Original article

Efficacy, toxicity and cost analysis for non-platinum triplet (gemcitabine and vinorelbine, followed by docetaxel) vs. platinum-based chemotherapy in IIIB/IV non-small-cell lung cancer: single-institution experience

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A new non-platinum sequential triplet combination chemotherapy regimen, comprising gemcitabine (1000 mg/m^2) and vinorelbine (25 mg/m^2), followed by docetaxel (60 mg/m^2), was compared in terms of efficacy, toxicity and cost with platinum-based chemotherapy regimens (comprising cisplatin plus one or more other anti-tumour drugs) for the treatment of advanced non-small-cell lung cancer in a matched, small-sample size, case–control study. Patients were selected from a single institution. Patients in the platinum and non-platinum groups were matched for clinical stage (IIIB/IV), performance status (0/1), age and sex. For the non-platinum and platinum groups, the overall response rates were 40% and 47%, and the median survival times were 14 and 14.5 months respectively. The most common grade 3–4 toxicity was neutropenia (27%) in the non-platinum group and nausea/vomiting (67%) in the platinum group. The total treatment cost did not differ significantly between the two groups. The non-platinum sequential triplet combination chemotherapy regimen studied was shown to be as effective as the traditional cisplatin-based combination chemotherapy regimen, and was associated with less toxicity.

Keywords: non-small-cell lung cancer, vinorelbine, gemcitabine, docetaxel, cisplatin.

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INTRODUCTION

Lung cancer is a major cause of deaths from cancer in Japan, the USA and the European Union. Non-small-cell lung cancer (NSCLC) accounts for about 80% of patients with lung cancer in Japan (Ministry of Health and Welfare 2000). Cisplatin (CDDP)-based chemotherapy has been shown to confer a certain survival benefit for patients with advanced NSCLC (Non-small Cell Lung Cancer Collaborative Group 1995), and use of CDDP has been found to be an independent predictor of survival (Grilli *et al.* 1993). A drawback of CDDP-based chemotherapy, however, is its serious toxicity; its side effects include severe nausea, vomiting, renal toxicity requiring adequate hydration, and neuropathy, which increases the difficulty associated with treating elderly patients and outpatients.

Recently, new chemotherapeutic agents, such as the taxanes, vinorelbine (VNR), gemcitabine (GEM), and several non-platinum combinations have been developed for the treatment of NSCLC. The new non-platinum combination of GEM plus VNR has been shown to be active for the treatment of NSCLC, and seems to be less toxic than platinum-based combinations, including those involving CDDP (Non-small Cell Lung Cancer Collaborative Group 1995; Lorusso *et al.* 1998; Feliu *et al.* 1999; Isokangas *et al.* 1999; Beretta *et al.* 2000; Chen *et al.* 2000; Frasci *et al.* 2000; Lorusso *et al.* 2000; Krajnik *et al.* 2000; Herbst *et al.* 2002; Gridelli *et al.* 2003). Treatment with docetaxel (DOC) alone has also been shown to confer a survival benefit, especially as a second-line treatment (Roszkowski *et al.* 2000). Recently, a new non-platinum sequential triplet combination, GEM plus VNR, followed by DOC, was evaluated for 44 chemotherapy-naïve patients with advanced NSCLC in a phase II study conducted by the Japan Multinational Trial Organization (JMTO). The response rate in that study was 47.7%, and the median survival time (MST) was 15.7 months, with a 1-year survival rate of 59%. Grade 3–4 neutropenia was seen in approximately 36% of patients during the GEM/VNR cycles, and in 39% of patients during the DOC cycles. Overall, only 2.3% of patients experienced grade 3–4 thrombocytopenia, and 4.5% experienced grade 3–4 anaemia (Hosoe *et al.* 2003). Given that this non-platinum combination has been found to be very active and well tolerated by patients, it is likely that the regimen will also be suitable for elderly patients and outpatients.

On the basis of these observations, we conducted a case-matched retrospective study as a part of the aforementioned phase II study to assess the non-platinum sequential triplet combination in terms of efficacy, safety and cost relative to platinum-based combinations.

PATIENTS AND METHODS

Patient selection

This study was performed as a part of the phase II trial (JMTO LC00-02) conducted by JMTO (Hosoe *et al.* 2003). The criteria for patient selection (eligibility and exclusion criteria) are summarized in Table 1. Fifteen patients who were enrolled in the phase II trial at the National Hospital Organization Kinki-chuo Chest Medical Center, who received non-platinum triplet chemotherapy (GEM and VNR, followed by DOC) during the period between May 2000 and February 2001, comprised the non-platinum group. For the platinum group, in order to ensure that the two groups were comparable, we selected 15 eligible patients from the pool of all NSCLC patients ($n = 124$) who received CDDP-based chemotherapy between April 1998 and February 2001 at the same institution, by matching each patient in the non-platinum group for stage (IIIB/IV), performance status (0/1), age and sex. The protocol of this study was approved by ethical committees at Kyoto University and the National Hospital Organization Kinki-chuo Chest Medical Center.

Chemotherapy regimens

Patients in the non-platinum group were first treated with both GEM (1000 mg/m^2) and VNR (25 mg/m^2) on days 1 and 8 of three cycles of 21 days each, followed by a further three cycles of 21 days each, during which DOC (60 mg/m^2) was administered on day 1 of each cycle (Hosoe *et al.* 2003). Patients in the platinum group received CDDP-

Table 1. Criteria for patient selection

Eligibility criteria
- Eastern Cooperative Oncology Group performance status 0–1
- Over 18 years old (no upper age limit)
- Stage IV or IIIB non-small-cell lung cancer (with malignant pleural effusion and/or pulmonary nodule(s) in the same lobe as the primary lesion)
- Unidimensionally measurable disease

Exclusion criteria
- Presence of apparent interstitial pneumonitis, massive pleural effusion requiring thoracentesis, uncontrollable diabetes mellitus, heart diseases, history of another cancer (excluding non-melanomatous skin cancer and *in situ* cervical cancer)
- Reduced bone marrow, pulmonary, renal or hepatic function
- Stage IIIB disease with pulmonary nodule(s) at the same lobe of the primary lesion (if they could be considered to indicate that the patient had undergone radiation therapy or operation)
- Presence of asymptomatic central nervous system metastases was not considered an exclusion criterion

based chemotherapy without any restrictions on other concomitant drugs, amount of medication, or number of treatment cycles.

Endpoints

The endpoints of this study were tumour response to chemotherapy, recurrence-free survival time, toxicity and cost of treatment. Haematological and non-haematological toxicity were evaluated using the National Cancer Institute's Common Toxicity Criteria, version 2.0. For patients who underwent two or more cycles of chemotherapy, the response was evaluated using the Response Evaluation Criteria in Solid Tumors (Therasse *et al.* 2000). The recurrence-free survival time refers to the period of time between the day treatments began and the day of recurrence or death. The recurrence-free survival time was censored at the end of follow-up. The total cost of treatment was evaluated using patients' receipts, and comprised the cost of chemotherapy (cost of drugs plus costs associated with drug administration) plus the cost of hospitalization, ambulatory care and supportive care for other adverse events or complications. The cost of granulocyte-colony stimulating factor (G-CSF) for each patient was also calculated. The average cost per month was calculated. The endpoints were evaluated during the period between the month in which the chemotherapy began and 1 month after the completion of chemotherapy.

Statistical methods

Differences between the characteristics of patients in the two groups were evaluated using the *t*-test for quantitative variables and Fisher's exact test for categorical variables. Comparisons of the response rate and the incidence of toxicity events between groups were carried out using Fisher's exact test. The survival rate was estimated for each group using the Kaplan-Meier method. Comparisons of survival between groups were performed using the log rank test. Monthly medical costs were compared using the Wilcoxon rank-sum test. Subgroup analyses were carried by dividing the patients into elderly (65 years or older) and non-elderly groups. Statistical analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The characteristics of patients participating in this study are summarized in Table 2. The distribution of these factors is almost identical between groups, because each patient in the platinum group was selected by matching each patient in the non-platinum group for stage (IIIB/IV), performance status (0/1), age and sex. With respect to histological diagnosis, the non-platinum group included a smaller number of patients with adenocarcinomas but a greater number of patients with large cell carcinomas than the platinum group. The dosage of CDDP in the platinum group was 70–80 mg/m^2 per day. The drugs combined with CDDP for treatment of patients in the platinum group are shown in Table 3. Eight patients received new anticancer agents (DOC: 6 patients; VNR: 2 patients) combined with CDDP, accounting for 53% of the platinum group as a whole. The mean number of chemotherapy cycles per patient was 3.9 for the non-platinum group and 3.1 for the platinum group.

