cases, pathological diagnosis was made using a biopsy specimen obtained on VATS in two cases.[2] In the remaining two cases, decortication[1] or complete *en bloc* resection[3] was performed under thoracotomy.

In Japan, EMR for gastric mucosa has been accepted as a treatment option for EGC where the probability of lymph node metastasis is low.[4] The specimen obtained on EMR as a single specimen is available for accurate histopathological determination of the submucosal invasion, vessel involvement and marginal invasion. For EMR for a larger EGC, the IT-knife was developed.[4–6] The IT-knife can dissect the gastric submucosa safely, and completely remove a carcinoma as a large single-piece specimen without severe crushing. The use of the IT-knife during thoracoscopic examinations has not previously been reported anywhere. Using this procedure we first obtained a large, single-piece, full-thickness and only slightly crushed specimen of the pleura and were able to study its histopathological features in detail. Previously such thoracoscopic study has been impossible because thoracoscopic biopsy specimens were tiny or crushed by the biopsy forceps.

Beyond expectation, the thoracoscopic IT-knife allowed detailed histopathological findings of pleural MALT lymphoma to be obtained. New histopathological findings for pleural MALT lymphoma are as follows: (i) lack of apparent evidence of plasmacytic differentiation; (ii) no recognition of lymphoid follicles; (iii) mesothelial cells not infiltrated by lymphoma cell clusters; (iv) thin layer of hyperplastic mesothelial cells continuously covering the surfaces; and (v) no proliferation of fibroblast-like submesothelial cells. This new thoracoscopic IT-knife is very useful for the detailed pathological study of pleural lesions including MALT lymphoma.

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Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study

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Summary

Background Platinum-containing two-drug combinations improve survival and cancer-related symptoms in patients with advanced non-small-cell lung cancer (NSCLC). However, survival benefit is modest and platinum-containing regimens cause substantial toxic effects. We did a prospective randomised open-label phase III study to compare an experimental platinum-free, triplet, sequential regimen of vinorelbine plus gemcitabine followed by docetaxel with the standard platinum-containing, doublet regimen paclitaxel plus carboplatin in patients with advanced NSCLC.

Methods Between March, 2001, and April, 2005, patients with stage IIIB (positive pleural effusion) or IV NSCLC, performance status 0 to 1, and adequate organ function, were randomly assigned to experimental treatment or to standard treatment. Randomisation was done centrally by use of a dynamic balancing algorithm. Patients were stratified by weight loss, lactate dehydrogenase concentration, and disease stage. Patients in the experimental group were scheduled to receive intravenous vinorelbine (25 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 every 21 days for three cycles, followed by intravenous docetaxel (60 mg/m^2) on day 1 every 21 days for three cycles. Patients in the standard group were scheduled to receive intravenous paclitaxel (225 mg/m^2) plus carboplatin (area under the curve=6) for 3 h on day 1, every 21 days for six cycles. The primary endpoint was overall survival, and secondary endpoints were progression-free survival, response, and toxic effects. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00079287.

Findings Of the 401 patients enrolled and randomised in the trial, five patients in the experimental group and three in the standard group were ineligible for analysis; thus 196 patients in the experimental group and 197 in the standard group were included in analyses. Patient characteristics were well-balanced between the two groups with regard to major prognostic factors. Median overall survival was 13·6 months (range 12·0–16·4) in the experimental group versus 14·1 months (11·9–17·5) in the standard group (p=0·97). 49 of 196 patients (25%) in the experimental group had a partial response compared with 73 of 197 patients (37%) in the standard group (p=0·012). There were no complete responses. Median progression-free survival was 5·5 months (95% CI 4·9–6·3) in the experimental group compared with 5·8 months (5·3–6·1) in the standard group (p=0·74). The incidence of grade 3 and 4 neutropenia, neuropathy, arthralgia, and myalgia was lower in the experimental group than in the standard group, although the incidence of pulmonary toxic effects was higher.

Interpretation Although platinum-containing regimens remain the standard treatment for advanced NSCLC, non-platinum regimens could provide equivalent efficacy with a different toxicity profile.

Funding Japan Multi-National Trial Organisation.

