developed interstitial lung disease (ILD), possibly due to gefitinib treatment. Out of approximately 80,000 patients who have now received gefitinib worldwide, the ILD incidence and mortality is 1.0%, and 0.4%, respectively (13). In a series of patients treated in a single institute study, 4/18 patients with NSCLC developed acute ILD possibly related to gefitinib treatment, but all had been former smokers (14). Although our case was a former smoker and underwent pneumonectomy and radiation therapy, pulmonary adverse events have not occurred for more than 12 months of gefitinib treatment.

In conclusion, we report that gefitinib is effective for at least 13 months in a patient with squamous cell carcinoma of the lung, without severe adverse events. In the light of his status as a male smoker with squamous cell carcinoma, more intensive basic and clinical research into the mechanisms of gefitinib action is needed.

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A phase I study and pharmacokinetics of irinotecan (CPT-11) and paclitaxel in patients with advanced non-small cell lung cancer

Katsuyuki Hotta*, Hiroshi Ueoka, Katsuyuki Kiura, Masahiro Tabata, Shoichi Kuyama, Ken Satoh, Toshiyuki Kozuki, Akiko Hisamoto, Shinobu Hosokawa, Keiichi Fujiwara, Mitsune Tanimoto

Departmnet of Internal Medicine II, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

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Irinotecan;
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Phase I study;
Non-platinum regimen;
Pharmacokinetics

Summary *Purpose:* To determine the maximum-tolerated dose (MTD) of irinotecan and paclitaxel in this two-drug combination, and to investigate a sequence-dependent effect in the pharmacokinetics of these drugs, we conducted a phase I study in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC). *Patients and methods:* Patients with stage IIIB/IV NSCLC were enrolled in this study. Both irinotecan and paclitaxel were administered on days 1 and 8, and repeated every 3 weeks. The starting dose of both drugs was 40 mg/m^2 which was then alternately increased by 10 mg/m^2 increments. In the first cycle, irinotecan was initially administered and followed by paclitaxel infusion, while the sequence of drug administration was reversed in the second cycle. Blood samples for pharmacokinetic analysis were obtained on day 1 of the first and second cycles. *Results:* Nine patients received a total of 12 cycles, which were evaluated for toxicity and efficacy. The main hematological toxicity was neutropenia. Grades 3 or more neutropenia was observed in 67% of cycles at dose level 2. The main non-hematological toxicities were grade 3 febrile neutropenia, supraventricular arrhythmia, and grade 2 hepatic dysfunction. The MTD of irinotecan and paclitaxel were 40 and 50 mg/m^2, respectively. In the pharmacokinetic analysis, the maximum concentration of paclitaxel was elevated in a dose-dependent manner. There was a trend toward elevation of the area under the plasma concentration–time curve (AUC) of irinotecan and a decline of the AUC of paclitaxel in cycle 1 (irinotecan followed by paclitaxel), compared with those in cycle 2 (paclitaxel followed by irinotecan). Hepatic toxicity was strongly associated with the AUC of irinotecan ($r = 0.894$. $P < 0.0001$). The objective response was not observed in the nine patients. *Conclusion:* The combination of irinotecan and paclitaxel with this schedule produced considerable toxicities without any antitumor effect for advanced NSCLC. The different schedule of administration or other combinations should be investigated.

*Corresponding author. Tel.: +81-86-235-7227; fax: +81-86-232-8226.
E-mail address: khotta@md.okayama-u.ac.jp (K. Hotta).

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1. Introduction

Lung cancer is the leading cause of death by cancer in many countries. Non-small cell lung cancer (NSCLC) accounts for approximately 75% of lung cancer cases and the 5-year survival rate for all stages is currently 13% [1]. The majority of patients with NSCLC have inoperable locally advanced or metastatic disease at the time of diagnosis. Although cisplatin-based chemotherapy has been extensively conducted in patients with advanced NSCLC for the past two decades, the survival benefit remains modest [2].

Recently, several new agents with novel mechanisms have been developed and shown to be highly effective for NSCLC [3]. Irinotecan (CPT-11), a unique semi-synthetic derivative of camptothecin, has been shown to have a favorable antitumor activity as a single agent with a response rate of 24.7% [4]. Paclitaxel, a new agent extracted from the bark of the pacific yew, has produced overall response rates of 24% in previously untreated patients with advanced NSCLC [5], with a significant survival advantage over the best supportive care alone [6]. The mechanisms of action and toxicity profiles of these two drugs are different, and an additive or synergistic effect when used in combination was demonstrated in preclinical studies [7].

