treated with paclitaxel plus carboplatin was better in the current study than in the SWOG S0003 trial (median overall survival 14·1 months [95% CI 11·9–17·5] *vs* 9 months, respectively).[14] The prolonged overall survival in the current study compared with the SWOG trial might have been due to post-study treatment.[31] About two-thirds of patients in each group received poststudy chemotherapy, with most receiving gefitinib. Docetaxel is the only cytotoxic chemotherapy that has been shown to prolong overall survival compared with supportive care alone in patients with NSCLC who have received previous chemotherapy, although some other agents have shown activity in this population.[32] The EGFR inhibitor erlotinib also prolongs survival in previously treated patients with NSCLC.[33] Furthermore, placebo-controlled trials have shown that EGFR gene mutations are also prognostic factors, irrespective of the EGFR inhibitor used as treatment.[34] More EGFR gene mutations have been reported in Japanese patients with NSCLC than in US patients.[34] Thus, biological differences in lung cancer might exist between Japanese and US patients.

Neutropenic fever has also been shown to be more common in Japanese patients than in US patients (12% *vs* 3%).[14] Similar findings were obtained when European and US data were compared with a Japanese phase III study that used 200 mg/m² of paclitaxel plus carboplatin AUC of 6.[35] The difference in these toxicities might be due to pharmacogenomics. Another possibility is the difference in the method of measuring serum creatinine concentrations. In Japan, most institutions use an enzymatic method,[36] whereas the colorimetric Jaffe method is more frequently used in the USA.[37] The enzyme method tends to give lower serum creatinine concentrations resulting in a higher carboplatin dose when using Calvert formula.[38] Because clinical trials of cancer chemotherapy are being done internationally, caution should be paid to these medical differences.

Platinum-containing regimens remain the standard treatment for advanced NSCLC. However, the non-platinum regimen used in this study could still provide equivalent efficacy with a different toxicity profile, increasing the options available to patients.

Contributors

MK was the chief investigator of the trial. KKu, MK, MO, MF, and KF designed the trial and wrote the protocol. KKu, MK, MO, YN, KKo, KM, and YF enrolled patients. ST was responsible for data management and statistical analysis. KKu, KM, and ST took part in writing the report. All authors reviewed and approved the report.

Trial co-investigators

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Conflicts of interest

KKu has received honoraria from Eli Lilly, Sanofi-Aventis, and Chugai. All other authors declared no conflicts of interest.

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ORIGINAL ARTICLE

A phase II trial of weekly chemotherapy with paclitaxel plus gemcitabine as a first-line treatment in advanced non-small-cell lung cancer

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Abstract
Purpose The efficacy and toxicity of combined paclitaxel (PTX) and gemcitabine (GEM) was evaluated as a protocol for first-line chemotherapy in 40 patients with advanced non-small-cell lung cancer (NSCLC).
Methods Paclitaxel, 100 mg/m^2, was administered intravenously (IV) as a 1-h infusion, followed by GEM, 1,000 mg/m^2, IV over 30 min on days 1 and 8 of a 21-day cycle. The median age of patients was 66 years with a range of 33–75 years. Nearly all patients (39/40) had an ECOG performance status of 0 or 1. Thirteen patients (32%) had initial stage IIIB disease and 27 patients (68%) had stage IV disease. Histological subtypes were adenocarcinoma (73%) and squamous cell carcinoma (25%).
Results Twenty-two patients (55%) achieved a partial response and none achieved a complete response, giving an overall response rate of 55% (95% confidence interval: 38.2–71.8%). Disease stability was achieved in 14 patients (35%), and 4 patients (10%) had progressive disease. The median survival time was 11.9 months (95% CI: 10.3–14 months), with a 1-year survival rate of 47.5%. Grade 3 or 4 hematological toxicities observed included neutropenia in 37.5%, anemia in 2.5%, and thrombocytopenia in 5.0% of these patients. Non-hematologic toxicities were mild, with the exception of grade 3 and 4 pneumonitis. There were no deaths due to toxicity.
Conclusion Weekly chemotherapy with PTX plus GEM is effective and is acceptable for the first line treatment of advanced NSCLC.

Keywords Non-small-cell lung cancer · First-line chemotherapy · Weekly chemotherapy · Gemcitabine · Paclitaxel

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Introduction

Lung cancer ranks among the most commonly occurring malignancies and currently is the leading cause of cancer-related deaths worldwide [21]. In Japan lung cancer is responsible for approximately 55,000 cancer-related deaths per year [5]. Even though the clinical usefulness of first-line chemotherapy has been established for the cases of advanced non-small-cell lung cancer (NSCLC), the prognosis is still extremely poor.

A number of new agents have become available recently for the treatment of unresectable and metastatic NSCLC in Japan, including the taxanes, gemcitabine (GEM), and vinorelbine. In randomized phase III trials, these agents in combination with a platinum compound have been associated with improved survival of patients having advanced NSCLC [8, 17, 23, 24]. However, a platinum compound is associated with a greater toxicity than other drugs used to treat NSCLC. In addition to nausea and vomiting, it causes neuropathy, profound fatigue, and renal toxicity. Some

patients are unable to tolerate the drug toxicity and terminate treatment early. Based on these observations, non-platinum regimens have been proposed as an alternative to the platinum-based combinations for treatment of advanced NSCLC [13].

Paclitaxel (PTX) and GEM are new anti-cancer agents having significant single-agent activity against advanced NSCLC. A recent clinical phase II study of 122 patients with previously untreated, unresectable stage III or IV NSCLC receiving a 3-h infusion of PTX at a dose of 210 mg/m^2 showed a good response rate of 35% [25]. Although PTX is usually given once every 3 weeks, Chan et al. [10] demonstrated that weekly administration of PTX at a dose of 80–90 mg/m^2 provides similar tolerability and a possible increase in efficacy.

Gemcitabine, a novel deoxycytidine analog, had a response rate of 20% with a single weekly administration in previously untreated advanced NSCLC [4]. As a first-line treatment, single-agent GEM has been shown to have antitumor activity equal to that of cisplatin/etoposide, resulting in less toxicity and a slightly better quality of life [27].

These agents have different mechanisms of action, and their toxicities are partially non-overlapping. Although the usual administration of PTX is once every 3 weeks, a weekly administration can increase efficacy with good tolerability [1, 2]. We demonstrated that weekly administration with PTX and GEM is a tolerable and active regimen for patients with advanced NSCLC previously treated with platinum-containing chemotherapy regimens [20]. Based on these findings, we designed a phase II trial to examine the efficacy and tolerance of the non-platinum-based combination of PTX and GEM administered weekly for patients with untreated advanced NSCLC.

Patients and methods

Patient selection

All patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase II trial. The subjects of this study were patients with clinical stage IV NSCLC or stage III with unresectable disease or for whom radiotherapy with curative intent is not possible. Patients with unresectable disease or radiotherapy with curative intent is not possible include those with pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those with an irradiation field exceeding one-half of one lung, those with metastasis to the contralateral hilar lymph nodes, and those with reduced lung function. Other eligibility criteria included: age older than 20 years and younger than 76 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; measurable lesions; life expectancy $\geq$12 weeks; adequate bone marrow reserve with a WBC count $\geq$4,000 per mm^3; platelet count $\geq 10 \times 10^4$ per mm^3; and hemoglobin level $\geq$9.0 g/dL; liver function with a AST and ALT $\leq 2.5 \times$ upper normal limit, unless as a result of liver metastases; and adequate renal function with a serum creatinine level $\leq$1.5 mg/dL. No prior radiotherapy treatment was allowed if the irradiated area was not the site of measurable lesion and the therapy was completed at least 2 weeks before enrollment into the study.