Lancet Oncol 2008; 9: 1135–42
Published Online November 13, 2008
DOI:10.1016/S1470-2045(08)70261-4

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Introduction

Lung cancer is the leading cause of cancer death worldwide and a growing concern in an ageing society.[1] Non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancer histology. Several third-generation agents are available for the treatment of NSCLC, including docetaxel, paclitaxel, gemcitabine, and vinorelbine, and the combination of one of these agents with a platinum compound (ie, cisplatin or carboplatin) has been considered the standard treatment option for advanced NSCLC on the basis of several randomised studies.[2–4]

Combination chemotherapy containing cisplatin has substantial toxic effects, including vomiting and renal impairment, making treatment of elderly patients or outpatients with this agent difficult. Carboplatin has fewer toxic effects than cisplatin, although it still causes vomiting and myelosuppression. Non-platinum, two-drug combinations using third-generation agents have shown an equivalent outcome compared with platinum-containing regimens in patients with NSCLC.[5,6] In the newer non-platinum combinations, vinorelbine plus gemcitabine has shown activity and a good toxicity profile.[7,8] Vinorelbine plus gemcitabine has also shown

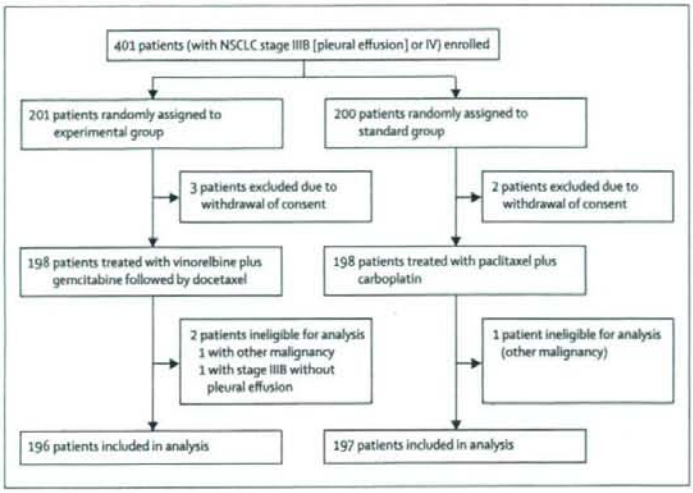

Figure 1: Trial profile

significantly better survival than vinorelbine plus carboplatin in a randomised trial.[9] Docetaxel is active against NSCLC and shows survival benefit in both chemotherapy naive patients, and patients previously treated with chemotherapy.[10,11] Docetaxel might be effective against subpopulations of lung-cancer cells (clones) resistant to first-line chemotherapy,[12] and some residual resistant clones might be eradicated by sequential administration of docetaxel before they grow and relapse.

We previously did a phase II trial of a sequential, non-platinum, triplet combination consisting of three cycles of vinorelbine (25 mg/m²) plus gemcitabine (1000 mg/m²) followed by three cycles of docetaxel (60 mg/m²). The resulting outcomes—21 of 44 patients [47·7%] had partial response, median overall survival was 15·7 months, and 1-year survival was 59%—were encouraging.[13] Therefore, we designed this phase III trial to identify whether vinorelbine plus gemcitabine followed by docetaxel offers better survival than the standard paclitaxel plus carboplatin regimen.

Methods

Patients

All patients enrolled in this study had histologically or cytologically confirmed NSCLC (categorised as squamous cell, large cell, adenocarcinoma, or NSCLC not otherwise specified), with stage IIIB (positive pleural effusion) or stage IV (no brain metastases) disease according to the International Staging System. Other eligibility criteria included: measurable or assessable disease; Eastern Cooperative Oncology Group performance status of 0 or 1; neutrophil count of at least $1·5\times10^9$ cells per L; platelet count above institutional lower limits of normal; haemoglobin concentration of a least 90 g/L; serum creatinine concentrations less than the institutional upper limit of normal (ULN) and a calculated or measured creatinine clearance of at least 50 mL/min; bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT), and alkaline phosphatase concentrations of 2×ULN or less, or 4×ULN or less if the patient had liver metastases. Patients were excluded if they had grade 2 or higher peripheral neuropathy or previous chemotherapy or biological therapy. Stratification at the time of registration was by weight loss (<5% *vs* ≥5% from measurements taken 6 months before enrolment), disease stage (IIIB *vs* IV), and serum lactate dehydrogenase concentration (normal *vs* abnormal). All patients provided written informed consent. This protocol was approved by the institutional review boards of all participating institutions and of the data centre (Translational Research Informatics Centre, Kobe, Hyogo, Japan).