In spite of these things, there have been few reports clinically evaluating a combination of these two drugs in patients with NSCLC [8,9]. Kasai et al. investigated a phase I study of this combination. Paclitaxel was administered on day 1 and irinotecan on days 1, 8 and 15. The starting doses of paclitaxel and irinotecan were 120 and 40 mg/m^2, respectively [8]. Although they concluded that this regimen produced a favorable response rate of 31% and well-tolerated toxicities, the administration of irinotecan on days 8 and 15 was cancelled in 12 (42.9%) of 28 planned cycles because of myelotoxicity even at the recommended dose level. Yamamoto et al. also performed a phase I study of the same combination, in which paclitaxel and irinotecan were administered on day 2 and on days 1, 8 and 15, respectively, with a starting dose of paclitaxel 135 mg/m^2 and irinotecan 50 mg/m^2 [9]. However, all patients at the initial dose level had dose-limiting myelotoxicity.

In addition, the optimal sequence of drug administration using a combination of these drugs has not been determined. Kasai et al. reported that preceding paclitaxel administration produced an alteration in the pharmacokinetics of irinotecan [8], whereas Yamamoto et al. demonstrated that administration of paclitaxel after irinotecan resulted in increased plasma concentration of irinotecan [9].

These results indicate that appropriate dose and schedule of this combination remain undetermined, although it appeared to be effective for NSCLC. Accordingly, we designed a phase I study of a combination two-drug combination chemotherapy consisting of irinotecan and paclitaxel in patients with advanced NSCLC. The primary objective was to determine the maximum-tolerated dose (MTD) for each drug. The secondary objectives were to observe antitumor activity and to evaluate whether the order of administration of these two drugs affects the pharmacokinetics and clinical toxicity.

2. Patients and methods

2.1. Eligibility criteria

Patients were required to fulfill the following eligibility criteria: pathologically proven, advanced and inoperable NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; age $\leq$ 75 years; no prior chemotherapy; presence of evaluable lesions; adequate reserves of hematologic function (WBC count $\geq$ 4000/μl, neutrophil count $\geq$ 2000/μl, hemoglobin level $\geq$ 9.5 g/dl, platelet count $\geq 10 \times 10^4/\mu$l), renal function (serum creatinine $\leq$ 1.5 mg/dl), hepatic function (total bilirubin $\leq$ 1.5 mg/dl, serum transaminases $\leq$ 2.5 $\times$ upper limit of normal range) and pulmonary function ($PaO_2 \geq$ 60 mmHg); acquisition of written informed consent. Patients with symptomatic brain metastasis were excluded from the study. Baseline pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiograph, electrocardiogram, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan. Staging was assessed according to the tumor, node, metastasis system [10]. The protocol was approved by the institutional review board of Okayama University Medical School.

2.2. Treatment scheme

In the first cycle, irinotecan, diluted in 300 ml of physiological saline, was intravenously administered over 1 h on days 1 and 8. After completion of the irinotecan infusion, paclitaxel, diluted in 300 ml of physiological saline, was intravenously administered over 1 h on the same days. Each patient was premedicated with intravenous administration of dexamethasone (16 mg) and ranitidine (50 mg), and oral administration of diphenhydramine (50 mg) 1 h

before paclitaxel infusion on both days 1 and 8. The treatment was repeated every 3 weeks. In the second cycle, the reversed sequence of drug administration, preceding administration of paclitaxel followed by irinotecan, was conducted on days 1 and 8. From the third cycle onwards the same schedule as that in the first cycle was planned, but repeating the sequence of the second cycle was accepted, if the toxicities experienced in the second cycle were milder than those in the first cycle. Five dose levels were planned. The starting dose of both irinotecan and paclitaxel was 40 mg/m^2, which was then increased in 10 mg/m^2 increments alternately.

Administration of irinotecan and paclitaxel on day 8 was cancelled if either hematological toxicities of grade 3 or greater, or non-hematological toxicities of grade 2 or greater were observed on the same day. Patients were treated with at least two cycles of chemotherapy unless there was disease progression, unacceptable toxicity in the first cycle, or withdrawal of their consent. Initiation of the next cycle of chemotherapy was delayed until recovery of a WBC count to $\geq$3000/μl, a neutrophil count to $\geq$1500/μl, a platelet count to $\geq 10 \times 10^4/\mu$l, and resolution of non-hematologic toxicities to $\leq$grade 1.