Patients were excluded for the following indications: $\geq$76 years of age (vinorelbine as single agent treatment), severe cardiovascular or cerebrovascular disease, uncontrolled diabetes or hypertension, active infection, pulmonary fibrosis, massive pleural effusion or ascites, active peptic ulcer, and severe neurological disorders. Patients were also excluded in case of previous malignancy and any evidence or history of hypersensitivity or other contraindications for the drugs used in this trial. Written informed consent was obtained from all patients.

Treatment

Paclitaxel, 100 mg/m^2, was administered IV during a 1-h infusion, followed by GEM, 1,000 mg/m^2, IV over 30 min on days 1 and 8 of 21-day cycle. Premedication for PTX consisted of dexamethasone 20 mg, diphenhydramine 50 mg, and ranitidine 50 mg IV for 30 min before PTX infusion. After the premedication for PTX was completed, a serotonin receptor antagonist was given as a 30-min infusion for prophylactic antiemetic therapy. Treatment was repeated every 3 weeks until maximum response plus two cycles or unacceptable toxicity. In stable disease, patients received a maximum of six cycles. At the investigator's discretion, patients were treated with up to eight cycles of the drug combination.

Dose modifications were planned according to hematologic and severe non-hematologic toxic effects. Once the doses were reduced, they were not increased. Patients who experienced grade 4 neutropenia, grade 4 thrombocytopenia, reversible grade 2 neurotoxicity, or liver dysfunction received reduced doses of both PTX, 75 mg/m^2, and GEM, 800 mg/m^2, for the next cycle. The next course of chemotherapy was started after 3 weeks when the leukocyte count was 3,000 per mm^3 or greater, the neutrophil count was 1,500 per mm^3 or greater, the platelet count was 75,000 per mm^3 or greater, serum creatinine was less than 1.5 mg/dL, GOT and GPT were less than twice the upper limit of the normal range, and the neurotoxicity was grade 1 or less. If hematologic recovery was not achieved by day 35 of treatment, the patient was withdrawn from the study.

Evaluation of responses and toxicity

Responses and toxicity were evaluated on the basis of tumor images obtained by computerized tomography (CT), laboratory results, subjective/objective symptoms, signs before, during, and after administration of the study drugs and during the period from completion of treatment to the final analysis. Measurable disease parameters were determined every 4 weeks by various means such as CT. Evaluation was performed in compliance with the response evaluation criteria in solid tumors (RECIST) guidelines for anti-tumor activity. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0). Patients were withdrawn from the study if evidence of tumor progression was observed. The institutional ethical review committee gave approval to the study.

Statistical analysis

The primary end point of the study was the response rate. Simon's two-stage design was used to determine sample size and decision criteria. It was assumed that a response rate of 40% in eligible patients would indicate potential usefulness, while a rate of 20% would be the lower limit of interest; $\alpha = 0.05$ and $\beta = 0.10$. Using these design parameters, the first stage of the study was to enroll 24 patients, and the regimen was rejected if fewer than five patients had an objective response. If six or more patients responded, the accrual was continued until 45 patients were enrolled (45 patients were required because of anticipated percentage of dropout cases). Combination therapy was considered effective if ≥ 14 of the 45 patients showed a response in the final analysis. Secondary end points were toxicity and overall survival. Response and survival rates were both calculated on an intent-to-treat basis. Overall survival and time to progression were measured from the start of this treatment until time of death or the date of the last follow-up clinical assessment. Survival curves were constructed using the Kaplan–Meier method (Fig. 1).

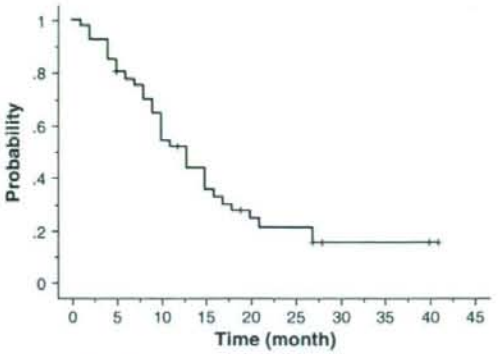

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 11.9 months; 1-year survival rate, 47.5%

Results

Patient characteristics

A total of 40 patients were enrolled in the study between September 2001 and July 2004. The majority of patients were treated as outpatients. The clinical characteristics of the patients are listed in Table 1. The median age was 66 years with a range of 33–75 years. Nearly two-thirds of the patients were men. Twenty-four patients had an PS of 0, and 15 had PS of 1. Histological subtypes were 73% (29/40) adenocarcinoma and 25% (10/40) squamous cell carcinoma.

Table 1 Patient characteristics

Eligible patients	40
Gender	
Male	26
Female	14
Age (years)	
Median	66
Range	33–75
Performance status	
0	24
1	15
2	1
Histology	
Adenocarcinoma	29
Squamous cell	10
Large cell	1
Stage	
III	13
IV	27
Number of metastatic sites	
Median	2
Range	0–3
Location of metastases	
Bone	12
Lung nodules	10
Liver	9
Lymph nodes	8
Adrenals	6
Brain	3
Subcutaneous	1

Toxicities

The toxicities observed during this study are provided in Table 2. Hematological toxicities were the most common, but grade 3–4 toxicities, including neutropenia (37.5%), thrombocytopenia (5.0%), and anemia (2.5%) were relatively modest. There were only two cases of febrile neutropenia (5.0%). Grade 1 nausea, fatigue, alopecia, neuropathy, and angialgia occurred with a greater frequency than the non-hematologic toxicities. Grade 3–4 non-hematologic toxicities were not seen except in cases of pulmonary toxicity. Two patients (5.0%) developed interstitial pneumonitis (grade 3; one patient, grade 4; one patient), and were responsive to steroid therapy.

Efficacy of treatment

The median number of cycles administered per patient was 4, and the number of cycles ranged from 1 to 8. Twenty-two patients exhibited a partial response. The overall response rate was 55% (22/40) [95% confidence interval (CI): 38.2–71.8%]. Stable disease was achieved in 14 patients (35%), and 4 patients (10%) had progressive disease. All 40 patients were included in the survival analysis. The overall median survival time was 11.9 months (95% CI: 10.3–14 months). The 1-year survival rate was 47.5% (19/40). The median time to disease progression was 6.4 months. Thirty patients (75%) received chemotherapy, and 4 patients (10%) received thoracic irradiation as second-line treatment.

Discussion

Although a standard regimen of first-line chemotherapy for advanced NSCLC is being established, it is important to develop a more active and well-tolerated regimen. Several published randomized studies reported that non-platinum-based chemotherapy in advanced NSCLC was as effective and less toxic than platinum-based regimens [13, 15, 18, 29]. Georgoulias et al. [13] compared the combination of a cisplatin and docetaxel regimen with the GEM and docetaxel regimen. Objective response rates were similar in the two groups, with 32.4% in the former and 30.2% in the latter. The two groups did not differ in the overall survival or 1- or 2-year survival rates. They concluded that both drug combinations had comparable activity and the non-platinum-based regimen had the more favorable profile.