The major reasons for discontinuing chemotherapy were patient refusal and the mental burden caused by adverse reactions in the platinum group, and disease progression in the non-platinum group. Adverse reactions were not a major factor for discontinuation of chemotherapy in the non-platinum group.

Table 2. Patient characteristics

Regimen characteristic	Non-platinum ($n = 15$) *n* (%)	Platinum ($n = 15$) *n* (%)
Sex*		
Male	11 (73)	11 (73)
Female	4 (27)	4 (27)
Median age in years (range)*	65 (42–74)	64 (48–76)
ECOG performance status*		
0	2 (13)	2 (13)
1	13 (87)	13 (87)
Stage*		
IIIB	3 (20)	3 (20)
IV	12 (80)	12 (80)
Histological diagnosis		
Adenocarcinoma	3 (20)	8 (53)
Squamous cell carcinoma	7 (47)	6 (40)
Large cell carcinoma	5 (33)	1 (7)

ECOG, Eastern Cooperative Oncology Group.
*Matching factor.

Table 3. Drugs apart from cisplatin used in CDDP-based chemotherapy regimens ($n = 15$)

Drug	*n*
Docetaxel	6
Vindesin	6
Vinorelbine	1
Mitomycin C	1
Mitomycin C + vinorelbine	1

Table 4. Response, toxicity and cost of platinum and non-platinum chemotherapy regimens

	Non-platinum ($n = 15$) n (%)	Platinum ($n = 15$) n (%)	P-value
Response			
Complete response	0	0	
Partial response	6	7	
Stable disease	5	6	
Progressive disease	4	2	
Response rate	6 (40)	7 (47)	1.000
MST (months)	14	14.5	0.264
(95% CI)	(8–14)	(11–31)	
Mean no. cycles administered	3.9	3.1	0.378
Grade 3–4 toxicity experienced	6 (40)	14 (93)	0.005
Haematological			
Neutropenia	4 (27)	2 (13)	0.651
Leukopenia	2 (13)	5 (33)	0.390
Non-haematological			
Nausea, vomiting	0 (0)	10 (67)	<0.001
Fatigue	0 (0)	3 (20)	0.224
Mean total treatment cost (yen/month)	475 372	443 979	0.147

MST, median survival time.

Table 5. Response and toxicity of platinum and non-platinum chemotherapy regimens for elderly patients

	Non-platinum ($n = 8$) n (%)	Platinum ($n = 6$) n (%)	P-value
Response			
Complete response	0	0	
Partial response	5	5	
Stable disease	2	1	
Progressive disease	1	0	
Response rate	5 (63)	5 (83)	0.580
Grade 3–4 toxicity experienced	5 (63)	5 (83)	0.580
Haematological			
Neutropenia	3 (38)	0 (0)	0.209
Leukopenia	2 (25)	2 (33)	1.000
Non-haematological			
Nausea, vomiting	0 (0)	4 (55)	0.015
Fatigue	0 (0)	1 (17)	0.429

Response, toxicity and cost

All results regarding response, toxicity and cost are summarized in Table 4. The overall response rate was 40% for the non-platinum group and 47% for the platinum group ($P = 1.000$). The MST was 14 months for the non-platinum group and 14.5 months for the platinum group ($P = 0.264$). The frequency of grade 3–4 toxicity was 40% for the non-platinum group and 93% for the platinum group, which was statistically significant ($P = 0.005$). The most frequently observed grade 3–4 haematological toxicity was neutropenia (27%) in the non-platinum group and leucopenia (33%) in the platinum group. There were no grade 3–4 non-haematological toxicity events in the non-platinum group, but 67% of patients suffered from nausea/vomiting in the platinum group ($P < 0.001$). As an index of overall efficacy and toxicity, the number of responders who did not experience grade 3–4 toxicity was 3 (20%) in the non-platinum group and 0 (0%) in the platinum group ($P = 0.100$). The number of non-responders who experienced grade 3–4 toxicity was 3 (20%) in the non-platinum group and 7 (47%) in the platinum group ($P = 0.128$). The average total treatment costs per month were ¥475 372 (approximately US$4080) and ¥443 979 (approximately US$3810) for the non-platinum and platinum groups respectively ($P = 0.141$). The average hospitalization costs per month were ¥265 663 (approximately US$2290) and ¥266 415 (approximately US$2296) for the non-platinum and platinum groups respectively. There was no statistically significant difference between the two groups with respect to cost. Three patients in each group received G-CSF. The average costs for G-CSF per patient were ¥12 797 (approximately US$110) and ¥22 073 (approximately US$190) in the non-platinum and platinum groups respectively ($P = 0.366$).

We carried out further analysis on a subgroup of elderly patients (those aged 65 years or older; the non-platinum group: 8 patients, and the platinum group: 6 patients). The response and toxicity data for the elderly patient subgroups are summarized in Table 5. In this subgroup, the overall response rate was 63% for the non-platinum group and 83% for the platinum group ($P = 0.580$). The frequency of grade 3–4 toxicity was 63% for the non-platinum group and 83% for the platinum group ($P = 0.580$). The most frequently observed grade 3–4 haematological toxicity was neutropenia (38%) in the non-platinum group and leucopenia (33%) in the platinum group. There was no grade 3–4 non-haematological toxicity event in the non-platinum group, but 67% of patients in the platinum group suffered from nausea/vomiting; the difference was statistically significant ($P = 0.015$). The number of responders who did not experience grade 3–4 toxic events was 2 (25%) in the non-platinum group and 0 (0%) in the platinum group. The number of non-responders who experienced grade 3–4 toxic events was 2 (25%) in the non-platinum group and 0 (0%) in the platinum group.

DISCUSSION

Although CDDP-based chemotherapy has become established as a standard therapy for the treatment of patients

with advanced NSCLC with good performance status, it has the drawback of serious toxicity, causing such symptoms as severe nausea, vomiting and renal toxicity, and is thus not suitable for elderly patients and outpatients. Recent trials of new anticancer drugs have indicated that some non-platinum-based combinations are almost as active as CDDP-based chemotherapy regimens, but are less toxic. In particular, the GEM/VNR combination has been shown to be well tolerated by patients, and to be very active (Non-small Cell Lung Cancer Collaborative Group 1995; Lorusso *et al.* 1998; Feliu *et al.* 1999; Isokangas *et al.* 1999; Beretta *et al.* 2000; Chen *et al.* 2000; Frasci *et al.* 2000; Lorusso *et al.* 2000; Krajnik *et al.* 2000; Herbst *et al.* 2002; Gridelli *et al.* 2003), and thus might be a good alternative to CDDP-based chemotherapy regimens. A new non-platinum sequential triplet combination, GEM and VNR, followed by DOC, was recently evaluated in a JMTO phase II study, and was found to be well tolerated, with one of the highest response rates yet reported for treatment of advanced NSCLC (JMTO LC00-02; Hosoe *et al.* 2003). Given these findings, a phase III randomized trial (JMTO LC00-03) began in April 2001 to compare this non-platinum sequential triplet combination with a platinum combination (carboplatin/paclitaxel). This phase III trial is ongoing in collaboration with the Southwest Oncology Group's (SWOG) trial (S0003) (carboplatin/paclitaxel versus carboplatin/paclitaxel + tirapazamine), using the same protocol for the common control arm (carboplatin/paclitaxel) (Williamson *et al.* 2005). We thus conducted a case-matched retrospective study in a single institution as a part of the multi-institutional phase II trial (JMTO LC00-02). The purpose of the present study was, in the context of JMTO LC00-02, to assess this non-platinum sequential triplet combination in terms of efficacy, toxicity and treatment cost relative to platinum-based combinations comprising CDDP plus one or more other anticancer drugs for the treatment of advanced NSCLC. Consequently, the present study provides some of the first results concerning a comparison of the new non-platinum sequential triplet combination with platinum-based combinations.

The non-platinum group in the present study was a subgroup of patients involved in the JMTO LC00-02 phase II trial, which included 44 patients from 17 institutions (response rate of 47.7%, median survival time of 15.7 months) (Hosoe *et al.* 2003). We believe that the selected patients were representative of the phase II study population as a whole, because there was no significant difference in the distribution of outcomes and patient characteristics between the group as a whole and the selected patients.

In order to ensure comparability between the non-platinum and platinum groups, we sourced patients from a single institution, and selected each patient in the platinum group from the pool of all patients who received CDDP-based chemotherapy during the study period by matching for stage (IIIB/IV), performance status (0/1), age and sex, all of which are considered to be important prognostic factors. The resulting number of patients in each group was small.

