symptom relief in 60% to 90% of cases, but most patients die of the disease within 2 years after diagnosis.[2] The standard regimen is a combination of cisplatin or carboplatin with etoposide. An objective tumor response rate of 73% and median overall survival of 10 months have been found in elderly patients with ED-SCLC who received these regimens.[4]

Amrubicin is a novel anthracycline derivative that has shown greater antitumor activity than doxorubicin against several human tumor xenografts implanted in nude mice.[5] A phase I study of amrubicin established a recommended dose for phase II studies of 45 mg/m^2/d for 3 consecutive days every 3 weeks.[6] A subsequent phase II study in previously untreated patients with ED-SCLC found an overall response rate of 76% and median survival of 11.7 months in 33 patients (age $\geq$ 70, 13; age $<$ 70, 20).[7] As second-line treatment, amrubicin gave a response rate of 44% to 53% and median survival of 9.3 to 11.6 months in patients with sensitive relapse and gave a response rate of 17% to 50% and median survival of 5.3 to 10.3 months in those with refractory relapse.[8-11] In these trials, hematologic toxicity, grade 3 to 4 neutropenia, febrile neutropenia, and thrombocytopenia occurred in 60% to 93%, 5% to 14%, and 20% to 40% of patients, respectively.

The objective of this study was to evaluate the efficacy and safety of amrubicin in comparison with carboplatin/etoposide combination therapy in elderly patients with ED-SCLC.

Patients and Methods

Study Design

This study was designed as a multicenter, randomized, nonblinded, phase III comparative study to test for noninferiority of amrubicin compared with carboplatin/etoposide in terms of survival. The primary endpoint was overall survival (OS), and the secondary endpoints were objective response rate, time to progression (TTP), and quality of life (QOL). The study was performed in accordance with the Declaration of Helsinki, the Japanese Pharmaceutical Affairs Law, and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and informed consent form were approved by the institutional review board at each institution. Signed informed consent for participation was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT00286169).

Patient Selection

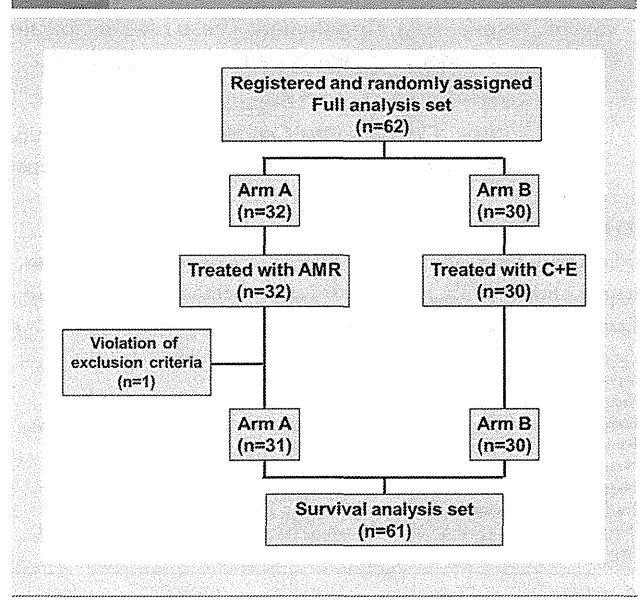
The eligibility criteria were histologically or cytologically proven SCLC; no previous chemotherapy; measurable disease; age $\geq$ 70 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; life expectancy of $\geq$ 2 months; adequate bone marrow function (white blood cell count of 4.0 $\times$ 10^9 to 12 $\times$ 10^9/L, neutrophil count $\geq$ 2.0 $\times$ 10^9/L, hemoglobin $\geq$ 9.5 g/dL, and platelet count $\geq$ 100 $\times$ 10^9/L); adequate liver function (aspartate aminotransferase and alanine aminotransferase $\leq$ 2.5 times the upper limit of the normal range and total bilirubin $\leq$ 1.5 mg/dL); adequate renal function (serum creatinine $\leq$ 1.5 mg/dL and glomerular filtration rate [GFR] calculated using the Cockcroft-Gault method $\geq$ 30 mL/min); adequate pulmonary function (PaO_2 $\geq$ 60 Torr under room air); adequate cardiac function (electrocardiogram without abnormal findings requiring treatment and left ventricular ejection fraction measured using echocardiography $\geq$ 60%); and written informed consent. Patients who received radiation or surgery for metastatic sites other than the primary site were eligible if they received these treatments 2 weeks or more before registration for this study.