Generally, non-cisplatin-containing treatment does not require supplemental hydration as does standard cisplatin-based chemotherapy. This may be advantageous for elderly patients, patients with poor PS, and patients with renal or cardiac impairment. Recchia et al. [22] conducted a trial of PTX plus GEM in advanced NSCLC patients with a low PS. The chemotherapy regimen consisted of 200 mg/m^2 PTX on day 1 plus 1,000 mg/m^2 GEM on days 1 and 8, repeated every 3 weeks, for a maximum of eight cycles. They achieved a reasonable response rate of 41.3%. Median overall survival time was 13.6 months; the authors concluded that a satisfactory clinical benefit could be obtained with GEM plus PTX regimen in NSCLC patients with a poor PS.

Thus, non-platinum-based chemotherapy may be used as alternative to platinum-based regimens. We conducted a phase II trial was designed to examine the efficacy and tolerance of the non-platinum-based combination of weekly PTX and GEM for patients with untreated advanced NSCLC. Results including an overall response rate of 55%, a median survival time of 11.9 months, and a 1-year survival probability rate of 47.5% suggested that this regimen might have anti-tumor activity equal to that of platinum-based regimens.

Weekly chemotherapy for lung cancer has recently been carried out at several facilities, and favorable results were reported [9, 16, 26, 30]. Compared to standard chemotherapy with administration of drugs at intervals of 3–4 weeks, weekly chemotherapy appears acceptable for the reduction of a single dose level of anti-cancer drugs with fewer side effects. In addition, weekly dose level is more easily adjusted according to the general clinical condition of individual patients or if hematologic toxicity develops. Belani et al. [6] conducted a randomized phase II trial of a 3-week schedule of GEM plus PTX (ArmA) versus a weekly schedule of GEM plus PTX (ArmB) in the treatment of NSCLC. It was concluded that a weekly schedule resulted in improved survival and lower hematologic toxicity than the 3-week schedule.

The clinical outcomes of weekly PTX and GEM therapy found in the literature [3, 6, 7, 11, 12, 14, 19, 28] and in our results are summarized in Table 3. The response rate ranges were from 23.1 to 55%; overall median survival time was 4.9–11.9 months; and 1-year survival rates were 26–53%. Most adverse reactions were hematologic (such as leukope-

Table 2 Maximum toxicity over 40 patients

	CTCAE v 3.0 grade (no. of patients)		Grade 3 or 4 (%)
	Grade 3	Grade 4	
Leukopenia	11	1	12 (30)
Neutropenia	11	4	15 (37.5)
Febrile neutropenia	2	0	2 (5.0)
Anemia	1	0	1 (2.5)
Thrombocytopenia	2	0	2 (5.0)
Pneumonitis	1	1	2 (5.0)

CTCAE v 3.0: Common Terminology Criteria for Adverse Events version 3.0

Table 3 PG regimens used as first-line treatment of advanced NSCLC

First author (ref.)	No. of patients		Regimen and schedule	Response rate (%)	Survival median	One-year (%)
Belani et al. [6]	50	Arm A	P 200 mg/m^2 day 1 q3w G 1 g/m^2 days 1, 8 q3w	28.2	7.5	34
	50	Arm B	P 100 mg/m^2 days 1, 8 q 3w G 1 g/m^2 days 1, 8 q3w	26.8	9.6	42
Bhatia et al. [7]	39		P 110 mg/m^2 days 1, 8, 15 q 4w G 1 g/m^2 days 1, 8, 15 q4w	38.2	4.9	26
De Pas et al. [12]	54		P 100 mg/m^2 days 1, 8, 15, 22 q 4w G 1 g/m^2 days 1, 8, 15, 22 q4w	46	9.6	53
Akerley et al. [3]	39		P 85 mg/m^2 days 1, 8, 15, 22, 29, 36 q 8w G 1 g/m^2 days 1, 8, 15, 22, 29, 36 q8w	23.1	7.5	32
Gillenwater et al. [14]	39		P 100 mg/m^2 days 1, 8, 15, 21 q 4w G 1 g/m^2 days 1, 8, 15, 21 q4w	35	4.9	35
Kosmidis et al. [19]	225		P 200 mg/m^2 day 1 q 3w G 1 g/m^2 days 1, 8, q3w	31	9.3	42
Treat et al. [28]	312		P 200 mg/m^2 day 1 q 3w G 1 g/m^2 days 1, 8, q3w	43.6	8.4	33
Our study	40		P 100 mg/m^2 days 1, 8, q 3w G 1 g/m^2 days 1, 8 q3w	55	11.9	47.5

NSCLC non-small-cell lung cancer, *P* paclitaxel, *G* demcitabine

nia and neutropenia of grade 3 or greater occurrence) in 28–53%. Variable toxicities may be due to population-related pharmacogenomics [11]. Overall, the non-hematologic toxicity was mild, and there were few adverse reactions of grade 3 or greater. A few patients had pneumonitis which was not responsive to steroid therapy. The treatment in our current study was reasonably tolerated, especially in the area of non-hematologic toxicity. Nausea, vomiting, and fatigue, which are often seen in cisplatin-containing regimens, were relatively mild; no patients developed renal toxicity.

In conclusion, weekly chemotherapy with PTX and GEM is a well-tolerated and effective regimen for previously untreated patients with advanced NSCLC. Further studies are expected for the application of this regimen to the elderly, and patients with a poor PS or suspected vulnerability to platinum compound toxicity.

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Conflict of interest statement None.

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Three-dimensional Conformal Radiation Therapy for In Situ or Early Invasive Central Airways Lung Cancer

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Introduction: Central airways lung cancer is occasionally discovered in early stage. Because of comorbidities, surgical resection is not always advisable for this type of lung cancer. Photodynamic therapy or endobronchial brachytherapy can produce cure for centrally located small lung cancers and is an alternative for surgery in selected patients. However, their application is limited by size and depth of invasion of the tumors or bronchoscopic access. External beam radiation can be applicable to almost all patients, when planned well. In this study, we evaluate the safety and efficacy of 3-dimensional conformal radiotherapy (3D-CRT) for in situ or early invasive central airways lung cancers.

Methods: Between November 2001 and December 2004, 8 patients with newly diagnosed or recurrent central airways lung cancer without nodal and distant metastasis were treated by 3D-CRT of 60 Gy in 3-Gy fractions. Target volume included the primary tumor but did not include regional lymph nodes. All patients were evaluated for disease control, survival, and complications.

Results: All lesions responded to the treatment. The median survival time was 36.8 months (30 to 50 mo), and the cause-specific survival time was 36.8 months (30 to 50 mo). Two-year overall, cause-specific survival, and locoregional control rate were 100%. Toxicity included pneumonitis observed in 1 patient, which resolved by conservative therapy.

Conclusions: 3D-CRT is a safe and effective treatment modality for in situ or early invasive central airways lung cancer when surgical resection or endobronchial therapy is not advisable.