Treatment

Patients were randomly assigned to either the experimental regimen or the standard regimen (figure 1). Central randomisation to each group was applied by use of a dynamic balancing algorithm to obtain a good balance between groups in terms of the stratified factors. Randomisation was done centrally by members of the Japan Multi-National Trial Organisation (JMTO) data centre at the Translational Research Informatics Centre, Kobe, Hyogo, Japan. After obtaining written informed consent, patients were registered via fax, and, if eligibility was confirmed, patients were allocated to one of the treatment groups by computer. Neither patients nor physicians were blinded to allocated treatment. In the experimental group, patients were assigned intravenous vinorelbine (25 mg/m²) and gemcitabine (1000 mg/m²) on days 1 and 8 every 21 days for three cycles. Single-agent docetaxel (60 mg/m²) was subsequently given intravenously on day 1 every 21 days for a further three cycles. Premedications, such as antiemetic agents or corticosteroids, were given as needed. All patients were assigned 8 mg of dexamethasone orally before docetaxel administration. The standard regimen consisted of intravenous paclitaxel (225 mg/m²) plus carboplatin (area under the curve [AUC]=6) for 3 h on day 1. Treatment was repeated every 3 weeks for six cycles. Patients in the standard group were assigned premedication with dexamethasone, diphenhydramine, and ranitidine or cimetidine. Use of additional antiemetics was left to the physician's judgment. Erythropoietin-stimulating agents were not approved in Japan for chemotherapy-related anaemia, and were thus not used. G-CSF was permitted at any time during the study except for prophylactic use in both groups. In the absence of progressive disease or intolerable toxic effects, patients in both groups were treated for six cycles.

Complete blood-cell count was checked either on the treatment day or the day before planned treatment during

	Experimental group (N=196)	Standard group (N=197)
Median age (range), years	64 (39–81)	65 (33–81)
Sex, n (%)		
Men	143 (73)	136 (69)
Women	53 (27)	61 (31)
Smoking, n (%)		
Non-smokers	47 (24)	51 (26)
Former smokers	52 (27)	55 (28)
Smokers	88 (45)	82 (42)
Unknown	9 (5)	9 (5)
Histology, n (%)		
Squamous cell	46 (23)	30 (15)
Adenocarcinoma	130 (66)	149 (76)
Other	20 (10)	18 (9)
Stage, n (%)		
IIIB	33 (17)	35 (18)
IV	163 (83)	162 (83)
Performance status, n (%)		
0	79 (40)	78 (40)
1	117 (60)	119 (60)
Weight loss, n (%)		
<5%	160 (82)	161 (82)
≥5%	36 (18)	36 (18)
LDH concentration, n (%)		
Normal	141 (72)	142 (72)
Abnormal	55 (28)	55 (28)

Experimental treatment=vinorelbine and gemcitabine followed by docetaxel. Standard treatment=paclitaxel and carboplatin. LDH=lactate dehydrogenase.

Table 1: **Characteristics of assessable patients**

	Treatment		p value
	Experimental group (N=196)	Standard group (N=197)	
Tumour response, n (%)			
Complete	0 (0)	0 (0)	..
Partial	49 (25)	73 (37)	..
No change	90 (46)	76 (39)	..
Progressive disease	32 (16)	20 (10)	..
Non assessable	25 (13)	28 (14)	..
Overall response (95% CI), %	25 (19·1–31·7)	37·1 (30·3–44·2)	0·012
Progression-free survival (PFS)			
Median (95% CI), months	5·5 (4·9–6·3)	5·8 (5·3–6·1)	..
1-year PFS	15·4%	12·0%	..
2-year PFS	6·7%	5·8%	..
HR* (95% CI)	0·966 (0·79–1·19)	1†	0·742
Overall survival (OS)			
Median (95% CI), months	13·6 (12·0–16·4)	14·1 (11·9–17·5)	
1-year OS	57·1%	56·6%	
2-year OS	28·7%	30·1%	
HR* (95% CI)	0·966 (0·78–1·27)	1†	0·974

Experimental treatment=vinorelbine and gemcitabine followed by docetaxel. Standard treatment=paclitaxel and carboplatin. HR=hazard ratio. *Adjusted for disease stage, weight loss, and lactate dehydrogenase concentration. †Reference group.

Table 2: **Treatment outcomes**

each of the cycles. During the vinorelbine plus gemcitabine cycles, serum AST and ALT were assessed. If neutrophil count was less than $1{\cdot}5\times10^9$ cells per L, platelet count less than 100×10^9/L, or AST or ALT more than 100 IU/L on day 1 of each cycle, vinorelbine plus gemcitabine administration was delayed by a week. If neutrophil count was less than $1{\cdot}0\times10^9$ cells per L, platelet count less than 70×10^9/L, or AST or ALT more than 100 IU/L, vinorelbine plus gemcitabine was not given on day 8. Docetaxel administration was delayed by a week when the neutrophil count was less than $1{\cdot}5\times10^9$ cells per L or platelet count was less than 75×10^9/L on day 1 of each cycle. Treatment dose was decreased to 80% if grade 4 leucocytopenia or neutropenia were present, if platelet count was less than 20×10^9/L, or if other unacceptable toxic effects, including grade 3 neutropenic fever or grade 3 or higher non-haematological toxic effects, were present during the preceding treatment cycle. The first cycle of docetaxel was given at full dose even if toxic effects were noted in the previous vinorelbine plus gemcitabine cycles. The dose of docetaxel was decreased to 80% only when toxic effects were noted subsequent to docetaxel administration.