Patients were excluded if they had symptomatic brain metastases; pleural or pericardial effusion or ascites that required drainage; superior vena cava syndrome; abnormal cardiac function that required treatment or a history of this condition; interstitial pneumonitis or lung fibrosis identified on chest radiograph; severe infection; serious syndrome of inappropriate secretion of antidiuretic hormone or uncontrolled diabetes mellitus; gastric or duodenal ulcer; or active prior malignancies with a disease-free interval of less than 5 years, except for carcinoma in situ. Pregnant or lactating women, men who had no intention of using contraception, and patients who had participated in registration-directed clinical trials in the previous 6 months were also ineligible.

Treatment Assignment and Drug Administration

The patients were randomly assigned to receive amrubicin monotherapy (arm A) or carboplatin/etoposide (arm B) by a prespecified minimization method of balancing the groups according to institution, age ($\geq$ 75 or $<$ 75 years), and PS (0-1 vs. 2). In arm A, amrubicin dissolved in 20 mL normal saline was administered once intravenously as a 5-minute infusion on days 1 to 3, every 3 weeks. At the start of the study, the dose of amrubicin was set at 45 mg/m^2/d for 3 days in patients aged $<$ 75 years and at 40 mg/m^2/d for 3 days in patients aged $\geq$ 75 years. However, 2 of the first 21 patients in arm A who received amrubicin at 45 mg/m^2/d died of severe infection associated with serious myelosuppression, and dose reduction was also required in subsequent cycles in 4 of 8 patients who started at 45 mg/m^2/d. In the amended protocol, the dose of

Figure 1 CONSORT Diagram. All Enrolled Patients (n = 62) Were Included as Participants for Treatment Delivery and Toxicity Analyses. One Patient in arm A was Excluded From the Efficacy Analysis Because of a Violation of Exclusion Criteria



Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide; CONSORT = Consolidated Standards of Reporting Trials.

amrubicin was set to 40 mg/m^2/d in all patients. In arm B, carboplatin was administered intravenously on day 1. The carboplatin dose was calculated using the Calvert formula, in which the target area under the curve (AUC) was 5 mg·min/mL. The GFR in the formula was calculated from the serum creatinine level using the Cockcroft-Gault method. Etoposide was administered intravenously at 80 mg/m^2 on days 1 to 3. In both arms, A and B, the chemotherapy was repeated every 3 weeks for a total of 4 to 6 cycles.

Toxicity Assessment and Treatment Modification

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The criteria for dose reduction were common to both arms, as follows: grade 4 neutropenia lasting ≥ 4 days, febrile neutropenia, grade 4 thrombocytopenia, and grade 3 or severe nonhematologic toxicity, except for general malaise and hyponatremia. If any of these criteria occurred, the dose of amrubicin was reduced by 5 mg/m^2/d (arm A) or doses were reduced to a target AUC of 4 mg·min/mL for carboplatin and 60 mg/m^2/d for etoposide (arm B) in subsequent cycles.

QOL Evaluation

QOL was assessed using the Lung Cancer Subscale (LCS) of the Japanese version of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire[12] and the Japanese version of the Euro-Qol 5-Dimension (EQ-5D) questionnaire.[13] QOL scores were obtained before chemotherapy, and 3 weeks (before the second cycle of chemotherapy), 3 months, 6 months, and 12 months after the start of chemotherapy.

Response Evaluation

Objective tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0,[14] using CT or MRI for target and nontarget lesions performed every 4 weeks, and every 2 months after the best tumor response was established.

Poststudy Anticancer Treatments

After completion of the protocol-defined chemotherapy, no therapy for SCLC was allowed until disease progression or new lesions occurred (with progressive disease as defined in the RECIST criteria), except for prophylactic cranial irradiation in patients who achieved a complete response.

Statistical Analysis

OS and TTP were measured from the date of registration. Survival distributions were calculated by the Kaplan-Meier method and compared by the log-rank test. For OS, the point estimation and 95% confidence interval (CI) of the hazard ratio (HR) of arm A to arm B were calculated using a Cox proportional hazard model including age (≥ 75 or < 75 years old) and PS (0-1 vs. 2) as covariates. For the response rates in both arms, 95% CIs were calculated using methods for exact binomial CIs. A Fisher exact test was used for comparison of categorical data.