Key Words: conformal radiotherapy, in situ or early invasive central airways lung cancer, local control, radical radiotherapy

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Lung cancer is occasionally detected as small centrally located tumors such as carcinoma in situ (CIS) or early invasive cancer. When lymph node and distant metastasis are not present, good clinical outcome including cure can be expected. Surgical resection, photodynamic therapy (PDT), and endobronchial brachytherapy are the modalities of treatment of choice. Although surgical resection is the standard treatment for early invasive central airways lung cancer, elderly patients or those with severe comorbidities are frequently determined medically inoperable. Additionally, as most of CIS or early invasive central airways lung cancers are smoking-related and have a tendency to be multifocal, conservative treatment is often sought. PDT is less invasive and effective for CIS or early invasive cancer, but complete remission is unlikely with large lesions and those deeper than bronchial cartilage.[1] In endobronchial brachytherapy, control of radiation dose is difficult and could lead to massive hemoptysis and exsanguination.[2]

Although external beam radiation remains an option for these patients, conventional one is associated with poor outcomes with 5-year survival rates of 25% to 30%.[3–17] Dose escalation of radiation using conventional fractionation and techniques would likely cause prohibitive toxicity. Three-dimensional conformal radiotherapy (3D-CRT) is intended to deliver higher doses of radiation, while minimizing damage to surrounding normal tissues. Because good results are reported in 3D-CRT for stage I peripheral lung cancer, 3D-CRT may have a potential to be curative for central-type lung cancers.[18] However, high-dose irradiation to hilar regions is still considered to be unsafe.[19] However, high but acceptable dose of irradiation seems to be necessary for centrally located small lung cancers.

Since 2001, we have been treating CIS and early invasive central airways lung cancer using 3D-CRT, when the lesions were inoperable or too invasive to treat with PDT. In this manuscript, we report the safety and efficacy of 3D-CRT for small centrally located lung cancers.

MATERIALS AND METHODS

Patient Characteristics

Between November 2001 and December 2004, 8 centrally located lung cancers without nodal (N0) and

TABLE 1. Patient Characteristics

Number	Age	BI	Localization	Size (mm)	Prior Therapy for Lung	Comorbidity
1	78	1200	Carina-rt., main-rt., second carina	35	Rt. B6 segmentectomy, rt. lower lobectomy	HT, cerebrovascular disease
2	56	1050	Lt. B6/basal bronchus spur-B8 + 9/10 spur	15	PDT for lt. second carina and lt. B6, lt. B6 segmentectomy, endobronchial brachytherapy for lt. B6	HT, chronic hepatitis
3	74	1320	Lt. upper bronchus	15	No	HT, COPD, hard of hearing
4	64	800	Rt. middle bronchus	25	PDT for rt. middle bronchus	Gastric ulcer, arrhythmia, COPD
5	80	1200	Rt. main	20	No	COPD
6	74	1000	Lt. upper bronchus	15	No	Renal dysfunction
7	67	800	Rt. basal bronchus	15	Lt. Lower lobectomy	No
8	71	1320	Rt. upper bronchus	25	Carina resection and tracheoplasty, Lt. basal segmentectomy	HT

BI indicates Brinkman Smoking Index; COPD, chronic obstructive pulmonary disease; HT, hypertension; Lt., left; PDT, photodynamic therapy; Rt., right; SCC, squamous cell carcinoma.

distant metastasis (M0) in 8 patients were treated with 3D-CRT with curative intent. Central lung cancer is defined as that originated from airways including and proximal to subsegmental bronchi.[20,21] All lesions were cytologically or histologically proved as squamous cell carcinoma and located from carina up to the segmental bronchus. No tumors could be detected by conventional chest computed tomography (CT). The local spread of the lesions was determined by conventional and autofluorescence bronchoscopy, together with endobronchial ultrasonography. Routine staging of the disease included chest x-rays and CT scans of thorax and abdomen. Brain CT/magnetic resonance imaging and bone scintigraphy/positron emission tomography were not mandatory in the cases of CIS.

Pretreatment characteristics of all 8 patients are shown in Table 1. They were all males and smokers/ex-smokers, whose Brinkman smoking indices were ranged between 800 and 1320. The median age was 71 (range: 56 to 80) years. Eastern Cooperative Oncology Group performance status was 0 in all patients. Most patients were considered to be inoperable, mostly as a result of comorbidities and poor pulmonary function owing to previous surgery, higher age, or chronic obstructive pulmonary disease. Two patients (nos. 1 and 8) experienced stump recurrences at the bronchial resection margins. In 1 patient (no. 7), a new primary lesion appeared away from the stump region. Another one (no. 2) was treated by PDT twice, surgery and endobronchial brachytherapy for the left lower lobe endobronchial cancer, yet developed recurrence. Another one (no. 4) had CIS and received prior PDT for the lesion, but complete regression could not be attained. The remaining 3 patients (nos. 3, 5, and 6) were considered to be inoperable mostly as a result of comorbidities and endobronchial therapy, such as PDT or brachytherapy, was not indicated owing to the extent of the lesions. Patient nos. 3 and 5 had CIS. As conformal radiotherapy (CRT) is considered to be the only available curative treatment, the modality was used after obtaining informed consent.

Treatment

Plain CT images of 0.5-mm thickness were obtained over whole lungs. The images were transferred to radiation planning computer (CADPLAN, Varian Medical Systems, Palo Alto, CA) to make 3D-CRT plans. As the tumor could not be depicted on CT images, clinical target volumes (CTVs) were defined as possible tumor length along the bronchial tree and tumor depth into the bronchial wall on the basis of bronchoscopical findings. Hilar, mediastinal, and supraclavicular nodal regions were not included in CTV. The planning target volume (PTV) was designed by enlarging CTV in all directions by 8 to 10 mm, taking both setup uncertainty and respiratory movement into considerations. Radiation fields were formed with multileaf collimator to achieve conformity with leaf margin of 5 mm and coplanner 5-beams arrangement. Beam energy was 6 or 10 MV x-ray. Figure 1 shows an example of 3D-CRT planning for a central-type lung cancer.

Total 60 Gy, prescribed at the isocenter, was administered by 3-Gy fraction, once a day for 4 weeks. V_{20} of the lungs was defined as the percentage of lung volume that received ≥ 20 Gy radiations in the treatment plan. The biologic effective dose (BED) was calculated using the following formula: $\mathrm{BED} = nd\ [1 + d/(\alpha/\beta)]$ where n = number of fractions, d = fraction dose, and α/β is assumed to be 10 for tumor cells or acute responding tissues.

Tumor response was evaluated by bronchoscopy and chest CT. Chest x-ray and CT were examined regularly. Radiation-induced toxicities were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Scheme. Pulmonary function tests including percent vital capacity and percent forced expiratory volume in 1 second and arterial blood gas analysis were obtained before and after the treatment to identify the risk factors for lung toxicity by 3D-CRT. Paired t test was used to compare respiratory function and PaO_2 values.

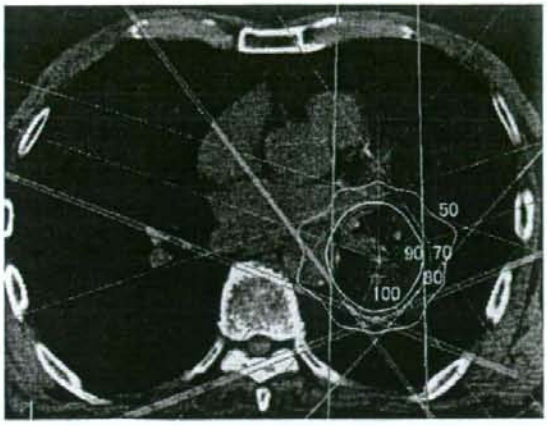

FIGURE 1. The 3-dimensional conformal plan beam arrangement. Circle lines represent the 50% to 100% isodose curves.