2.3. Assessment of toxicity and dose escalation

Toxicity was graded according to modified version of the National Cancer Institute-Common Toxicity Criteria [11]. Dose-limiting toxicity (DLT) was defined as development of at least one of the following adverse events: any non-hematologic toxicities $\geq$grade 3 except for alopecia, nausea, vomiting, and hyponatremia; platelet count $\leq 2 \times 10^4/\mu$l; grade 4 leukopenia; persistence of grade 4 neutropenia for more than 5 days; grade 3 or greater neutropenia with fever $\geq$38 °C or with infection; the cancellation of irinotecan and paclitaxel on day 8; and failure to recover from toxicities enough to begin a next cycle of treatment by day 29.

Six patients were scheduled to enter the study at each dose level. If fewer than three of six patients experienced DLT, then the next group of patients was treated at the next higher dose level. The MTD was defined as a dose level that produced any of the DLTs developed in three or more patients among a maximum of six patients, and further dose escalation was not permitted. All treatment cycles were analyzed to determine the DLT and MTD, although the decision to increase to the next higher dose level was based on the toxicities in the first cycle. Dose escalation above starting doses in the individual patient was not allowed. The recommended dose was defined as the dose level below the MTD. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was noted, the use of granulocyte colony-stimulating factor was permitted. The dose could be reduced in the subsequent cycles if patients experienced DLT in the previous cycle, but this decision was left to the discretion of the physician.

2.4. Assessment of antitumor activity

Standard Response Evaluation Criteria in Solid Tumors [12] was used to evaluate responses. The best overall response was defined as the best response recorded from the start of the treatment until disease progression or recurrence. The smallest measurement recorded during the treatment was used as a reference to assess the case as the disease progressed. A radiologist reviewed all response assessments.

2.5. Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were obtained during the first day of the first and the second cycles, from an indwelling venous catheter placed in the arm contralateral to that used for drug infusion. For kinetic analyses of paclitaxel, irinotecan, and 7-ethyl-10-hydroxy-camptothecin (SN-38), 10 ml of blood was collected in heparinized tubes before drug administration, at 0.5 and 1 h during the infusion of irinotecan, and 0.5, 1, 2, 5, 8 and 23 h after the end of the infusion in the first cycle. In the second cycle, blood was collected at the same points before, during and after the infusion of paclitaxel. After centrifugation, the plasma was obtained and stored at −80 °C until assay. The plasma concentrations of paclitaxel, irinotecan, and SN-38 were measured by high-performance liquid chromatography (HPLC), as previously described [13]. The area under the plasma concentration–time curve (AUC) was calculated using WINNONLIN Standard Edition Version 1.5. Differences in the AUCs between dose level 1 and dose level 2, or the first cycle and the second cycle were evaluated by the unpaired *t*-test. The correlations between pharmacokinetic parameters and clinical toxicities such as leukopenia, neutropenia, diarrhea, and hepatic toxicity, were assessed with Pearson's correlation coefficient. Statistical analyses were performed using the STATVIEW 5.0 program (Brainpower, Calabasas, CA). A P value of less than 0.05 was considered statistically significant.

Table 1 Hematological toxicity of grade 2 or greater (all cycles)

Toxicity	Grade	No. of cycles (%)	
		Dose level 1 (nine cycles)	Dose level 2 (three cycles)
Leukopenia	2	1 (11%)	0 (0%)
	3	0 (0%)	2 (67%)
	4	0 (0%)	0 (0%)
Neutropenia	2	0 (0%)	0 (0%)
	3	0 (0%)	2 (67%)
	4	1 (11%)	0 (0%)
Anemia	2	1 (11%)	1 (33%)
	3	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)

3. Results

3.1. Patients' characteristics

Nine patients with advanced NSCLC were enrolled in this trial between October 2001 and September 2002. There were five men and four women with a median age of 70 ranging from 55 to 75. All patients had ECOG performance status of 1. Six patients were treated at dose level 1 and three at dose level 2. Eight patients had adenocarcinoma and one non-classified non-small cell carcinoma. Clinical stage was IV in eight patients and postoperative recurrence in one. Five dose levels (irinotecan/paclitaxel) were planned as follows: 40/40, 40/50, 50/50, 50/60 and 60/60 mg/m^2. A total of 12 chemotherapy cycles were administered, with a median number of one cycle per patient (range, 1–2). Six patients (67%) received only one cycle of chemotherapy, because of unacceptable toxicity in five patients and the patient's refusal in one. All patients and cycles were assessable for safety.