Dose modifications for paclitaxel and carboplatin were consistent with the Southwest Oncology Group Trial (SWOG) S0003.[14] In brief, if the neutrophil nadir was less than $0{\cdot}5\times10^9$ cells per L, the platelet nadir less than 50×10^9/L, or the patient had febrile neutropenia, the dose of carboplatin was decreased to an AUC of 5. If a patient developed grade 2 neurotoxicity at any time during a cycle, the dose of paclitaxel was decreased to 200 mg/m^2. Chest pain or arrhythmia during infusion resulted in immediate discontinuation and patient assessment. Patients with symptomatic arrhythmias, atrioventricular block (except first degree), or a documented ischaemic event discontinued the study.

Pretreatment and follow-up assessments

Baseline assessment and staging consisted of a physical examination; chest radiography; brain, chest, and abdominal CT or MRI; complete blood-cell count and serum chemistry; a bone scan if clinically indicated; and an electrocardiogram. A physical examination and complete blood work-up were done before each cycle. Scans or radiographs used to assess response were obtained every two cycles. Once treatment was finished, a follow-up assessment was done every 3 months.

Response and toxicity criteria

Patients were assessed every two cycles for an objective response, according to the Response Evaluation Criteria in Solid Tumors.[15] Confirmed responses required repeat measurements at a minimum of 4 weeks. Responses

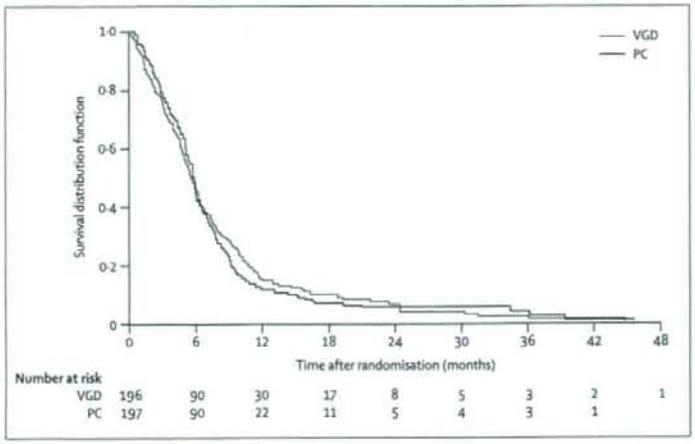

Figure 2: **Kaplan-Meier estimates of progression-free survival**
VGD=vinorelbine and gemcitabine followed by docetaxel. PC=paclitaxel and carboplatin.

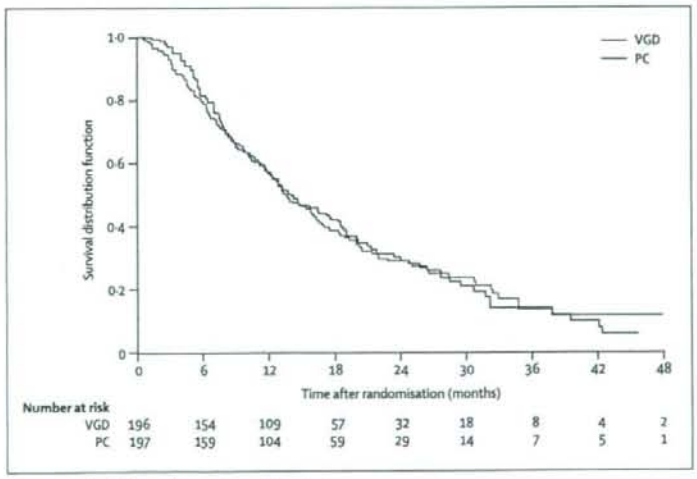

Figure 3: **Kaplan-Meier estimates of overall survival**
VGD=vinorelbine and gemcitabine followed by docetaxel. PC=paclitaxel and carboplatin.

were assessed by attending physicians, and a central review was not done for response evaluation. Grading of toxic effects was done in accordance with the US National Cancer Institute Common Toxicity Criteria, version 2.0.[16] Patients were removed from the study as a result of progression of disease, toxic effects, or at the patient's request. Appropriate procedures were undertaken for all unexpected or fatal toxic effects.

Statistical analyses

The primary objective of this study was to determine whether the experimental regimen (vinorelbine and gemcitabine followed by docetaxel) produced a survival advantage compared with the standard regimen (paclitaxel plus carboplatin) in patients with advanced NSCLC. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, response, and toxic effects. Analyses were done by intention to treat.