RESULTS

The planned treatment was safely performed in all 8 patients with no or minimal acute adverse events. No acute esophageal toxicity was observed. Grade 1 acute radiation pneumonitis (RTOG) was observed in 1 patient. Local response was evaluated by both bronchoscopy and chest CT in 6 patients, but the other 2 patients were considered unsuitable for bronchoscopy and their response was evaluated by sputum cytology and chest CT.

The median follow-up period was 36.8 months (range: 30 to 50 mo). Median survival time was 36.8 months (range: 30 to 50 mo). The 2-year locoregional control rate was 100%. Six patients were alive and 2 died of intercurrent disease without recurrence of centrally located lung cancer. Local failure did not occur in any patient. During follow-up period, secondary lung cancer (adenocarcinoma in both patients) was developed in 2 of 8 patients and they underwent additional 3D-CRT. One of them died of secondary lung cancer due to primary failure at 31 and 10 months after the first and second CRT, respectively. The other patient is alive in the presence of metastasis to the bone and brain, whereas 2 primary sites were maintained to be well controlled in all examinations, including positron emission tomography.

No patient experienced late toxicities at 90 days from the first day of radiation therapy. Table 2 depicts the PTV and the V_{20} values. The median PTV was 45.5 mL (range: 27.6 to 61.8mL) and the median V_{20} value was 10.7% (range: 8.3 to 17.0). We did not encounter interstitial changes in the irradiated lung field with this focal radiation therapy in any of our patients (Figs. 2A, B). Bronchoscopically, the irradiated bronchus was slightly stenotic and scarred (Figs. 3A, B). Respiratory functions and arterial blood gas analysis were unaffected in all patients who underwent the evaluation (Figs. 4A–C). Some patients did experience acute radiation esophagitis, yet it was in grade 2 or less at each occasion.

DISCUSSION

Natural history of CIS and severe dysplasia in the respiratory tract is not clarified completely, and therefore, their treatment strategy is still controversial. Although all of these lesions do not necessarily progress to clinically relevant lung cancers,[22] appreciable proportions of them have high risk of becoming invasive carcinoma. Their risk to progress to a clinical lung cancer was reported to be 33% at 1 year and 54% at 2 years.[23] Therefore, these lesions should be treated in their early stages.

Surgery is the standard treatment for early invasive central airways lung cancer in the patients with good performance status. In Japan, 5-year survival rates of the patients with lung cancer treated surgically are 72% for cIA and 49.9% for cIB and 79.5% for pIA and 60.1% for pIB.[24] On the other hand, Kato et al[1] reported that PDT yielded an initial complete response rate of 84.8% for centrally located early-stage lung cancer. PDT is considered as an effective alternative for surgery for centrally located stage 0 (TisN0M0) and stage I (T1N0M0) early invasive lung cancer, when surgical intervention is difficult or the patients refuse surgery. PDT is especially attractive for elderly patients or those in poor physical condition. Whereas PDT is reported to be effective only for the superficial tumors of < 1 cm in diameter with visible peripheral margin and which is located no more peripherally than subsegmental bronchi, another modality is necessary for the tumors that do not fulfill at least 1 of these conditions.

For many years, the mainstay of treatment for inoperable lung cancer was radiation of nearly 60 Gy of total dose with 2 Gy/fraction over 6 weeks. Conventional external beam radiation of 60 to 70 Gy alone is reported to result in 15% of 5-year overall survival rate, 25% intercurrent death rate, and 50% of treatment failures in local site alone, in the expense of grade 3 to 5 complications of $< 5\%$.[25] These results are not satisfactory for stage I lung cancer. On the basis of dose-response data, Mehta et al[26] estimated that it would take a dose of approximately 85 Gy to achieve 50% long-term control rate using standard 2-Gy daily fractions. It seems that higher doses and shorter treatment times are required to achieve better disease control. However, radiation dose escalation using conventional fractionation and

TABLE 2. Planning Target Volume and V_{20}

Number	PTV (mL)	V_{20} (%)
1	58.24	8.50
2	36.30	9.80
3	36.00	11.78
4	61.80	11.42
5	47.40	9.14
6	36.32	9.35
7	27.60	8.30
8	60.02	16.95

V_{20} was defined as the percentage of lung volume that received ≥ 20 Gy radiations in the treatment plan.
PTV indicates planning target volume.

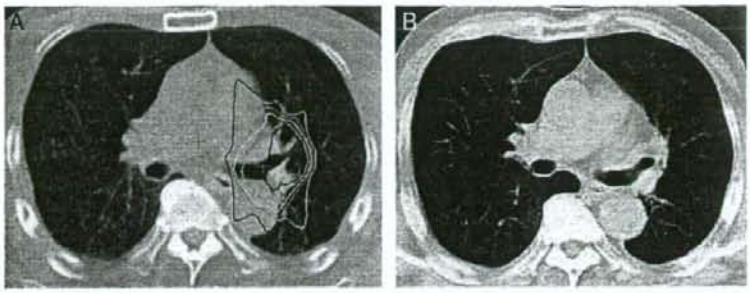

FIGURE 2. A, An example of the dose coverage on an axial CT image in the 74-year-old patient with cancer located at left upper bronchus. B, CT scan at 1-year follow-up shows a complete response without post-treatment interstitial lung changes. CT indicates computed tomography.

techniques would likely cause prohibitive toxicity. 3D-CRT is intended to deliver higher dose of radiation while minimizing damage to surrounding normal tissues. We treated the patients by CRT with 20 fractions of 3 Gy. The biologically effective dose (BED) of this radiation is calculated to be almost equal to 78 Gy in conventional fractionation (assuming α/β of 10). Almost no, at most minimal, interstitial changes were observed in the irradiated lung fields (Figs. 2A, B). This observation was further supported by the fact that respiratory functions were unaffected by the treatment in all patients. These are ascribed to very limited PTV with a median of 45.5 mL. Lagerwaard et al[27] showed that central location of tumors (endobronchial tumor extension) was the only factor that significantly reduced local progression-free survival in 3D-CRT for lung cancer. Our good results can be ascribed to small size of the tumors, which do not require large dose of radiation compared with established invasive cancer. Recently, stereotactic radiotherapy (SRT) is showing favorable results in the treatment of peripherally located stage I lung cancer. Timmerman et al[19] reported a phase 2 trial of SRT with 60 to 66 Gy in 3 fractions during 1 to 2 weeks in 70 patients with medically inoperable early-stage lung cancer. Grade 3 to 5 toxicity occurred in 14 patients (20%). In 2-year follow-up after SRT, 83% of the patients with peripherally located lung cancer experienced no severe complications, whereas 54% of those with centrally located cancer did. The patients with centrally located tumors have 11-fold increased risk of experiencing severe complications compared with those with lung cancer located more peripherally. Their conclusion was that SRT of this regimen should not be used for the patients with tumors located near the central airways because of excessive complications. Similarly, Le et al[28] reported the results of dose-escalation study using single-fraction SRT of 15 to 30 Gy for lung tumors. Majority of the patients who showed grade 2 or greater complications had either centrally located tumors and/or the tumors with treatment volumes greater than 50 mL. The toxicities observed included pneumonitis, pleural effusion, pulmonary embolism, and tracheoesophageal fistula. These results indicate that high-dose radiation by limited fractions is dangerous for perihilar structure of the lung. As small lung cancer,