3.2. Hematological toxicity

The main toxicity of this combination was myelosuppression (Table 1). Both grade 3 or 4 neutropenia and leukopenia were observed in 67% of cycles at dose level 2, whereas they developed in 11 and 0% of cycles at dose level 1, respectively. Two patients, one each in dose levels 1 and 2, were unable to receive irinotecan and paclitaxel on day 8 of the first cycle, because they developed grade 3 neutropenia and leukopenia on day 8, respectively. These toxicities were, therefore, considered to be DLT. Anemia and thrombocytopenia were relatively mild, and no transfusions were required.

Table 2 Non-hematologic toxicity of grade 2 or greater (all cycles)

Toxicity	Grade	No. of cycles (%)	
		Dose level 1 (nine cycles)	Dose level 2 (three cycles)
Nausea/ vomiting	2	0 (0%)	0 (0%)
	3	2(22%)	1 (33%)
Febrile neutropenia	2	0 (0%)	0 (0%)
	3	0 (0%)	1 (33%)
Arrhythmia	2	0 (0%)	0 (0%)
	3	0 (0%)	1 (33%)
Hepatotoxicity	2	1 (11%)	1 (33%)
	3	0 (0%)	0 (0%)
Hyponatremia	2	0 (0%)	0 (33%)
	3	1 (11%)	0 (0%)
Peripheral neuropathy	2	1 (11%)	0 (0%)
	3	0 (0%)	0 (0%)

No grade 4 non-hematologic toxicity was noted.

3.3. Non-hematological toxicity

Febrile neutropenia occurred in one patient (11%) receiving a level 2 dose in the first cycle (Table 2), however, it was reversible with appropriate supportive care. One patient who was treated at dose level 1 was unable to receive irinotecan and paclitaxel on day 8 because of grade 2 hepatic dysfunction, which was also considered to be DLT. Another patient receiving a level 2 dose experienced paroxysmal supraventricular tachycardia (grade 3) soon after the administration of paclitaxel on day 8 of the first cycle. He had a past history of artrial premature beat, and the condition improved with the administration of digoxin. Grade 3 hyponatremia during the first cycle at dose level 1 and grade 3 nausea at both dose levels were reversible toxicities. Diarrhea, arthralgia, myalgia, and peripheral neuropathy were mild, and no intensive management was required.

3.4. Maximum-tolerated dose

DLT was observed in two of six patients at dose level 1 (cancellation of irinotecan and paclitaxel on day 8 because of myelosuppression and hepatic dysfuntion), and in all three patients at dose level 2 (febrile neutropenia, supraventricular arrhythmia, and cancellation of irinotecan and

paclitaxel on day 8 because of myelosuppression). There were no treatment-related deaths. We determined the MTD of irinotecan and paclitaxel to be 40 and 50 mg/m^2, respectively.

3.5. Antitumor activity

All patients were assessable for response. Objective tumor response was not observed, although eight patients (88.9%) achieved a stable disease. The one remaining patient developed a progressing disease (11.1%).

3.6. Pharmacokinetic analysis

Pharamacokinetic parameters were obtained during the first day of the first cycle in nine patients and the first day of the second cycle in three patients. The maximum concentration (C_{max}) of paclitaxel at dose level 2 was higher than that at dose level 1 (1753.3 ± 270.0 versus 1041.8 ± 94.1 ng/ml, $P = 0.016$), whereas the other parameters of the two drugs were comparable between dose levels 1 and 2 (Table 3). We also evaluated differences of several parameters between cycles 1 and 2 in order to investigate a sequence-dependent effect on the pharmacokinetics of irinotecan and paclitaxel. As listed in Table 4, there was a tendency for the AUC of irinotecan to be relatively high in cycle 2 (paclitaxel followed by irinotecan) compared with that in cycle 1 (irinotecan followed by paclitaxel), while the AUC of paclitaxel in cycle 1 was slightly higher than that in cycle 2.