We calculated our sample size based on an anticipated median overall survival of 8·0 months in the standard group[17] and an expected 40% increase in median overall survival (to 11·2 months) in the experimental group (chosen on the basis of the findings of our previous phase II study of the experimental regimen, which showed a median survival of 15·7 months[13]). This difference in median overall survival is equivalent to a 2-year survival of 12·5% in the standard group compared with 22·6% in the experimental group (HR 0·714). On the basis of these assumptions, we calculated that we would need 200 patients per group to detect such a difference, with a power of 0·85 using a two-sided Log-rank test at a significance level of 0·05. Survival curves were estimated by the product-limit method and compared by use of the Log-rank test, stratified by predetermined prognostic factors.[18,19] Cox regression analysis was used to estimate hazard ratios (HRs) for overall survival and progression-free survival.[20] Fisher's exact test was used to test the difference between treatment groups for response and toxic effects. Unless otherwise indicated, all reported p values are two sided. A planned interim analysis was done by the data monitoring committee when 300 patients had been enrolled, with early study termination to occur if the null hypothesis of no difference for the experimental group was rejected at the one-sided 0·0025 level.

Role of the funding source

This trial was sponsored by the JMTO, and members of JMTO were responsible for the design, set-up, and data collection of the trial. All authors had full access to the raw data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

401 patients were enrolled in the trial between March 29, 2001, and April 13, 2005, from 45 institutions in Japan. Eight patients (2·0%) were ineligible for analysis: five withdrew informed consent, two had other malignancies, and one had stage IIIB disease without pleural effusion. Thus, 393 patients were eligible for analysis, 196 in the experimental group and 197 in the standard group. Patient characteristics are listed in table 1. Although the proportion of patients with adenocarcinoma histology was higher in the standard group than in the experimental group, there was no significant difference between the two groups.

Overall response (ie, best confirmed response during study treatment) was 25% (49 of 196 patients with PR) in the experimental group and 37% (73 of 197 patients with PR) in the standard group (p=0·012; table 2). No patients

had a complete response. 17 of 196 patients (8·7%) had a partial response after three cycles of treatment with vinorelbine plus gemcitabine, as reported by the attending physicians. The difference in response between the two groups was larger in patients with squamous-cell histology (15% [seven of 46 patients] in the experimental group *vs* 63% [19 of 30 patients] in the standard group; p<0·0001) than in patients with adenocarcinoma histology (26% [34 of 130 patients] in the experimental group *vs* 32% [47 of 149 patients] in the standard group; p=0·356), and the proportion of patients with squamous-cell histology who had progressive disease was higher in the experimental group (33% [15 of 46]) than in the standard group (13% [four of 30]). The comparison of response by the Mantel-Haenszel test (adjusted for the distribution imbalance of histology) was also significant (p=0·007). Median progression-free survival was 5·5 months (95% CI 4·9–6·3) in the experimental group and 5·8 months (5·3–6·1) in the standard group (p=0·742; figure 2 and table 2), and median overall survival was similar between groups, at 13·6 months (12·0–16·4) in the experimental group and 14·1 months (11·9–17·5) in the standard group (p=0·97; figure 3 and table 2). For overall survival, the HR was 1·06 (95% CI 0·80–1·41; p=0·688) in patients with adenocarcinoma histology and 0·94 (0·56–1·57; p=0·802) in patients with squamous-cell histology. For progression-free survival, the corresponding values were 0·98 (0·77–1·25; p=0·848) and 1·04 (0·65–1·68; p=0·861), respectively. Thus, there was no interaction between treatment and histology ($p_{interaction}$=0·794 and 0·773, respectively). In terms of other factors (ie, age, sex, smoking history, Eastern Cooperative Onology Group performance status, weight loss, disease stage, and lactate dehydrogenase concentration), there were no significant interactions between treatment and factor (data not shown).

196 patients in the experimental group and 197 patients in the standard group were assessable for toxic effects (table 3). The standard regimen resulted in a significantly increased incidence of grade 3 or 4 neutropenia, neuropathy, arthralgia, and myalgia compared with the experimental regimen. However, the incidence of pulmonary toxic effects was significantly higher in the experimental group than in the standard group. Only one patient assigned the standard regimen developed grade 1 to 4 drug-related pneumonitis compared with 17 patients assigned the experimental regimen (p<0·0001). Of these 17 patients, 14 developed pneumonitis during vinorelbine plus gemcitabine treatment, whereas the remaining three patients had pneumonitis during docetaxel treatment. Almost all patients improved with corticosteroids. There was no significant difference in neutropenic fever, anaemia, and thrombocytopenia between the two groups. Treatment-related death occurred in two patients. One patient had pneumonitis after the fourth cycle of the experimental regimen. Despite improvement of pneumonitis with corticosteroids, steroid-induced exacerbation of hepatitis C, followed by deterioration of pneumonitis, resulted in death due to respiratory failure. Another patient died of pneumonia after the fourth cycle of the experimental regimen.