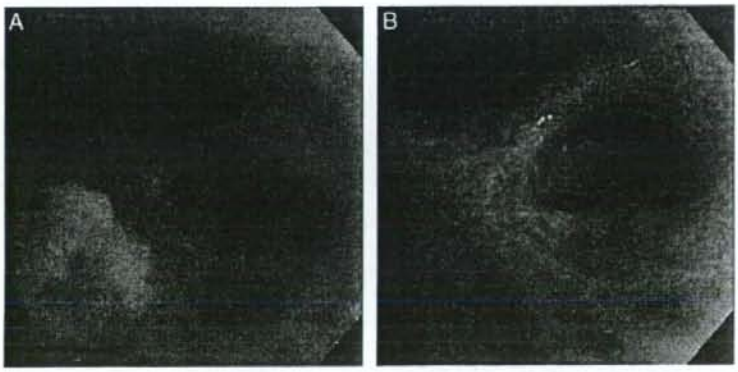

FIGURE 3. A case of 74-year-old patient with central type lung cancer. A, Squamous cell carcinoma located at left upper bronchus. B, After 6 months of 3D-CRT, the irradiated bronchus was slightly stenotic and scarred. 3D-CRT indicates 3-dimensional conformal radiotherapy.

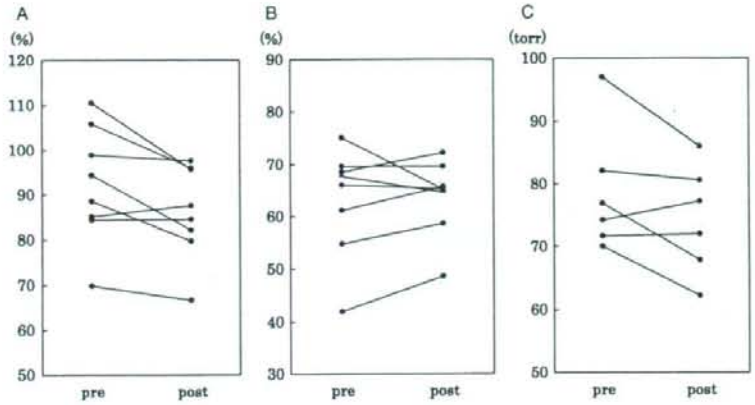

FIGURE 4. Respiratory function values of preradiotherapy and postradiotherapy. A, %VC: percent vital capacity. B, FEV1.0%: percent forced expiratory volume in 1 second. C, PaO_2: arterial blood gas analysis.

such as CIS and early invasive cancer, is curative by radiation with sufficient dose, determination of total dose and fractionation is critical to treat small lung cancer located in the central airways. Although the number of the patients entered into this study is small, our method may afford a good clue.

CONCLUSIONS

As small lung cancer, such as CIS and early invasive cancer, is curative by radiation with sufficient dose, determination of total dose and fractionation is critical to treat small lung cancer located in the central airway. 3D-CRT given by 20 fractions of 3 Gy is a safe and effective treatment for inoperable CIS or early invasive central airways lung cancer.

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ORIGINAL ARTICLE

Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer

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Abstract
Purpose We conducted a phase II study of combination chemotherapy with nedaplatin (NP) and irinotecan (CPT) followed by gefitinib to determine the effects and toxicities in patients 70 years or older with unresectable non-small cell lung cancer (NSCLC).
Methods Eligible patients were entered to receive 3 courses of 50 mg/m^2 NP and 60 mg/m^2 CPT on days 1 and 8 every 4 weeks and sequential gefitinib 250 mg po once a day was followed until tumor progression.
Results Twenty-eight patients received NP and CPT combination chemotherapy. One patient achieved CR, 10 PR, 14 SD and 3 PD, and the response rate was 39.3%. Twenty-one patients received gefitinib 250 mg per day until tumor progression after completion of the NP and CPT chemotherapy. Two patients with SD after NP and CPT chemotherapy achieved PR. For the 3-drug combination, there were 13 responders and the overall response rate was 42.9%. Of the toxicities associated with NP and CPT chemotherapy, grade 4 neutropenia, and grade 3 febrile neutropenia were observed in 24 (33.8%) and 3 (4.2%) courses, respectively. Of the toxicities associated with gefitinib treatment, grade 3 anemia, and SGOT and SGPT elevation were observed in one patient (4.8%) each, respectively. The median survival time was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively.
Conclusion NP and CPT followed by gefitinib is feasible for elderly patients with unresectable NSCLC.

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Keywords Nedaplatin · Irinotecan · Gefitinib · Lung cancer · Elderly

Introduction

Current chemotherapy regimens for metastatic non-small cell lung cancer (NSCLC) are not particularly effective. Regimens based on combinations of new anticancer agents such as vinorelbine, gemcitabine, docetaxel and paclitaxel with platinum compounds have emerged as a gold standard for such patients [1].

In a subset analysis of randomized trials, the response rate, toxicity and survival rates in fit, elderly patients with NSCLC receiving platinum-based treatment appeared to be similar to those in younger patients [2]. However, elderly patients with normal organ function had been selected as subjects for the analysis. A feasibility study of standard cisplatin-based chemotherapy in elderly lung cancer patients with normal organ function showed that only 29% satisfied the eligibility criteria, and that these patients experienced severe neutropenia after cisplatin-based chemotherapy [3]. It is generally believed that elderly patients are less able to tolerate aggressive chemotherapy than their younger counterparts. The randomized Elderly Lung Cancer Vinorelbine Study Group trial demonstrated that elderly patients treated with vinorelbine—in combination with best supportive care (BSC)—have a significantly improved chance of survival and quality of life in comparison with patients treated with BSC alone [4]. The Multicenter Italian Lung Cancer in the Elderly Study trial demonstrated that the use of a combination of gemcitabine plus vinorelbine in this patient population did not further improve the survival rate or quality of life in comparison with either vinorelbine or gemcitabine monotherapy [5]. Thus, standard combination chemotherapy

has not been established for elderly patients with advanced NSCLC.

Three-dimensional analysis models have demonstrated a remarkable synergistic interaction of concurrently administered nedaplatin (NP) and irinotecan (CPT) [6]. In our previous phase I/II study, a combination of NP and CPT showed high activity against NSCLC: the response rate was 31.0%, and the 1-year survival rate was 45.2% [7]. A phase II study of combination chemotherapy with NP and CPT in 38 patients aged 70 years or older with advanced NSCLC demonstrated a 65.8% response rate, a median survival time of 418 days, and a 1-year survival rate of 55.3% [8]. However, seven of the 38 patients could not receive a second cycle of the chemotherapy because of toxicities such as vomiting, diarrhea and febrile neutropenia. Dose or schedule modifications are therefore required to make the NP and CPT combination safe for elderly patients.

The epidermal growth factor receptor (EGFR) superfamily was identified early on as a potential target for therapy of solid tumors. Given the biological importance of the EGFR molecular network in carcinomas, several molecules that can inhibit the EGFR tyrosine kinase domain have been synthesized. The inhibitor gefitinib at 250 mg per day demonstrated an 18.4% objective response in 103 patients with previously treated advanced NSCLC [9]. Adverse events associated with use of the drug were mainly skin reactions and diarrhea. As no hematological adverse events or infections related to chemotherapy safety in elderly patients with NSCLC were observed in a trial of gefitinib at 250 mg per day, gefitinib treatment is considered to be feasible for such patients.