Differences in the distribution of histological diagnoses between the two groups were found: the non-platinum group included a smaller number of patients with adenocarcinomas but a larger number of patients with large cell carcinomas than the platinum group. We performed subgroup analysis according to histological diagnosis to evaluate the effects of treatment. The overall response rate for patients with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma were 67% (2/3), 29% (2/7) and 40% (2/5) respectively in the non-platinum group, and 50% (4/8), 34% (2/6) and 100% (1/1) respectively in the platinum group. There was no significant difference in overall response rate between the non-platinum and platinum groups when subgroups of patients with similar histological diagnoses were compared.

In previous studies regarding therapy for NSCLC, the response rate and MST were found to be 13% and 6 months respectively for treatment with DOC alone (Roszkowski *et al.* 2000), and 19% and 6.5 months respectively for treatment with VNR alone (The Elderly Lung Cancer Vinorelbine Italian Study Group 1999). As for combined regimens, the response rate and MST have been found to be 17% and 7.4 months (Schiller *et al.* 2002) and 37% and 11.7 months (Takeda *et al.* 2000) respectively for DOC + CDDP, and 30% and 9.3 months (Le Chevalier *et al.* 1994), and 26% and 8 months (Wozniak *et al.* 1998) respectively for VNR + CDDP. The response rate and MST of the platinum group in the present study (40%, 13.5 months respectively) were greater than those found in previous studies of combination regimens comprising CDDP and new anticancer drugs. In the present study, the MST of the platinum group was comparable to that of the non-platinum group. This might be partly due to additional treatments, such as radiotherapy and/or other chemotherapeutic agents, received by patients in the platinum group.

With respect to toxicity, some patients in the platinum group suffered from adverse reactions accompanied by symptoms such as leucopenia (one-third of patients) and nausea/vomiting (two-thirds or more). In addition, six patients who suffered a physical and/or mental burden from these toxicities refused further chemotherapy and withdrew from treatment early. It should be noted that

because the toxicity information in the platinum group was obtained from medical charts, a certain proportion of toxicity events may not have been reported, and thus the event rates may have been underestimated. In contrast, a thorough reporting system was used for patients in the non-platinum group because they were involved in a phase II trial. In the non-platinum group, one-fourth of patients had grade 3–4 neutropenia, but no patients presented with any severe non-haematological toxicity. In fact, the major reason for interruption of chemotherapy in the non-platinum group was progression of the primary cancer (8 cases). Furthermore, for five patients in the non-platinum group who began receiving chemotherapy in an ambulatory setting in the middle of the follow-up period, no severe adverse events were observed, and emergency hospital admission was not required.

In the subgroup of elderly patients (65 years or older), the overall response rate was higher than that in each group as a whole. No elderly patients in the non-platinum group suffered grade 3–4 non-haematological toxicity events, including nausea and vomiting or fatigue, whereas 55% and 17% of elderly patients in the platinum subgroup experienced these adverse reactions respectively.

As we have already seen, the incidence of toxic events in the non-platinum group was significantly lower than that in the platinum group, and in each group the incidence was similar in the subgroup of elderly patients and the group as a whole. We thus conclude that this new non-platinum regimen could be established as a standard treatment, especially for elderly patients or outpatients.

Because most participants in this study were inpatients, even in the non-platinum group, there was no difference in the cost of treatment between the two groups. The cost of hospitalization was also equal in each group. Because management of adverse events is required to a lesser extent for patients receiving non-platinum regimens, chemotherapy could be administered in an ambulatory setting rather than in an inpatient setting. If chemotherapy can be administered in an ambulatory setting, the medical cost would become substantially lower, much lower than that of CDDP-based chemotherapy, which usually requires hospitalization.

In an overall assessment of efficacy and toxicity, the number of responders who did not experience grade 3–4 toxic events, which represents one of the most positive outcomes for patients, was 3 (20%) in the non-platinum group and 0 (0%) in the platinum group. The number of non-responders who experienced grade 3–4 toxic events, which represents the worst outcome for patients, was 3 (20%) in the non-platinum group and 7 (47%) in the platinum group.

In conclusion, these results indicate that the chemotherapy regimen used for the non-platinum group was equally beneficial and less burdensome than those used for the platinum group. Although this study is retrospective and could be considered a preliminary study, given its limited small sample size, the results suggest that the new non-platinum sequential triplet combination could replace CDDP-based chemotherapy as first-line treatment for advanced NSCLC, and that this regimen would be particularly useful for elderly patients and outpatients.

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Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer

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Background: The duration of, resources required for and cost of clinical trials could be reduced if a surrogate end point was to be used in place of survival. We assessed the extent to which the objective response rate (ORR) is predictive of mortality, how much difference in the ORR is needed to predict an obvious survival difference and what factors could affect the association between the two parameters during the first-line treatment of extensive disease (ED)-small-cell lung cancer (SCLC).

Methods: We used the ORRs and median survival times (MSTs) from 48 phase III trials of first-line chemotherapy involving 8779 randomised patients with ED-SCLC in a linear regression analysis. The MST difference was calculated as the difference in MST between the investigational and reference arms; the ORR difference was similarly defined.

Results: ORR difference between the treatment arms was modestly associated with the MST difference in the overall trials ($R^2 = 0.3314$). In contrast, the relationship was stronger among only trials in which prophylactic cranial irradiation was given to those having an objective response to the initial chemotherapy ($R^2 = 0.6279$). In this trial setting, large differences in ORR were needed to predict a survival advantage (1.2-day survival advantage per 2% increase in ORR).

Conclusions: In the first-line treatment of ED-SCLC, a favourable relationship was detected between the two parameters in the selected trial setting. Large ORR differences were needed to predict a survival benefit, clearly suggesting the need for new chemotherapeutic agents.

Key words: lung cancer, objective response, overall survival

original article

introduction

Lung cancer is a leading cause of cancer-related death, and small-cell lung cancer (SCLC) accounts for ~15% of all lung cancer cases. SCLC is clinically categorised according to the disease extent as either limited disease (LD)- or extensive disease (ED)-SCLC. The standard first line of treatment of ED-SCLC is platinum-based chemotherapy with cisplatin–etoposide or cisplatin–irinotecan [1, 2]. The outcome, however, is unsatisfactory, with a median survival time (MST) of ~1 year, indicating the need for novel anticancer agents.

In developing new agents, the most important issue is whether they prolong survival. This is usually evaluated in phase III trials, in which the primary end point is traditionally overall survival (OS). Phase III trials, however, are both expensive and time consuming. Moreover, a recent review of all North American phase III randomised trials for patients with ED-SCLC conducted from 1972 to 1990 determined that only 5 (24%) of 21 trials found a significant, but small, survival advantage, with a survival difference ranging from 0.8 to 3.0 months in the experimental arm compared with the control arm [3]. Considering these findings, early and accurate screening of the agents to be investigated in phase III trials is essential.

As spontaneous cancer regression is a rare event, assuming that tumour regression after treatment is attributable entirely to a treatment effect is reasonable. For this reason, the objective response rate [ORR; complete response (CR) rate and partial response (PR) rate] has historically been considered a clear indicator of antitumour activity and a surrogate for clinical benefit [4]. The ORR has the additional advantage of being an early clinical trial end point, generally reached within just 2–3 months of treatment initiation [5].

The duration, human resources required for and cost of clinical trials could be reduced if a surrogate end point was to be properly used in place of survival. To date, however, (i) the extent to which the OR is predictive of mortality in the first-line treatment of patients with ED-SCLC has not been fully assessed, even though an association itself between OR and OS has been reported [5]. In addition, (ii) how much time of OS increases as ORR increases in this disease has not been formally

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evaluated. Furthermore, (iii) knowing what factors can affect the association between the ORR and OS would be of interest to generate relevant hypotheses in future studies. Here, we investigated the association between ORR and OS to address each of the above-mentioned points.

methods

search for trials

We searched for trials that had been conducted from January 1990 to August 2008, as previous reports relied on studies that had been conducted within the past 15–20 years. To avoid publication bias, published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008) using the terms lung neoplasm, carcinoma, small cell, chemotherapy and randomised controlled trial. The search was also guided by a thorough examination of reference lists from original articles, review articles, relevant books and the Physician Data Query registry of clinical trials.