	Treatment		p value
	Experimental group (N=196), n (%)	Standard group (N=197), n (%)	
Haematological toxic effects			
Leucopenia	79 (40·3)	89 (45·2)	0·359
Neutropenia	116 (59·2)	137 (69·5)	0·035
Neutropenic fever	23 (11·7)	24 (12·2)	1·000
Thrombocytopenia	6 (3·1)	14 (7·1)	0·106
Anaemia	9 (4·6)	16 (8·1)	0·214
Non-haematological toxic effects			
Allergic reaction	0 (0)	4 (2·0)	0·123
Fatigue	10 (5·1)	14 (7·1)	0·528
Constipation	3 (1·5)	7 (3·6)	0·337
Nausea	8 (4·1)	17 (8·6)	0·097
Vomiting	2 (1·0)	6 (3·0)	0·284
Anorexia	16 (8·2)	22 (11·2)	0·394
Neuropathy (motor)	1 (0·5)	8 (4·1)	0·037
Neuropathy (sensory)	1 (0·5)	19 (9·6)	<0·0001
Arthralgia	0 (0)	17 (8·6)	<0·0001
Myalgia	0 (0)	14 (7·1)	<0·0001
Dyspnoea	11 (5·6)	3 (1·5)	0·032
Drug-related pneumonitis	9 (4·6)	1 (0·5)	0·011
Pneumonia	14 (7·1)	1 (0·5)	0·0004
Liver dysfunction	6 (3·1)	5 (2·5)	0·771

Experimental treatment=vinorelbine and gemcitabine followed by docetaxel. Standard treatment=paclitaxel and carboplatin.

Table 3: **Grade 3 and 4 toxic effects occurring in ≥3% of patients in at least one group**

The median number of cycles delivered was six (range one to six) for the experimental regimen and four (one to six) for the standard regimen. There was no difference in the number of patients receiving four or more cycles between the groups. The proportion of patients receiving six cycles was significantly higher in the experimental group (97 of 196 [49%]), than in the standard group (57 of 197 [29%]; p<0·0001). The proportion of patients who needed a dose reduction was 29% (57 or 196) in the experimental group and 51% (100 of 197) in the standard group (p<0·0001).

128 of 196 patients (65%) in the experimental group and 133 of 197 patients (68%) in the standard group received post-protocol chemotherapy of any type. In the experimental group, 44 of 196 patients (22%) received paclitaxel plus carboplatin, 35 (18%) received gefitinib, 17 (9%) received additional docetaxel, nine (5%) received vinorelbine plus gemcitabine, and 23 (12%) received other regimens. In the standard group, 40 of 197 patients (20%) received gefitinib, 38 (19%) received docetaxel, 23 (12%) received vinorelbine plus gemcitabine, six (3%) received additional paclitaxel plus carboplatin, and 26 (13%)

received other regimens as second-line chemotherapy. In both groups, around 35% of patients received more than one additional line of chemotherapy. Gefitinib was used as any line treatment after the study protocol in 75 of 196 (38%) patients in the experimental group and in 78 of 197 (40%) patients in the standard group, respectively.

Discussion

This study assessed whether a non-platinum, sequential, triplet (vinorelbine and gemcitabine followed by docetaxel) regimen[13,21] produced a survival advantagecompared with a standard platinum-containing regimen in patients with advanced NSCLC. The experimental regimen did not result in better overall survival than the standard regimen of paclitaxel plus carboplatin.

Although some baseline imbalances existed in terms of histology between the two groups, histology (adenocarcinoma *vs* others) was not an independent prognostic factor for overall survival (adjusted HR 0·96 [95% CI 0·73–1·27]; p=0·80) and the effect of imbalance on the endpoints was small. The proportion of patients receiving six cycles of treatment was higher in the experimental group than in the standard group; however, a median number of four cycles (range one to six) with standard treatment is the usual standard of care, and therefore, it is unlikely that the difference in number of cycles affected the outcomes of the study.