Here we report a phase II study of combination chemotherapy with NP and CPT followed by sequential gefitinib treatment for elderly patients with advanced NSCLC. We modified the NP arm so that it was divided on days 1 and 8, in order to ensure safety and to allow continuous use of gefitinib after completion of the NP and CPT chemotherapy until tumor progression.

Patients and methods

The Institutional Review Board of Kanagawa Cancer Center reviewed and approved this study prior to commencement.

Patients

Patients with histologically or cytologically proven unresectable NSCLC were registered for the NP and CPT combination followed by gefitinib chemotherapy. Eligibility criteria for the chemotherapy were: no prior chemotherapy, expected survival of at least 6 weeks, age $\geq$ 70 years, Eastern Cooperative Oncology Group PS score $\leq$ 2, leukocyte count $\geq$ 4,000/μl, hemoglobin count $\geq$ 9 g/dl, platelet count $\geq$ 100,000/μl, total serum bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase $\leq$ 90 IU/l, serum creatinine $\leq$ 1.5 mg/dl, and creatinine clearance more than 40 ml/min. We did not attempt their geriatric assessment in the present study. Patients experiencing postoperative recurrence and patients who had received radiotherapy for metastatic lesions were eligible for the present study, and at least 4 weeks' rest was required after prior surgery or radiation therapy. Patients with massive pleural effusion, pericardial effusion, symptomatic brain metastasis, paralytic ileus, severe infection or pneumonitis were excluded. Patients with uncontrolled ischemic heart disease, severe cardiac insufficiency, hypertention or diabetes mellitus were also excluded. Written informed consent was obtained in every case.

Chemotherapy

Patients exhibiting no progression of the disease were treated every 4 weeks with 60 mg/m^2 CPT and 50 mg/m^2 NP on days 1 and 8. Patients received 5-HT$_3$ antagonist IV and 8 mg dexamethasone IV before administration of the anticancer drugs. Both drugs were administered on day 8 when the following criteria were satisfied: leukocyte count $\geq$ 3000/μl, neutrophil count $\geq$ 1,500/μl, platelet count $\geq$ 75,000/μl, non-hematologic toxicity of less than grade 2 except for alopecia, and leukocyte or neutrophil count greater than 1,000/μl or 500/μl respectively during the period between day 2 and 8. Recombinant human granulocyte colony-stimulating factor (G-CSF), 50 mg/m^2 per day or 2 μg/kg per day, was administered subcutaneously once a day when the patient's leukocyte or neutrophil counts were below 1,000 and 500/μl, respectively. Subsequent cycles of chemotherapy were started when patients were able to satisfy the organ function eligibility criteria, with the exceptions of hemoglobin count and creatinine clearance, for entry to the study. The doses of CPT and NP were reduced by 10 mg/m^2 for the subsequent cycle if dose-limiting toxicities (DLT) were observed, such as grade 4 neutropenia lasting $\geq$4 days or grade 4 neutropenia with fever $\geq$38°C, grade 4 thrombocytopenia, other grade 4 blood/bone marrow toxicities, except for leukocyte and hemoglobin toxicities, grade 4 vomiting, grade 4 anorexia, grade 4 constipation, grade 4 stomatitis/pharyngitis, grade 4 metabolic/laboratory toxicities, grade 4 coagulation toxicities, or grade 3 or 4 other non-blood/bone marrow toxicities, except for nausea and vomiting. The NP and CPT chemotherapy was repeated for a maximum of three cycles unless the disease progressed, or if severe toxicities developed, such as septic shock, irreversible renal failure, grade 4 hepatic toxicity, grade 4 cardiovascular toxicity, grade 4 pulmonary toxicity, grade 4 diarrhea, grade 4 CNS cerebrovascular

ischemia, or grade 4 CNS hemorrhage/bleeding. Tumor responses were evaluated according to the RECIST criteria [10]. Toxicities were evaluated according to the NCI-CTC ver.2 criteria [11].

Sequential chemotherapy with gefitinib 250 mg po once a day was started after completion of the NP and CPT combination chemotherapy when the following criteria were satisfied: PS score ≤ 2, leukocyte count $\geq 4{,}000/\mu l$, hemoglobin count ≥ 9 g/dl, platelet count $\geq 100{,}000/\mu l$, total serum bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 90 IU/l, serum creatinine ≤ 1.5 mg/dl. Sequential gefitinib treatment was interrupted for a maximum 14 days until the toxicities became less than grade 2, if grade 4 hematological toxicities, grade 3 skin toxicity, grade 3 diarrhea, or grade 3 other non-hematological toxicities appeared. The sequential chemotherapy was stopped if the disease progressed, toxicities did not recover to grade 0 or 1 within 14 days, 2 breaks of treatment were required due to toxicities, or patients refused the treatment.

Study design

We chose a 60% response rate as a desirable target level for the NP and CPT regimen, and considered a 40% response rate as not significant. The study design had the power to detect responses greater than 90%, with less than 10% error. Therefore, we required 28 assessable patients in the first stage and 13 in the second stage, according to the Minimax design of Simon [12]. We decided to stop the study if less than 11 patients responded to NP and CPT in the first stage. This regimen was defined as active if the number of responders out of 41 patients was $\geqq 21$, and inactive if the number of responders was $\leqq 20$ [12, 13]. Overall survival was estimated using the method of Kaplan and Meier.

We also defined toxic regimen when one-third patients experienced grade 4 thrombocytopenia, grade 3 neutropenic fever or other grade 3 non-hematological toxicities in this study.

Results

Between November 2002 and July 2005, 28 patients were registered in the study. Patient characteristics are summarized in Table 1. Twenty patients were male and 8 were female, with a median age of 74 years (range 70–81 years). Six patients had a performance status (PS) of 0 and the other 22 patients had a PS of 1. Twenty-three patients had adenocarcinoma, 4 had squamous cell carcinoma, and 1 had non-small cell carcinoma. Seven and 21 patients were stage IIIB and stage IV, respectively. All 28 patients were assessed for response, toxicities and survival. Twenty-five patients received 2 or 3 cycles of NP and CPT combination chemotherapy. Three patients dropped out the study after the first cycle of NP and CPT chemotherapy: 1 with disease progression, 1 with febrile neutropena requiring 15 days for improvement, and 1 with grade 2 diarrhea and grade 3 CNS cerebrovascular ischemia. Treatment-related toxicities during the total 71 courses of NP and CPT chemotherapy are listed in Table 2. Of the hematological toxicities, grade 4 anemia and neutropenia were observed during 2 (2.8%) and 24 (33.8%) courses, respectively. There was no grade 4 thrombocytopenia, and none of the patients required transfusion. Of the non-hematological toxicities, grade 3 febrile neutropenia was observed in three courses (4.2%). Grade 3 diarrhea and grade 3 CNS cerebrovascular ischemia was observed in 1 course (1.4%) each, respectively. Other non-hematological toxicities were mild. The outcome of the NP and CPT regimen in 28 patients were 1 CR, 10 PR, 14 SD and three PD, and the response rate was 39.3%. Thus, the study was stopped in the first stage.