selection of trials

Phase III randomised controlled trials were considered if they compared first-line, systemic chemotherapy for ED-SCLC that included cytotoxic agents, providing year of trial initiation. Trials were excluded if they investigated immunotherapeutic regimens or if they enrolled only responders to the initial round of chemotherapy. Trials that were initially designed to assess combined modality treatments, including radiotherapy and surgery concurrently with the initial chemotherapy, were also considered ineligible, whereas those involving the sequential use of these therapies or prophylactic cranial irradiation (PCI) after the induction of chemotherapy were allowed. Some phase III trials included patients with both LD- and ED-SCLC. These were considered eligible only if survival data for the patients with ED-SCLC could be obtained. The definitions of LD- and ED-SCLC varied somewhat in the different groups, but we could not reallocate the patients because of our inability to access each patient database. Instead, we applied the definitions described in each original report to this study. If no relevant descriptions were documented, we assumed that the definitions in the trial were based on the guidelines that existed at the time the trial was initiated [6, 7]. The control arms in each phase III trial were identified based on the statement in each trial.

data abstraction

To avoid bias in the data-abstraction process, four medical oncologists (IO, NO, YF and KH), one of whom holds a board certificate for medical oncology (KH), independently abstracted the data from the trials and subsequently compared the results. The following information was obtained from each report: the year of trial initiation (year when the first patient was accrued), the number of patients enrolled and randomised, the median patient age, the proportion of patients who had a good performance status (PS), the proportion of patients who were male and who had brain metastasis, the chemotherapeutic regimen, the definition of ED, the description of the administration of sequential thoracic irradiation, surgery or PCI as part of the trial design and the MST (per treatment arm). All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. For trials with more than two treatment arms, we constructed multiple pairs for the investigational and reference arms.

quantitative data synthesis

To investigate the association between differences in ORR and MST, we defined the MST difference as the difference in MST between the investigation and reference arms; similarly, the ORR difference was defined as the ratio of the ORR in the investigation arm to the ORR in the reference arm (all measures in months). The information from the phase III trials was evaluated using a multiple stepwise regression model (with the following stepping method criteria: probability of F to enter of ≤ 0.05 and to remove of ≥ 0.10) to determine whether the following factors independently affected the MST difference: ORR difference, year of study, definition of ED, ratio of patients with a good PS in the investigational arm to those in the reference arm and a trial design including PCI for those with an OR (CR/PR) to the induction of chemotherapy. All analyses were weighted by trial size. The data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies. All P values corresponded to two-sided tests; significance was set at $P < 0.05$. The strength of each association was defined a priori using commonly accepted criteria for the proportion of variation (R^2) as follows: 0–0.29, little or no association; 0.30–0.69, moderate or weak association and 0.70–1.00, strong association [8].

results

trials included in the analysis

Of the 2166 trials screened, 48 trials for ED-SCLC were identified as having data regarding OS and ORR (Figure 1). A total of 8779 patients were randomly allocated to 100 chemotherapeutic arms. Of these 48 trials, two had three treatment arms and one had four treatment arms; thus, 52 trial pairs were in the investigational arm versus the reference arm (Table 1). Of these trials, most had high proportions of male patients and patients with a good PS. The response criteria were described in 43 of the 52 trials. Approximately half of the trials used the response criteria of the World Health Organisation (WHO). Regarding the chemotherapeutic regimens, cisplatin plus etoposide-containing regimens were most frequently evaluated in both the investigational and reference arms (25 and 27 arms, respectively), while a cyclophosphamide, adriamycin and vincristine regimen was used in 17 and 23 arms, respectively.

degree of association between the MST and ORR differences

We plotted the MST and ORR differences (Figure 2). A modest relationship was detected between the ORR and MST differences ($R^2 = 0.3314$), suggesting that the ORR difference between the investigational and reference arms could predict 33.1% of the variance in the MST difference between the arms.

Next, we assumed that this association would be closer if the trials were limited to those in which the response criteria were clearly defined; the relationship between the two parameters, however, was not as so different as expected ($n = 43$; $R^2 = 0.1949$). In addition, we assessed whether the association could be affected by the type of response criteria, but it was nearly consistent irrespective of using the WHO criteria for response assessment [$R^2 = 0.1340$ ($n = 23$) versus 0.2765 ($n = 20$) for those trials in which the WHO criteria and other criteria were used, respectively].

To rule out potential confounding variables between the ORR difference and other trial characteristics, we conducted a multiple linear regression analysis for the MST difference. The stepwise multiple regression model used excluded all covariates

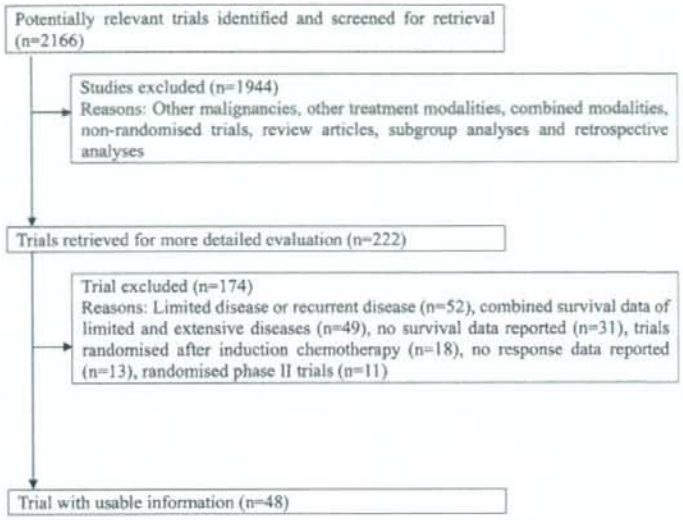

Figure 1. Flowchart showing the review process for the trials.

Table 1. Trial demographics and chemotherapeutic regimens in the 52 trial pairs

Trial characteristics	
Median no. of randomly assigned patients per trial (range)	142 (33–784)
Published year (median, range)	1997 (1990–2008)
Year of trial initiation (median, range)	1990 (1983–2006)
Percentage of patients with a good PS (median, range)	80 (35–100)
Percentage of male patients (median, range)	81 (56–93)
Trials including the administration of PCI to those with an objective response to the initial treatment (yes/no)	20/32
Definition of extensive disease (yes/no)	36/16
Description of the response criteria (yes/no)	43/9
World Health Organisation	23
European Cooperative Oncology Group	2
RECIST	1
Japan Lung Cancer Society	1
Described, but no criteria type documented	16

Good PS was defined as a PS of zero or one.
PS, performance status; PCI, prophylactic cranial irradiation; RECIST, response evaluation criteria in solid tumours.

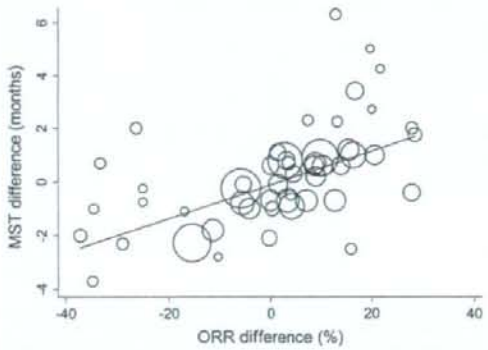

Figure 2. Correlations between the median survival time (MST) difference between the investigational and reference arms and differences in the objective response rate (ORR) in the eligible trial pairs weighted by the number of randomised patients ($R^2 = 0.3314$). The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain 33.1% of the variance in the MST difference between the arms. Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

except the ORR difference. This turned out to be a significant factor affecting the MST difference ($P = 0.003$); however, only 31.6% of the variance in the MST ratio was accounted for even by this model ($R^2 = 0.3156$).

association between the MST and ORR differences in several subgroups

To investigate whether the trial setting could affect the relationship between the MST and ORR differences, eligible

Table 2. Degree of association between the ORR and MST differences in various clinical settings in the simple regression analysis

	No. of trials	Regression coefficient	R^2
Overall	52	0.063	0.3314
Various subgroups			
Trials including PCI for those with an objective response to the initial therapy			
Yes	20	0.083	0.6279
No	32	0.053	0.2254
CAV regimen			
Yes	24	0.062	0.3302
No	28	0.063	0.3264
PE regimen			
Yes	32	0.062	0.3376
No	20	0.064	0.3185
Trial design of additional thoracic irradiation			
Yes	14	0.061	0.4954
No	38	0.063	0.2937
Published year			
1996 or before	26	0.037	0.2346
1997 or later	26	0.094	0.4671
% of good PS patients			
≥80[a]	12	0.061	0.3351
<80[a]	13	0.092	0.4505

All analyses were weighted by trial size.
[a]Median percent of patients with good PS.
ORR, objective response rate; MST, median survival time; R^2, the proportion of variation; PCI, prophylactic cranial irradiation; CAV, cyclophosphamide, doxorubicin and vincristine; PE, cisplatin and etoposide; PS, performance status.

trial pairs were divided into several subgroups (Table 2). We found a stronger association between the two parameters for those trials in which all the patients with an OR to the initial chemotherapy were given PCI ($R^2 = 0.6279$; Figure 3A), whereas a weaker association was found in those trials without that type of design ($R^2 = 0.2254$; Figure 3B). None of the other characteristics assessed seemed to affect the association (Table 2).

predicted MST difference based on the fitted model for those trials with the PCI setting

We next constructed a fitted formula for predicting the MST difference using the actual ORR difference for those trials that included PCI as part of their design in which a high R^2 value was obtained:

Predicted MST difference between the investigational and reference arms = 0.083 × (actual ORR difference) − 0.125.