Although there was no difference between the regimens in terms of efficacy, the experimental, non-platinum regimen did show some benefits compared with the platinum-containing regimen. The regimen was well tolerated and 97 of 196 (49%) patients completed the planned six cycles. Furthermore, the incidence of grade 4 neutropenia, grade 3 or 4 neuropathy, arthralgia, and myalgia was significantly higher in the standard group; however, the incidence of pulmonary toxicity was higher in the experimental group. Of the 17 (8·7%) cases of grade 1 to 4 drug-related pneumonitis in the expermental group, 14 (82%) occurred during treatment with vinorelbine plus gemcitabine. In another Japanese study using vinorelbine plus gemcitabine, grade 3 or higher drug-related pneumonitis occurred in two of 62 patients (3%), resulting in one death.[22] A few cases of drug-related pneumonitis have also been reported when vinorelbine or gemcitabine is combined with cisplatin.[3] Interstitial lung disease due to inhibitors of epidermal growth factor receptors (EGFR) is also problematic in Japan,[23,24] either because of ethnic differences in drug-related pneumonitis or greater vigilance in diagnosing pneumonitis in Japan. Further studies are thus crucial.

Because docetaxel is active as second-line chemotherapy, sequential administration of docetaxel after other chemotherapy regimens might be effective for clones resistant to previous chemotherapy.[12] Edelman and colleagues[25] did a randomised phase II trial of carboplatin plus gemcitabine followed by paclitaxel, or cisplatin plus vinorelbine followed by docetaxel. Both regimens resulted in survival data comparable to platinum-based two-drug combinations and few patients showed an improvement in response with sequential taxane therapy.[25] In the present study, of the patients who achieved partial response in the experimental group, about a third (17 of 49) had their best response during treatment with vinorelbine plus gemcitabine, whereas nearly two-thirds (32 of 49) achieved partial response with docetaxel monotherapy. Although we should be careful when interpreting these data, because central review for response assessment was not done and the protocol specified response assessment every two cycles, which might have been too early to detect the real response to treatment with vinorelbine plus gemcitabine, data from this study suggest that alternative sequential therapy could be effective for NSCLC if highly active regimens are selected and administered in the optimum sequence. Preliminary findings from a randomised phase III study comparing immediate with delayed second-line chemotherapy in patients with stage IIIB or IV NSCLC suggest that median overall survival might be improved by giving docetaxel immediately after completion of a full course of first-line treatment (median overall survival 11·9 months for immediate docetaxel and 9·1 months for delayed docetaxel; p=0·071).[26] Pemetrexed has comparable efficacy to docetaxel as second-line chemotherapy.[27] Pemetrexed plus cisplatin showed similar overall survival to gemcitabine plus cisplatin in chemotherapy-naive patients with advanced NSCLC, and overall survival was better with pemetrexed plus cisplatin than with gemcitabine plus cisplatin in adenocarcinoma and large-cell carcinoma histology.[28] By contrast, a significant improvement in overall survival was shown with gemcitabine plus cisplatin in patients with squamous-cell histology.[28] Maintenance chemotherapy with pemetrexed after four cycles of platinum-based chemotherapy improved overall survival compared with supportive care in patients with non-squamous NSCLC, with a median survival of 14·4 months for pemetrexed and 9·4 months for the placebo group.[29] Furthermore, a subgroup analysis of a randomised trial of maintenance gefitinib after chemotherapy versus chemotherapy alone showed a significantly better overall survival favouring gefitinib in patients with adenocarcinoma.[30] Although the present study did not show better survival with the experimental regimen than with the standard regimen of carboplatin plus paclitaxel, further study of sequential chemotherapy in selected patients with stage IIIB or IV NSCLC is warranted.

The present study was done as a JMTO-SWOG common-arm trial with identical eligibility, staging, response, and toxicity criteria to SWOG S0003.[14] Dose, schedule, and dose modifications for paclitaxel and carboplatin were consistent with SWOG S0003. Patient baseline characteristics were similar in the two studies. Overall survival in patients

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.[33] 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.

Acknowledgments

We thank all the participating institutions and Translational Research Informatics Centre for data management and statistical analyses. We also thank Steve Olsen and Takashi Shimamoto for their scientific advice, Madoka Chishima for editorial assistance, Chikako Toyooka for data management, and Shigeto Hosoe for help in forming the protocol.

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Cancer Chemother Pharmacol
DOI 10.1007/s00280-008-0846-z

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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Received: 21 June 2008 / Accepted: 23 September 2008

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).

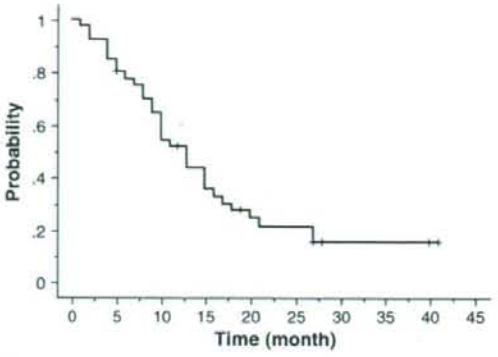

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 11.9 months; 1-year survival rate, 47.5%

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.

Acknowledgments This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare (Tokyo, Japan), and by the second-term comprehensive 10-year strategy for cancer control.