Table 1 Patient characteristics

	No. of patients
Total	28
Age (years)	
Median	74
Range	70–81
Gender	
Male	20
Female	8
Performance status (ECOG)	
0	6
1	22
Smoker	22
Clinical stage	
IIIB	7
IV	18
Postoperative recurrence	3
Histology	
Adenocarcinoma	23
Others	5
No. of metastatic organs	
1	16
$\geqq 2$	5
Brain metastasis	1

Twenty-one patients received sequential gefitinib treatment, and 7 patients were unable to do so, 3 because of decreased PS, 3 due to refusal, and 1 because of the need for whole brain irradiation for progressive brain metastasis. The median duration of sequential gefitinib treatment was 68 days (range 21–932 days). Two patients, whose

Table 2 Toxicities in NP and CPT combination chemotherapy

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	7	21	27	14	2	22.5
Leukocytes	10	9	24	23	5	39.4
Neutrophils	10	5	10	22	24	64.8
Platelets	19	27	9	16	0	22.5
Bilirubin	68	1	2	0	0	–
SGOT	56	15	0	0	0	–
SGPT	63	7	1	0	0	–
Creatinine	62	7	2	0	0	–
Fatigue	2	48	16	5	0	7.0
Fever	65	6	0	0	0	–
Alopecia	48	22	1	0	0	–
Rash/desquation	68	3	0	0	0	–
Diarrhea	37	27	6	1	0	1.4
Nausea-vomiting	40	25	6	0	0	–
Febrile neutrophenia	62	6	0	3	0	4.2
CNS cerebrovascular ischemia	70	0	0	1	0	1.4
Neuropathy	71	0	0	0	0	–
Pneumonitis	71	0	0	0	0	–

response to NP and CPT was SD, responded to gefitinib treatment, and the overall response rate for NP and CPT followed by gefitinib was 42.9%. Treatment-related toxicities for the total of 21 patients who received gefitinib treatment are listed in Table 3. Of the hematological toxicities, grade 3 anemia was observed in one patient (4.8%). Of the non-hematological toxicities, infection with grade 3 SGOT and SGPT elevation was observed in one patient (4.8%). Other hematological and non-hematological toxicities were mild.

The overall survival curve is shown in Fig. 1. Five patients survived and the other 23 patients died during the follow-up period. The median survival time was 8.7 months. The 1- and 2-year survival rates were 42.9 and 32.1%, respectively.

Discussion

The combination of NP with CPT followed by gefitinib treatment showed activity against NSCLC in the present study. We chosen 60% response rate as a desirable target level in NP and CPT regimen. The responders in 28 entered patients of first stage were required 12 patients, the responders were 11 and this regimen was concluded inactive. However, two patients, whose response to NP and CPT was SD, responded to gefitinib treatment. Thus, overall response rate 42.9% for NP and CPT followed by gefitinib was considered to be active. A previous study of NP and CPT combination chemotherapy showed that it was effective for elderly patients with advanced NSCLC, although 29% of patients experienced febrile neutropenia [8]. In the present study design, we defined toxic when one third patients experienced grade 4 thrombocytopenia, grade

Table 3 Toxicities in gefitinib treatment

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	1	12	7	1	0	4.8
Leukocytes	16	4	1	0	0	–
Neutrophils	18	2	1	0	0	–
Platelets	15	4	2	0	0	–
Bilirubin	19	2	0	0	0	–
SGOT	13	7	0	1	0	4.8
SGPT	16	4	0	1	0	4.8
Creatinine	17	3	1	0	0	–
Fatigue	1	18	2	0	0	–
Fever	21	0	0	0	0	–
Alopecia	19	2	0	0	0	–
Dry skin	12	9	0	0	0	–
Nail change	20	1	0	0	0	–
Pruritis	13	8	0	0	0	–
Rash/desquation	7	12	2	0	0	–
Anorexia	20	1	0	0	0	–
Diarrhea	15	6	0	0	0	–
Gastritis	20	1	0	0	0	–
Nausea-Vomiting	19	2	0	0	0	–
Epistaxix	20	1	0	0	0	–
Infection	20	0	1	0	0	–
Neuropathy	21	0	0	0	0	–
Pneumonitis	21	0	0	0	0	–

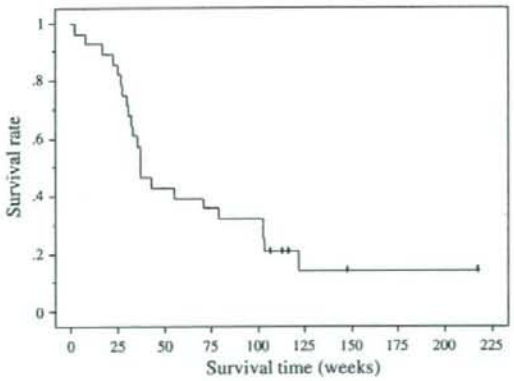

Fig. 1 Survival curves constructed by the Kaplan–Meier method. Five of the 28 patients were alive, the MST was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively

3 neutropenic fever or other grade 3 non-hematological toxicities. Only five patients (17.9%) experienced these toxicities and the treatment was concluded to be safe. We also considered the incidence of 33% for grade 4 neutropenia and 4.2% for grade 3 neutropenic fever to be acceptable in this study. Although the response rate of 39.3% for NP and CPT chemotherapy was not high, 25 of 28 patients (89.3%) were able to receive 2–3 cycles of the combination chemotherapy. Division of the NP arm on days 1 and 8 with CPT was confirmed to be safe for elderly patients with NSCLC.

Sequential gefitinib treatment resulted in tumor regression in only 2 of 21 patients (9.5%) achieving SD or PD with NP and CPT treatment. We considered that this small adjuvant effect of gefitinib after NP and CPT treatment may have been due to gefitinib resistance in most of the elderly patients who entered the trial. However, the response rate in the present study was higher than that in a study of gefitinib monotherapy for 40 elderly patients with pretreated NSCLC, which demonstrated a 5% objective response [14]. Responsiveness to gefitinib has been demonstrated in distinct subgroups of patients, such as women, patients who have never smoked, patients with adenocarcinoma, and Asians [15–17]. Twenty-two and 21 of the 28 patients registered in this study were smokers and males, respectively. Only four patients in this study were women who had never smoked, and were sensitive to gefitinib. This may have accounted for the small impact of gefitinib treatment in this study. Median survival time was 8.7 months, but nine patients (32.1%) survived more than 2 years. The presence of such long survivors suggested that gefitinib treatment could be effective for some elderly patients who are gefitinib-sensitive. Although the level of EGFR protein expression is not associated with the response to gefitinib, specific missense and deletion mutations in the tyrosine kinase domain of the EGFR gene have been reported to be associated with gefitinib sensitivity [18, 19]. A retrospective study demonstrated that NSCLC patients with EGFR mutations had a better outcome with gefitinib treatment than patients with the wild-type EGFR gene [20]. Our recent study has also demonstrated a significantly higher gefitinib response in patients with EGFR mutation than in those with wild-type EGFR (90.9 vs. 14.3%), and significantly longer overall and progression-free survivals in patients with EGFR mutation [21]. Unfortunately, the patients in the present study were not analyzed their EGFR genetic status, gefitinib treatment seems to be of some benefit to patients with EGFR mutation.

In conclusion, sequential gefitinib treatment added to NP and CPT combination chemotherapy does not improve the response rate but can have a longer survival benefit for at least some elderly patients with advanced NSCLC. Gefitinib treatment can be considered when candidate patients have EGFR mutation in NSCLC.

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