The predicted MST differences are listed in Table 3 according to the various ORR differences. For example, when the investigational regimen was expected to yield a 10% increase in the ORR as compared with the state-of-the-art regimen, the MST was predicted to increase only by 0.7 months (21.2 days) in the investigational arm.

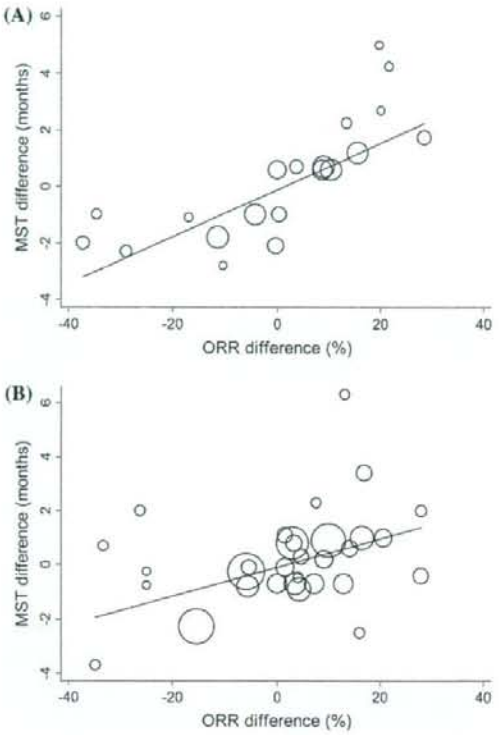

Figure 3. Correlations between the median survival time (MST) difference and objective response rate (ORR) difference between the investigational and reference arms in trials (**A**) designed to administer prophylactic cranial irradiation (PCI) to those with an objective response to the inductive therapy ($R^2 = 0.6279$) or (**B**) not ($R^2 = 0.2254$). The analysis was weighted by the number of randomised patients. The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain as much as 62.8% of the variance in the MST difference between the arms in trials including PCI, while in the trials without PCI, the MST difference was less exactly accounted for by the ORR difference (22.5%). Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

discussion

In this study, we found a modest association between the ORR and MST differences in the complete trial ($R^2 = 0.3314$; Figure 2). In contrast, the design of PCI setting for all responders to the initial chemotherapy favourably affected the relationship ($R^2 = 0.6279$; Figure 3A). In this setting, large differences in ORR were needed to predict a survival benefit (1.2-day survival advantage per 2% increase in ORR).

Note that the relationship was stronger only for those trials in which PCI was assigned to all patients with an OR to the initial treatment ($R^2 = 0.6279$; Figure 3A). One would postulate that this result is related to the ability of anticancer agents to penetrate the blood–brain barrier (BBB). Apart from clinically

Table 3. Predicted MST difference according to the ORR difference

ORR difference[a] (%)	Predicted MST difference[a], months (days)
2.5	0.1 (2.5)
5.0	0.3 (8.7)
7.5	0.5 (14.9)
10.0	0.7 (21.2)
12.5	0.9 (27.4)
15.0	1.2 (33.6)
17.5	1.4 (39.8)
20.0	1.6 (46.1)

[a]Difference between the investigational and reference arms. For example, when an investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by 0.7 months (21.2 days) in the investigational arm.
ORR, objective response rate; MST, median survival time.

obvious cranial metastases, which would be sensitive to systemic chemotherapy because of an impaired BBB [9], radiologically undetected micrometastases in the brain, which are common in patients with ED-SCLC, are generally considered to be insensitive to chemotherapy because they are able to hide behind the still-intact BBB [9]. Thus, even if systemic chemotherapy was effective against detectable extracranial diseases, such small undetectable cranial diseases could continue to grow without the use of PCI, possibly resulting in a poor outcome. That could explain why a tight association was not observed between the radiological response and survival data. However, with the PCI setting for responders to the initial chemotherapy, such a difference in the response pattern between extracranial and intracranial diseases would theoretically be minimised. This may be why a stronger association between the radiological response and survival was observed when only those trials that included PCI as part of their design were assessed in the analysis (Figure 3A). This hypothesis requires further study. Other clinical factors including PS examined did not seem to influence the relationship between ORR and MST (Table 2), while a number of studies have shown that PS has impacts on outcome [10–12]. This would simply reflect that good PS patients can respond well to chemotherapies and survive longer and that poor PS patients hardly respond to them, resulting in the poor outcome.

In addition, knowing how much of a difference in ORR is needed to predict an obvious survival difference in ED-SCLC is also clinically necessary. In their abstracted database study, Johnson et al. [13] investigated the role of ORR as a surrogate marker in the treatment of advanced non-small-cell lung cancer (NSCLC) by comparing incremental differences in MST between the arms with those in ORR. The formula they used to predict the MST difference was nearly identical to ours, except for the difference in cancer type: MST difference = 0.090 × (the ORR difference) − 0.048. Using this formula for patients with NSCLC, if the investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by only 0.9 months (25.6 days) in the investigational arm. Given either formula, one could intuitively predict the survival benefit of a new therapy by comparing the OR data from their early clinical trials with the ORR for the state-of-the-art therapy. At any rate, both sets of results indicate that, irrespective of the small- or non-small-cell subtype, the survival advantage would be small even if a relatively large ORR difference was obtained.

Few randomised trials of metastatic lung cancer have reported hazard ratios, and predictions based on this measure would not be representative and could be biased. Additionally, differences in follow-up duration between trials could affect the calculated hazard ratios. For these reasons, the MST was used in this study to ensure that all trials were long enough to capture the relevant end points in at least half of the patients. The reason for this pragmatic approach is that the value of a treatment of metastatic disease is usually measured in terms of incremental survival gains rather than the proportional or absolute risk of death [13].

Trial-level surrogacy as described here is not necessarily linked to individual-level surrogacy; thus, our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. Analyses based on data derived from both sources have strengths and weaknesses [14]. Although the use of individual patient data (IPD) restricts the analysis to a limited number of trials and the analysis is not easily replicated by independent researchers, it allows better characterisation of important covariates that affect survival. Future investigations using IPD could show a more precise relationship between survival and the response to treatment. In addition, as a point to be discussed, assessment of response rate would be variable and unreliable. It is well documented that response rates have dropped in recent years as more rigorous criteria are used. This is borne out by the fact that the correlation dropped in studies with clearly defined response criteria. Using differences in response rates rather than absolute values would help address this.

In conclusion, in this study, we found a favourable relationship between the ORR and MST differences for trials in which those who responded to the initial chemotherapy subsequently received PCI. Given the recent finding of a survival advantage from PCI even in patients with ED-SCLC [15], the frequency at which PCI is used for responders to the initial treatment will likely increase. Considering such circumstances, ORR data may be useful for predicting how much improvement in OS can be obtained. In contrast, large differences in ORR are needed to predict a survival benefit, strongly suggesting the need for the development of new chemotherapeutic agents in ED-SCLC.

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A phase I study of combination S-1 plus cisplatin chemotherapy with concurrent thoracic radiation for locally advanced non-small cell lung cancer

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ABSTRACT

A combination of S-1, a newly developed oral 5-fluorouracil derivative, and cisplatin is reported to show anti-tumour activity against advanced non-small cell lung cancer (NSCLC). Because S-1 shows synergistic effects with radiation, we conducted a phase I study to evaluate the maximum tolerated doses (MTDs), recommended doses (RDs), and dose-limiting toxicities (DLTs) of cisplatin and S-1 when combined with concurrent thoracic radiation (total dose of 60 Gy with 2 Gy per daily fraction) in patients with locally advanced NSCLC. Chemotherapy consisted of two 4-week cycles of cisplatin administered on days 1 and 8, and S-1 administered on days 1–14. S-1/cisplatin dosages (mg/m^2/day) were escalated as follows: 60/30, 60/40, 70/40, 80/40 and 80/50. Twenty-two previously untreated patients were enrolled. The MTDs and RDs for S-1/cisplatin were 80/50 and 80/40, respectively. DLTs included febrile neutropaenia, thrombocytopaenia, bacterial pneumonia and delayed second cycle of chemotherapy. No patient experienced radiation pneumonitis > grade 2 and only one patient experienced grade 3 radiation oesophagitis. The overall response rate was 86.4% with a median survival time of 24.4 months. These results indicate that combination cisplatin-S-1 chemotherapy with concurrent thoracic radiation would be a feasible treatment option and a phase II study is currently under way.