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

(*J Bronchol* 2008;15:146–151)

Received for publication April 8, 2008; accepted May 8, 2008.

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There is no conflict of interest.

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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: $BED = nd\ [1 + d/(\alpha/\beta)]$ 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.

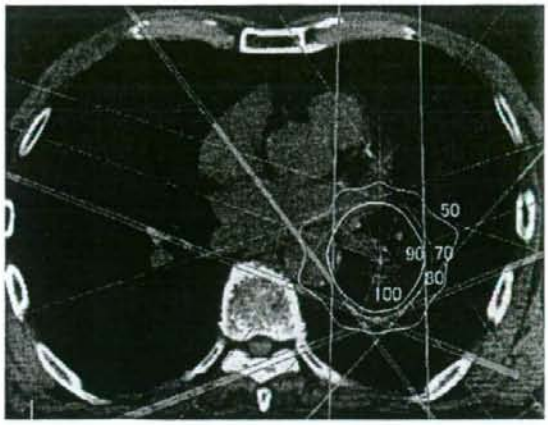

FIGURE 1. The 3-dimensional conformal plan beam arrangement. Circle lines represent the 50% to 100% isodose curves.

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.

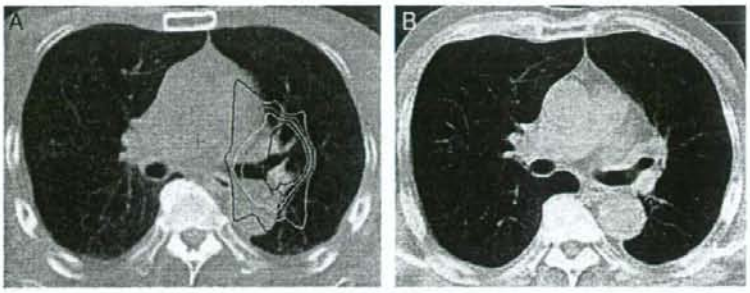

FIGURE 2. A, An example of the dose coverage on an axial CT image in the 74-year-old patient with cancer located at left upper bronchus. B, CT scan at 1-year follow-up shows a complete response without post-treatment interstitial lung changes. CT indicates computed tomography.

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,

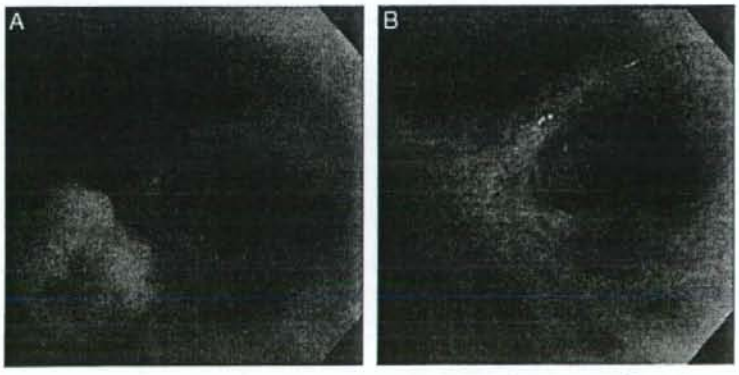

FIGURE 3. A case of 74-year-old patient with central type lung cancer. A, Squamous cell carcinoma located at left upper bronchus. B, After 6 months of 3D-CRT, the irradiated bronchus was slightly stenotic and scarred. 3D-CRT indicates 3-dimensional conformal radiotherapy.

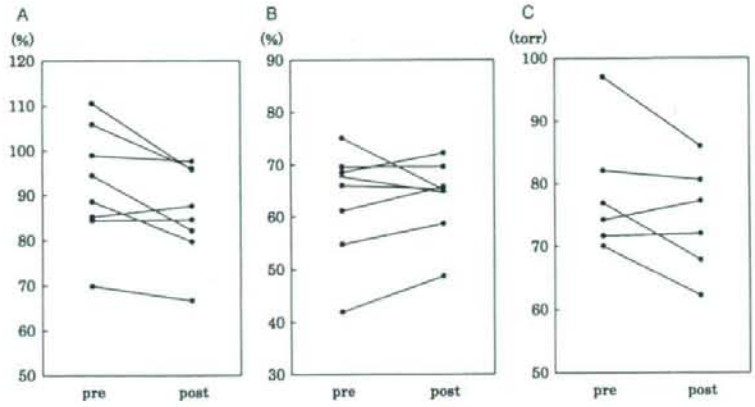

FIGURE 4. Respiratory function values of preradiotherapy and postradiotherapy. A, %VC: percent vital capacity. B, FEV1.0%: percent forced expiratory volume in 1 second. C, PaO_2: arterial blood gas analysis.

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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