Noninferiority in OS would be obtained if the upper limit of a 2-sided 95% CI of the HR for OS was lower than 1.33. Based on previous studies, 1-year survival rates in arms A and B were assumed to be 48.5% and 36.0%, respectively. At a significance level of 5%,

Table 1 Patient Characteristics

	Arm A (n = 32) (AMR)		Arm B (n = 30) (C + E)		*P*
	n	(%)	n	(%)	
Sex					
Male	24	(75)	24	(80)	.764[a]
Female	8	(25)	6	(20)	
Age (years)					
71-74	14	(44)	13	(43)	1.000[a]
≥75	18	(56)	17	(57)	
Median (range)	76 (70-88)		75 (70-82)		.849[b]
PS					
0	5	(16)	7	(23)	.775[a]
1	20	(63)	17	(57)	
2	7	(22)	6	(20)	
Stage					
IIIB	6	(19)	1	(3)	.105[a]
IV	26	(81)	29	(97)	
Brain Metastasis					
No	27	(84)	22	(73)	.357
Yes	5	(16)	8	(27)	
LDH					
Median (range)	249 (144-1243)		376 (137-1081)		.0502

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide; LDH = L-lactate dehydrogenase; PS = performance status.
[a]Fisher exact test.
[b]Wilcoxon rank-sum test.

Table 2 Hematologic Toxicities of Grade ≥ 3

	Arm A (n = 32) (AMR)				Arm B (n = 30) (C + E)				
	3	4	≥3	(%)	3	4	≥3	(%)	P^a
Leukopenia	15	10	25	(78)	10	4	14	(47)	.017
Neutropenia	8	21	29	(91)	9	15	24	(80)	.294
Febrile Neutropenia	11	0	11	(34)	1	0	1	(3)	.003
Lymphopenia	11	0	11	(34)	4	0	4	(13)	.076
Thrombocytopenia	5	1	6	(19)	4	3	7	(23)	.759
Anemia	7	1	8	(25)	7	0	7	(23)	1.000

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Fisher exact test.

60 evaluable patients per arm were needed to obtain 90% power. Thus, the sample size was determined to be 130 patients (65 per arm).

QOL was evaluated using the score on the LCS of the FACT-L and the EQ-5D utility index. The changes in QOL scores from baseline to each time point were compared between arms A and B using analysis of covariance (ANCOVA). A repeated-measures analysis of variance (ANOVA) was used to evaluate the difference in QOL score curves between the 2 arms. The quality-adjusted life-year (QALY) value was calculated from the area under a line drawn with survival time on the horizontal axis and the EQ-5D utility index on the vertical axis. QALYs in the 2 arms were compared by log-rank test and generalized Wilcoxon test.

Results

Enrollment

Between July 4, 2006, and September 5, 2007, 21 and 22 patients were enrolled in arms A and B, respectively. Two patients in arm A treated with amrubicin at 45 mg/m^2/d died from severe infection associated with grade 4 neutropenia (sepsis in the first cycle in one patient and pneumonia in the third cycle in the other). There were no treatment-related deaths in arm B. The dose of amrubicin was reduced to 40 mg/m^2/d in subsequent cycles in 4 of 8 patients who started at 45 mg/m^2/d. After a recommendation from the Data Monitoring Committee (DMC), the protocol was amended and amrubicin was administered at 40 mg/m^2/d in all patients registered in arm A thereafter. From December 2007 to April 2008, 11 and 8 patients were added to arms A and B, respectively. Of these patients, one in arm A died of amrubicin-induced pneumonitis. Enrollment of patients was then terminated early after a DMC recommendation. Thus, 32 and 30 patients were enrolled in arms A and B, respectively (Fig. 1). Patient characteristics were well-balanced between the arms (Table 1). No patients had received palliative radiotherapy before the study registration except for one patient in arm B, who had received whole-brain irradiation for brain metastases.

Table 3 Nonhematologic Toxicities of grade ≥ 3

	Arm A (n = 32) (AMR)					Arm B (n = 30) (C + E)			
	3	4	5	≥3	(%)	3	≥3	(%)	P^a
Fatigue	0	1	0	1	(3)	1	1	(3)	1.000
Nausea	0	0	0	0	(0)	1	1	(3)	.484
Anorexia	3	0	0	3	(9)	3	3	(10)	1.000
Paralytic Ileus	0	1	0	1	(3)	0	0	(0)	1.000
Bacterial Pneumonia	3	0	1	4	(13)	3	3	(10)	1.000
Sepsis	0	0	1	1	(3)	0	0	(0)	1.000
Other Neutropenic Infection	1	0	0	1	(3)	1	1	(3)	1.000
Other Nonneutropenic Infection	0	0	0	0	(0)	3	3	(10)	.107
Interstitial Lung Disease	3	0	1	4	(13)	0	0	(0)	.114
Cardiotoxicity	0	0	0	0	(0)	1	1	(3)	.484
Cerebrovascular Stroke	1	0	0	1	(3)	0	0	(0)	1.000
Cholecystitis	0	1	0	1	(3)	0	0	(0)	1.000
Elevated ALT	0	0	0	0	(0)	1	1	(3)	.484
Hyperbilirubinemia	0	0	0	0	(0)	1	1	(3)	.484
Hypokalemia	0	0	0	0	(0)	1	1	(3)	.484
Hyponatremia	4	0	0	4	(13)	2	2	(7)	.672
Miscellaneous	4	0	0	4	(13)	2	2	(7)	.672

No grade 4 or 5 nonhematologic toxicity occurred in arm B.
Abbreviations: ALT = alanine aminotransferase; AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Fisher exact test.