1. Introduction

Based on the results of several randomised controlled trials, cisplatin-based chemotherapy with concurrent thoracic radiation therapy is used as the standard treatment for locally advanced non-small cell lung cancer (LA-NSCLC), with a response rate of approximately 80%. However, despite the initial marked response, this treatment is usually accompanied by severe toxicity, including myelosuppression and radiation pneumonitis, with a treatment-related mortality rate of 5% [1–3]. Furthermore, the majority of patients with LA-NSCLC experience recurrence, with a 5-year survival rate of approximately 20%. To further improve the treatment outcome of LA-NSCLC, new cytotoxic agents with more potent anti-cancer activity and fewer adverse effects are required.

S-1 is a fourth-generation oral fluoropyrimidine that contains tegafur, a prodrug of 5-fluorouracil (5-Fu). This agent also contains 5-chloro-2,4-dihydroxypyridine (CDHP) to inhibit 5-Fu catabolism and prolong its activity, and potassium oxonate (Oxo) to reduce 5-Fu-induced diarrhoea [4]. In addition, Oxo reduces 5-Fu-induced immunosuppression, which was evaluated in terms of natural killer activity and interleukin-2 production in rats [5]. The consecutive administration of S-1 at 80 mg/m^2/day for 4 weeks followed by a 2-week rest period was well tolerated, with only mild myelosuppression and diarrhoea [6]. The objective response rate and median survival time (MST) were 22.0% and 10.2 months, respectively. Subsequently, a phase II trial for combination chemotherapy with S-1 at 80 mg/m^2/day for 21 days and cisplatin at 60 mg/m^2 on day 8 showed a response rate of 47.3%, with a MST of 11 months [7].

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Only 5% of cases showed grade 4 neutropaenia, and no patient showed grade 4 thrombocytopaenia or non-haematologic toxicity. Thus, this combination chemotherapy may have potential in terms of tumour reduction, increased survival and relatively mild toxicity.

Additive or synergistic effects were observed between cisplatin and 5-Fu treatment in NSCLC cells [8]. Cisplatin and 5-Fu also sensitise cancer cells to radiation [9–11]. In a previous study, we demonstrated that combination chemotherapy using cisplatin and 5-Fu with concurrent radiotherapy was both effective and feasible for LA-NSCLC [3]. Ichinose et al. also showed that UFT, a drug consisting of tegafur and uracil, with cisplatin and concurrent radiotherapy was effective in the treatment of LA-NSCLC. In pre-clinical studies, S-1 also enhanced sensitivity to radiotherapy [12,13]. Combined treatment with S-1 plus 2 Gy irradiation was significantly more effective against NSCLC xenografts than S-1 or 2 Gy irradiation alone, and the effect of this combination was nearly equivalent to that of 5 Gy irradiation alone [14]. A combination of S-1 plus 2 Gy irradiation was also more effective than the same dose of radiation plus cisplatin or UFT. Note that CDHP alone was found to potentiate sensitivity to radiation, although it showed neither anti-tumour nor toxic activity [14]. Thus, a combination of cisplatin and S-1 appears to enhance sensitivity to thoracic radiotherapy.

Based on these previous reports, we conducted a phase I study to evaluate the maximum tolerated doses (MTDs), recommended doses (RDs) and dose-limiting toxicities (DLTs) for S-1 and cisplatin when combined with concurrent thoracic radiation in patients with LA-NSCLC. The standard administration schedule of S-1 without radiation was 4-week schedule followed by 2-week rest [7]. Compared with this schedule, 2-week administration followed by 1-week rest seems to be more tolerable and safer [15]. In addition, 2-week administration of S-1 was feasible in the phase I study of concurrent chemoradiation with S-1 and cisplatin in patients with head and neck cancer [16]. As for cisplatin schedule, we reported split administration of cisplatin and docetaxel at days 1 and 8 with concurrent thoracic radiotherapy [17]. The chemotherapy doses with radiotherapy in the trial were similar to or higher than those in the previous phase II trials that did not include concurrent thoracic radiotherapy. Thus, we adopted 2-week administration of S-1 and split schedule of cisplatin at days 1 and 8 in order to reduce toxicity and to strengthen synergistic interaction of cisplatin, S-1, and radiation.

2. Patients and methods

2.1. Eligibility criteria

Patients with pathologically confirmed unresectable stage IIIA or IIIB NSCLC were eligible for the study [18]; however, those with T3N1 disease, contralateral mediastinal lymph node metastasis, malignant pleural effusion, pericardial effusion or pleural dissemination were excluded. Other eligibility criteria included previously untreated disease, any measurable lesion, Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 0–1, age 75 years or less and no history of malignancy within the previous 5 years. Before enrollment, each patient provided a complete medical history and underwent physical examination, laboratory examination and staging assessments. Patients were required to have a neutrophil count $\geq 2000/\mu L$, platelet (PLT) count $\geq 100{,}000/\mu L$, haemoglobin level ≥ 9 g/dL, serum bilirubin level ≤ 1.5 mg/dL, serum aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the upper normal limit, serum creatinine level ≤ 1.5 mg/dL, 24-h endogenous creatinine clearance ≥ 60 mL/min, arterial oxygen pressure (PaO_2) ≥ 60 mmHg on room air and 1-s forced expiratory volume ≥ 1.6 L. Patients were excluded if they had interstitial pneumonitis, uncontrolled diabetes mellitus, any serious underlying diseases or complications or were taking phenitoin or warfarin. Women who were pregnant, breast feeding or of child bearing age were also excluded. Staging work-up included a chest radiograph, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, bronchoscopy and radionuclide bone scan. A mediastinal lymph node ≥ 1 cm along the short axis by CT scan was defined as a metastatic lymph node. Written informed consent was obtained from all patients. The protocol (UMIN clinical trial ID: C000000079), was approved by the review board of each of the participating institutions.

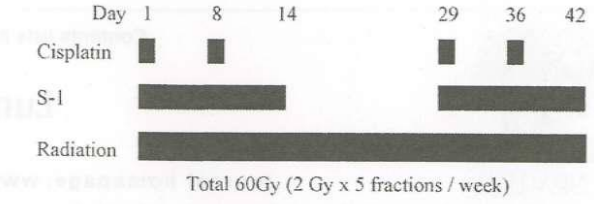

Fig. 1. Treatment scheme.

2.2. Treatment schedule

Chemotherapy consisted of two 4-week cycles of cisplatin and S-1 treatment, as shown Fig. 1, with five dose levels (Table 1). The starting doses of S-1 and cisplatin were 60 mg/m^2/day and 30 mg/m^2/day, respectively, which represent 75% of the RDs established in a phase I clinical trial for cisplatin and S-1 chemotherapy with radiation for patients with advanced head and neck cancer [16]. Patients received an oral dose of S-1 twice daily after meals from days 1 to 14 of each 28-day cycle. Because S-1 is only available for use in 20- or 25-mg capsules, the individual daily dose was set as follows: 60 mg/m^2/day dose for body surface area (BSA) < 1.25 m^2; 50 mg/day, 1.25 m^2 $\leq$ BSA < 1.5 m^2; 80 mg/day, 1.5 m^2 $\leq$ BSA; 90 mg/day, at 70 mg/m^2 dose, BSA < 1.25 m^2; 80 mg/day, 1.25 m^2 $\leq$ BSA < 1.5 m^2; 90 mg/day, 1.5 m^2 $\leq$ BSA; 100 mg/day, at 80 mg/m^2/day dose, BSA < 1.25 m^2; 80 mg/day, 1.25 m^2 $\leq$ BSA < 1.5 m^2; 100 mg/day, 1.5 m^2 $\leq$ BSA; 120 mg/day.

Cisplatin, diluted in 300 mL of physiological saline, was administered intravenously over a 1-h period before radiation therapy on days 1 and 8 of each cycle. Before and after cisplatin administration, all patients were hydrated with a total of 2500 mL infusion. Each patient was also intravenously pre-medicated with dexamethasone (8 mg) and granisetron (3 mg) 30 min prior to cisplatin injection.

Table 1
Dose escalation schedule.