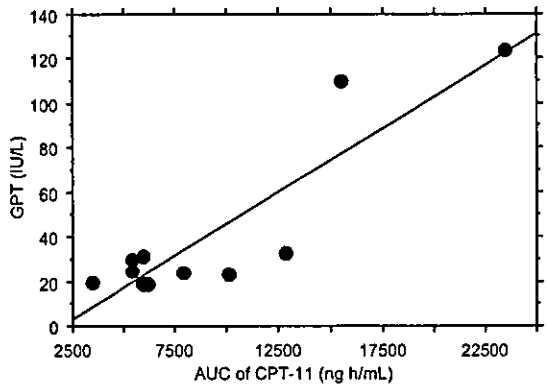

Fig. 1 The correlation between the maximum levels of GPT and the area under the plasma concentration–time curve of irinotecan. Pearson's correlation coefficient was 0.894 with 95% confidential interval of 0.656–0.970 ($P < 0.0001$). AUC: area under the plasma concentration–time curve; CPT-11: irinotecan.

3.7. Pharmacodynamic analysis

The correlation of several toxicity profiles with the pharmacokinetic parameters of the drugs was analyzed. The AUC of irinotecan was strongly correlated to the elevation of GPT after treatment (Pearson's $r = 0.894$, $P < 0.0001$) (Fig. 1). Maximal hepatic toxicity was observed early after the drug administration (median: day 8, range: day 2–day

Table 3 Various pharmacokinetic parameters of the drugs at dose levels 1 and 2

	Level 1 (PTX 40 mg/m^2) (no. of patients: 6)	Level 2 (PTX 50 mg/m^2) (no. of patients: 3)	P
CPT-11			
T_{max} (h)	1	1	
C_{max} (ng/ml)	779.4 ± 119.4	775.2 ± 37.5	0.981
AUC (ng h/ml)	8588.1 ± 3030.7	9950.3 ± 2873.1	0.582
CL (l/h)	6.7 ± 1.3	4.2 ± 1.3	0.284
SN-38			
T_{max} (h)	3	2	
C_{max} (ng/ml)	46.6 ± 14.1	54.4 ± 5.2	0.718
AUC (ng h/ml)	334.7 ± 80.6	458.2 ± 52.5	0.348
CL (l/h)	182.6 ± 57.5	89.5 ± 9.7	0.306
PTX			
T_{max} (h)	1	1	
C_{max} (ng/ml)	1041.8 ± 94.1	1753.3 ± 270.0	0.016
AUC (ng h/ml)	1786.4 ± 342.7	2454.3 ± 509.6	0.304
CL (l/h)	26.2 ± 4.5	22.9 ± 6.0	0.677

Each data represents the mean values and standard errors. CPT-11: irinotecan; PTX: paclitaxel; AUC: area under the plasma concentration–time curve; CL: clearance.

Table 4 Various pharmacokinetic parameters of the drugs on cycles 1 and 2

	Cycle 1 (CPT-PTX) (no. of patients: 3)	Cycle 2 (PTX-CPT) (no. of patients: 3)	P
CPT-11			
T_{max} (h)	1	1	
C_{max} (ng/ml)	615.1 ± 109.0	742.4 ± 100.0	0.438
AUC (ng h/ml)	5761.6 ± 1293.9	7399.0 ± 1354.3	0.431
CL (l/h)	7.8 ± 2.0	5.7 ± 0.9	0.390
SN-38			
T_{max} (h)	3	1	
C_{max} (ng/ml)	46.3 ± 25.3	38.6 ± 8.6	0.788
AUC (ng h/ml)	336.3 ± 133.4	214.4 ± 41.6	0.433
CL (l/h)	165.7 ± 63.8	205.7 ± 49.3	0.647
PTX			
T_{max} (h)	1	1	
C_{max} (ng/ml)	937.0 ± 178.5	1020.3 ± 135.4	0.729
AUC (ng h/ml)	1417.3 ± 288.0	1315.1 ± 214.0	0.790
CL (l/h)	31.2 ± 7.5	32.5 ± 6.3	0.905

Each data represents the mean values and standard errors. CPT-11: irinotecan; PTX: paclitaxel; AUC: area under the plasma concentration–time curve; CL: clearance.

26). Two of nine patients had hepatic metastasis; however, they did not encounter any hepatic toxicity. No significant correlation was observed between the other pharmacokinetic parameters and the degree of leukopenia, neutropenia, or diarrhea.