Dose level	Dose (mg/m^2/day)		No. of patients	
	S-1[a]	Cisplatin[b]	Enrolled	DLT
1	60	30	3	1
2	60	40	4	1
3	70	40	3	0
4	80	40	6	2
5	80	50	6	4

DLT: dose-limiting toxicity.
[a] S-1 was administered orally from days 1 through 14 and 29 through 42.
[b] Cisplatin was administered intravenously on days 1, 8, 29 and 36.

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2.3. Radiation therapy

Radiation therapy was administered from day 1 of chemotherapy using a linear accelerator (4–10 MeV). Each patient received a single 2-Gy daily fraction for five consecutive days each week, until reaching a total dose of 60 Gy.

Before concomitant chemoradiotherapy, the curative radiation field was defined using chest radiography and contrast-enhanced CT. The initial planned radiation field did not exceed 50% of ipsilateral lung. The initial dose (up to 40 Gy) was administered to the original volume, which consisted of the primary tumour and a 2-cm margin to include tissue subject to respiratory motion. The volume also included all enlarged hilar and mediastinal lymph nodes detected *via* CT scan with a 1-cm margin, extending inferiorly to 3 cm below the carina if subcarinal lymph nodes were involved. Other prophylactic radiation fields were not established. The supraclavicular region was not routinely included if lymph node metastasis was not detected. Subsequently, an additional 20-Gy dose was administered to boost the volume, including the sites of the primary tumour and hilar/mediastinal lymph nodes, according to tumour- and lymph node-shrinkage on day 29 or later and as determined by contrast-enhanced CT. The original volume was treated with an anteroposterior parallel-opposed pair of portals. The boost volume was treated with the same pair of portals, or with a pair of oblique fields if the cumulative radiation dose to the spinal cord exceeded 40 Gy.

2.4. Assessment of toxicity and treatment modulation

Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. A complete blood cell count was performed at least twice weekly, with a complete serum chemistry profile at least once weekly during treatment. Non-haematologic toxicities were evaluated on a daily basis *via* interview and physical examination throughout the treatment period. Patients experiencing grade 3 neutropaenia with infection or grade 4 leukopaenia or neutropaenia received a subcutaneous dose of recombinant human granulocyte colony-stimulating factor (2 μg/kg), and S-1 administration was halted until leukocyte or neutrophil count recovered. If patients experienced grade 3 or 4 haematologic toxicity on day 8 of each cycle, cisplatin administration was withheld within that cycle. If haematologic toxicity occurred on day 29, the next course of chemotherapy was delayed until toxicity decreased to grade 2 or less. If, in the first cycle, 24-h creatinine clearance decreased to 30–60 mL/min, cisplatin administration was reduced to half of the planned dose in the second cycle; if 24-h creatinine clearance decreased to less than 30 mL/min in the first cycle, cisplatin treatment was withdrawn completely in the second cycle. For serum creatinine levels of 1.5–2.0 mg/dL, S-1 administration was withheld in the evening. If serum creatinine levels rose above 2.0 mg/dL, S-1 administration was halted completely and restored only if serum creatinine returned to normal levels.

If patients experienced grade 3 or 4 oesophagitis or a decrease in PaO_2 of >10 mmHg compared to baseline, radiotherapy was withheld until oesophagitis improved to grade 2 or a clinically acceptable toxicity level. If grade 3 or 4 haematologic toxicity occurred, radiation was withheld until recovery to grade 2.

All treatment courses were analysed to determine DLTs and MTDs, although the dose level was elevated based on toxicity within the 8-week treatment protocol. For the first 2 years after completion of therapy, patients were followed monthly with chest radiography and every 6 months with CT of chest and abdomen and MRI of brain. If the radiation pneumonitis was clinically suspected, CT of chest was immediately taken.

2.5. Dose escalation

DLT was defined as development of at least one of the following adverse events: grade 4 haematologic toxicity sustained over 4 days, grade 3 or 4 febrile neutropaenia, any delay of thoracic radiation for 3 weeks or more, any delay of scheduled oral intake of S-1 for 2 weeks or more or grade 3 or higher non-haematologic toxicity, with the exception of controlled nausea and/or vomiting, anorexia and fatigue. Initially, three patients were scheduled to enter the study at each dose level; if all three patients at a given dose level developed DLT, that dose was designated the MTD. If only two patients experienced DLT, three additional patients were subjected to the same dose level. The MTD was defined as the dose at which three or more patients amongst six developed any of the specified DLTs. The RD was defined as the dose level immediately below the MTD.

2.6. Assessment of response

Treatment response was evaluated according to the Standard Response Evaluation Criteria in Solid Tumours [19] and confirmed in a blinded extramural review. The progression-free survival (PFS) time and overall survival time were calculated from the date of registration in this study until the first documented instance of disease progression or death, respectively, using the Kaplan–Meier method. All statistical analyses were performed using the SPSS software package (version 11.0J; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Between October 2005 and March 2007, 22 patients (15 men, 7 women) with a median age of 66 years (range, 52–75 years) were enrolled in this study (Table 2). Nine and 13 patients had PS scores of 0 and 1, respectively. Eleven patients had adenocarcinomas, nine patients had squamous cell carcinomas and two patients had unclassified NSCLCs. Six patients were at clinical stage IIIA, and 16 patients were at IIIB. Two patients had weight loss of 10% or more.

Table 2
Patient characteristics.

No. of patients enrolled	22
Median age (year (range))	66 (52–75)
Sex: male/female	15/7
Performance status	9/13
Histology	
Adenocarcinoma	11
Squamous cell carcinoma	9
Unclassified	2
Stage of disease: IIIA/IIIB	6/16
T1N2	1
T2N2	4
T3N2	1
T4N2	7
T1N3	1
T2N3	5
T4N3	3
Body weight loss	
<5%	20
5–9%	0
10% or more	2

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Table 3
Principal toxicities observed during the treatment protocol.

Level		1	2	3	4	5
No. of patients enrolled		3	4	3	6	6
DLT		1	1	0	2	4
Neutropaenia	Grade 3	2	2	3	1	2
	Grade 4	0	0	0	1	3
Febrile neutropaenia	Grade 3	0	0	0	0	2[a]
Thrombocytopaenia	Grade 3	0	0	1	1	0
	Grade 4	0	0	0	0	1
Hypokaraemia	Grade 3	0	0	0	0	1
Infection	Grade 3	0	0	0	1[a]	1[a]
Oesophagitis	Grade 2	1	0	3	1	0
	Grade 3	0	0	0	0	1[a]
Pneumonitis	Grade 1	0	0	0	3	0
	Grade 2	0	0	0	0	1
Chemotherapy delayed over 14 days		1[a]	1[a]	0	1[a]	1[a]

[a] DLT: dose-limitting toxicity

3.2. Toxicities and determination of MTD

Toxicities were assessed in all 22 patients and profiled in Table 3. Amongst the three patients enrolled at dose level 1, one patient developed DLT, which was a 2-week delay in the initiation of the second cycle of chemotherapy due to prolonged neutropaenia. At dose level 2, the first, second and fourth patients did not develop DLTs; however, in the third patient, the second cycle of chemotherapy was postponed for 5 weeks due to prolonged neutropaenia. No DLT was observed at dose level 3. At dose level 4, two patients developed DLTs; one patient developed bacterial pneumonia and the second patient developed prolonged neutropaenia, resulting in delayed chemotherapy. An additional three patients were enrolled at dose level 4, but none of these patients developed DLTs. At dose level 5, two of the first three patients developed DLTs, consisting of febrile neutropaenia in one patient and grade 4 thrombocytopaenia in the other. After assigning an additional three patients to dose level 5, two patients developed DLTs, including grade 3 febrile neutropaenia in one patient and prolonged neutropaenia requiring postponement of the second cycle of chemotherapy in the other. Therefore, dose level 5 (80 mg/m^2/day of S-1 and 50 mg/m^2/day of cisplatin) was designated the MTD, and the RDs in the currently ongoing phase II trial are 80 mg/m^2/day of S-1 and 40 mg/m^2/day of cisplatin.

Other toxicities included grade 1 serum creatinine elevation at dose level 4 and grade 1 oral mucositis at dose level 4 in each patient. Grade 1 acute radiation pneumonitis was observed in three patients at dose level 4. Only one patient experienced grade 2 pneumonitis at dose level 5; 4 months later, the patient received steroid therapy for progression of pneumonitis, which was considered late radiation toxicity (grade 3). Only one patient developed grade 3 acute radiation oesophagitis. No patient delayed the second cycle of treatment due to thoracic irradiation-induced toxicity, and no treatment-related deaths occurred.

3.3. Dose intensities of chemotherapy and radiotherapy

Dose intensities for cisplatin, S-1 and radiotherapy are shown in Table 4. The relative dose intensities of cisplatin and S-1 at level 4, administered over the projected drug dosage (mg/m^2/week), were 73% and 83%, respectively. At level 5, dose intensity of S-1 decreased to 68%. Radiation intensity also decreased at dose level 5, although radiation was administered almost without delay until dose level 4.

3.4. Response and survival

Amongst the 22 patients, 19 (86.4%) displayed partial responses (PRs) and three (13.6%) showed stable disease (SD). No patient exhibited progressive disease (PD). All 13 patients at levels 2–4 showed PRs. Eventually, 17 patients demonstrated disease progression. The initial progression sites were local ($n = 5$), local plus distant ($n = 2$) or distant ($n = 10$; three of 10 patients had brain metastases alone). Overall survival and PFS curves for the 22 patients are shown in Fig. 2. At a median follow-up time of 21.0 months (range 11.0–29.5 months), 9 (40.9%) patients had died of disease progression, whereas 5 (38.5%) of the 13 surviving patients showed no evidence of progression. The median PFS time and MST were 7.6 months (95% confidence interval [CI], 5.0–10.1 months) and 24.4 months (95% CI: 22.6–26.2 months), respectively.

4. Discussion

In this phase I clinical trial, the principal toxicity was myelosuppression, which was tolerable under the dose and schedule modifications described in this protocol. Only one patient developed grade 4 neutropaenia at a dose lower than the MTD. One patient developed grade 2 acute radiation pneumonitis, followed by grade 3 late radiation fibrosis. Although other late pulmonary or oesophageal toxicities were not observed during the follow-up period, further observation is necessary.

Previously, we performed a phase I/II study of docetaxel and cisplatin with concurrent thoracic radiotherapy for LA-NSCLC, which showed promise in terms of treatment outcome and feasible tox-

Table 4
Dose intensities for cisplatin, S-1 and radiotherapy.

	Level				
	1	2	3	4	5
Cisplatin (%)[a]	72	80	79	73	74
S-1 (%)[a]	76	82	82	83	68
RT (%)[b]	100	100	97	100	90

[a] Administered drug dose (mg/m^2/week)/projected drug dose (mg/m^2/week)
[b] Actual RT dose (Gy/week)/projected RT dose (Gy/week).

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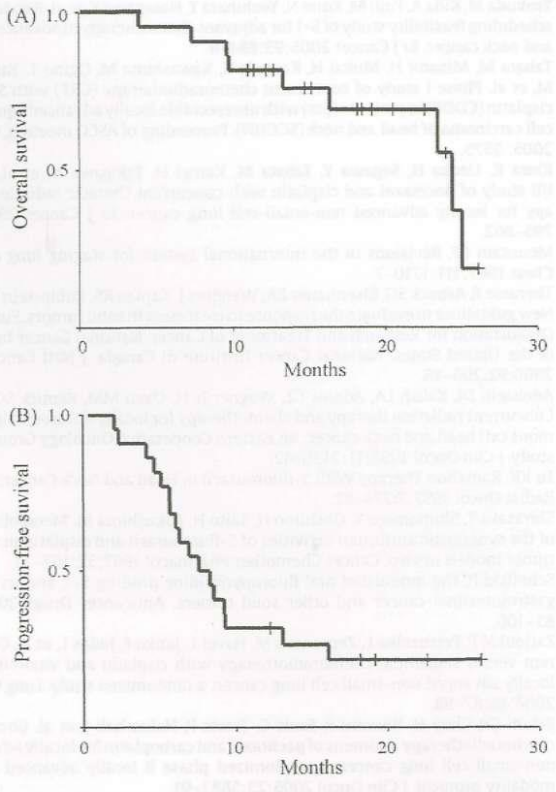

Fig. 2. (A) Overall survival. Median survival time was 24.4 months (95% confidence interval: 22.6–26.2 months). (B) Progression-free survival. Median progression-free survival time was 7.6 months (95% confidence interval: 5.0–10.1 months).

icities [17]. The doses of cisplatin and docetaxel administered intravenously on days 1, 8, 29 and 36 were very similar to the standard doses used in combined cisplatin–docetaxel chemotherapy (administered only on day 1) without radiotherapy in the Japanese clinical setting. Furthermore, skipping drug administration was easy when early myelosuppression occurred. Therefore, split administration in chemotherapy provides greater flexibility in the treatment schedule and provides the clinician an opportunity to reduce unexpected toxicities. However, split administration of cisplatin may delay the treatment schedule and reduce the dose intensity of S-1. Compared to a previous study in which S-1 and cisplatin were administered at doses of 80 mg/m^2/day for 21 days and 60 mg/m^2 on day 8 every 5 weeks, respectively, without radiotherapy [7], the projected dose intensity of cisplatin at level 4 is higher in our study (20 mg/m^2/week *vs* 12 mg/m^2/week), whereas the dose intensity of S-1 at level 4 is lower (280 mg/m^2/week *vs* 336 mg/m^2/week).

The severity of chemoradiation-induced acute oesophagitis was also relatively mild in our study. Grade 2 oesophagitis was observed in five patients (23%) and grade 3 oesophagitis occurred in only one patient at dose level 5. In several previous clinical studies, mucositis represented a major toxicity for patients with head and neck cancer treated with 5-Fu and irradiation [20,21]. Because Oxo accumulates to a greater extent in gastrointestinal tissues than in other tissues, it reduces gastrointestinal toxicities, such as diarrhoea and mucositis [22,23]. In this study, the Oxo-induced reduction in 5-Fu-induced gastrointestinal toxicities might result in relatively mild oesophagitis during chemoradiotherapy. Grade 3 or 4 radiation oesophagitis occurred between 18% and 30% in the study using a new agent such as paclitaxel or vinorelbine in platinum-based concurrent chemoradiotherapy [24–26]. Only 5% of radiation oesophagitis ≥ grade 3 in this study seemed favorable, although further investigations are warranted.

Our results demonstrate that the treatment protocol described here seems more feasible than the standard chemoradiotherapy for LA-NSCLC. In Japan, the standard concomitant chemoradiotherapy regimen consists of cisplatin, vindesine and mitomycine, based on a previous study by Furuse et al. [27]. In that report, 119 of 156 (76.3%) patients showed grade 4 neutropaenia and 27 (17.3%) patients showed grade 4 thrombocytopaenia. Seventy-seven (49.3%) patients halted treatment after the second cycle of chemotherapy. Other clinical trials for LA-NSCLC showed similar toxicities [1–3].

A major flaw in our study protocol is that we did not utilise dose-volume histograms (DVH) generated during three-dimensional computed radiation treatment planning. However, because this study was a multicentre trial, it was not possible to analyse DVH parameters in all participating institutions. DVH parameters such as the percent of the total lung volume exceeding 20 Gy (V20) are useful to predict the risk of radiation pneumonitis [28]. Although our manner of defining the initial radiation field (i.e., less than 50% of ipsilateral lung) was perhaps outdated, it was feasible in the context of a multicentre study with varying technological capacities. Notably, one patient with a V20 value of 51% developed severe late radiation fibrosis. Therefore, patients with V20 values > 35% may be excluded from the future trial.

Although this was a phase I study, we also analysed survival. The MST (24.4 months) and PFS time (7.6 months) were comparable to those observed for the standard concurrent chemoradiotherapy protocol used in Japan (MST, 16.5 months; PFS time, 8.3 months) [27]. These results were also comparable with our own previous phase II studies on concurrent chemoradiotherapy with cisplatin and 5-Fu or docetaxel [29]. The combinations of paclitaxel plus carboplatin or vinorelbine plus cisplatin were investigated in comparative studies using a new agent in platinum-based concurrent chemoradiotherapy. Belani et al. [25] and Vokes et al. [26] reported that MSTs were 16.3 months and 12 months, respectively, in the concurrent weekly paclitaxel plus carboplatin, and thoracic radiation arm. Zatloukal et al. [24] conducted that the MST was 16.6 months in the concurrent chemoradiotherapy with cisplatin and vinorelbine arm. Compared with these studies, the combination presented here may have potential effect, in spite of a phase I study.

In conclusion, we performed for the first time a phase I study of combined cisplatin-S-1 chemotherapy with thoracic radiation in patients with LA-NSCLC. Chemotherapy consisting two 4-week cycles of cisplatin (40 mg/m^2/day) on days 1 and 8, and S-1 (80 mg/m^2/day) on days 1–14 with concurrent thoracic radiation (total dose of 60 Gy with 2 Gy per daily fraction) was recommended for the further investigation. A phase II multicentre trial is currently under way to evaluate the efficacy and safety of this regimen.

Conflict of interest

None declared.

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