4. Discussion

The present study demonstrated that the combination of irinotecan and paclitaxel in this schedule had considerable toxicities despite no promising activity for advanced NSCLC. Several toxicity profiles in this combination have been previously reported. Yamamoto et al. documented that all patients receiving this combination at the initial dose level (irinotecan 50 mg/m^2: days 1, 8 and 15; and paxlitaxel 135 mg/m^2: day 2) had severe dose-limiting myelotoxicity [9]. Rosen et al. also reported that dose escalation of the two drugs above the starting dose (irinotecan 225 mg/m^2 and paxlitaxel 100 mg/m^2, once every 3 weeks) was impossible because of neutropenic fever or severe diarrhea [14]. On the other hand, Murren et al. investigated the combination of the two drugs in a weekly schedule for patients with advanced various cancers, and concluded that this combination was well tolerated, although they experienced several adverse events in the patients treated with the recommended dose [15]. These results suggest that the combination of irinotecan and paclitaxel produces relatively severe toxicities, compared with other regimens containing irinotecan or paclitaxel such as cisplatin plus irinotecan or carboplatin plus paclitaxel [5,16]. However, we considered that fractionated schedule of the two drugs might be less toxic and promising, and we planned the current study.

In the previous dose escalation studies, a range of MTDs was reported, however, this may be attributable to differences in the definition of DLT. In our study, the MTD was determined to be dose level 2, which was much lower than that in the previous reports. The major cause may be our strict criteria for DLT, especially assessing the cancellation on day 8 as DLT, which was encountered in three patients because of grade 3 neutropenia, grade 2 hepatic dysfunction, or grade 3 leukopenia.

In the previous pharmacokinetic analysis, Kasai et al. [8] showed the elevation of the AUC of irinotecan by the preceding administration of a relatively high dose of paclitaxel, and speculated that the competitive inhibition of metabolism was the possible mechanism, since both drugs were metabolized by cytochrome P450 (CYP) 3A4 [17,18]. However, no pharmacokinetic analysis of paclitaxel was investigated in their study. Our study revealed the possibility that the preceding administration of paclitaxel increased the AUC of irinotecan, and the preceding irinotecan also increased the AUC of paclitaxel, which suggests that irinotecan and paclitaxel might have affected each others'

metabolic pathways, possibly by the consumption of CYP3A4. However, the results in the present study were not statistically significant, which might result from the following reasons. Firstly, the doses of irinotecan and paclitaxel in the present study were relatively low, and secondly, both drugs are metabolized not only by CYP3A4 but also by other enzymes such as carboxylesterase or CYP2C8 [19,20].

Unfortunately, an objective response was not obtained in the present study. Kasai et al. previously documented the favorable antitumor effect (response rate of 31%) for advanced NSCLC. The difference in the antitumor activity between Kasai's study and ours might be partly attributable to the insufficient doses of the two drugs in our study. As another possible explanation, the difference in the schedule of administration should be considered. Kano et al. reported the antagonistic effect of the two drugs when exposed to human lung cancer cell lines simultaneously, whereas sequential exposure produced an additive effect [21]. Debernardis et al. also demonstrated the antagonistic effect with simultaneous exposure of the two drugs [22]. Kasai et al. administered paclitaxel on day 1, and irinotecan on days 1, 8 and 15. Furthermore, irinotecan was infused following a 2 h rest period after completion of paclitaxel administration on day 1 [8], while we gave both drugs sequentially on the same days without a rest period, which was much closer to the simultaneous exposure of the two drugs than Kasai's study. This difference in the treatment schedules might have produced different antitumor effects.

In the pharmacodynamic analysis, we demonstrated that the AUC of irinotecan was strongly associated with the elevated serum levels of GPT. To our knowledge, this relationship has never been reported, though the pharmacokinetic/pharmacodynamic relationship between irinotecan AUC and myelosuppression, and between SN-38 pharmacokinetic variables and diarrhea has been identified in the previous studies [23]. Accordingly, monitoring of the AUC of irinotecan may be useful for the early prediction of hepatic toxicity in our treatment schedule. Further investigation is warranted to confirm the role of monitoring the AUC of irinotecan.

In conclusion, this phase I study was able to show neither feasibility nor effectiveness of this two-drug combination consisting of irinotecan and paclitaxel for patients with advanced NSCLC. Other drug administration schedules or different combinations should be investigated to establish more optimal combination chemotherapy in patients with advanced NSCLC.

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