Figure 2 Time to Progression in Arm A (Amrubicin, n = 31; Pink) and Arm B (Carboplatin/Etoposide, n = 30; Blue). The Median Times to Progression Were 4.7 Months and 4.4 Months for Arms A and B, Respectively (P = .28 by log-Rank Test)

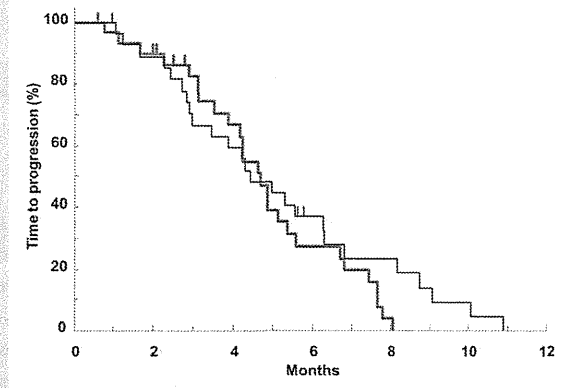
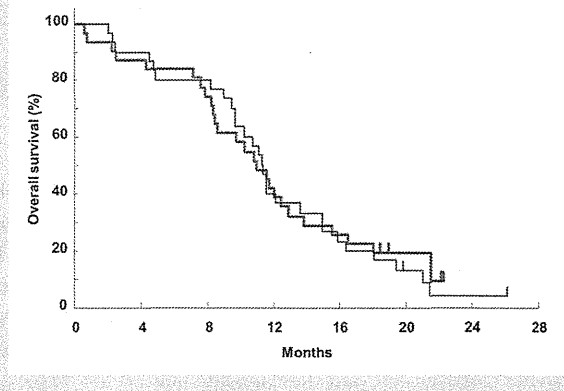


Figure 3 Overall Survival in Arm A (Amrubicin, n = 31; Pink) and Arm B (Carboplatin/Etoposide, n = 30; Blue). The Median Survival Times Were 10.9 Months and 11.3 Months for Arms A and B, Respectively (P = .74 by log-Rank Test)



Treatment Delivery

The median number of chemotherapy cycles per patient was 4 (range, 1-6) in both arms, and the total number of cycles was 130 in arm A and 120 in arm B. The dose of chemotherapy for subsequent cycles was reduced in 14 (44%) of 32 patients in arm A. Thus, the dose of amrubicin was 45 mg/m^2 in 23 cycles (18%), 40 mg/m^2 in 71 cycles (55%), and 35 mg/m^2 in 36 cycles (28%). Dose reduction was required in 12 (40%) of 30 patients in arm B. Full doses of carboplatin/etoposide were administered in 89 cycles (74%), but the doses were reduced to AUCs of 4 mg·min/mL for carboplatin and 60 mg/m^2 for etoposide in 31 cycles.

Although it was not provided in the protocol, 2 patients in arm B received prophylactic cranial irradiation before disease progression, but none in arm A did so.

Toxicity

Grade 3 febrile neutropenia occurred in 34% of patients in arm A but in only 3% of patients in arm B (P = .003) (Table 2). Bacterial pneumonia and sepsis developed during grade 4 neutropenia in one patient each in arm A, and they were fatal (grade 5). Another patient (a 78-year-old man) developed grade 5 interstitial lung disease and died from respiratory failure on the 23rd day of amrubicin chemotherapy. His underlying pulmonary diseases were emphysema and mild interstitial pneumonitis detected by chest CT scan before chemotherapy. In contrast, there was one case with grade 1 interstitial lung disease, but no grade 2 or severe cases, in arm B (Table 3).

Efficacy

One patient in arm A was excluded from the analysis of efficacy because of a violation of the exclusion criteria owing to drainage of pleural effusion before treatment (see Fig. 1). The median TTP was 4.7 months (CI, 3.9-5.4) in arm A and 4.4 months (CI, 3.0-6.3) in arm B (P = .279) (Fig. 2). The median OS was 10.9 months (CI, 8.4-12.9) in arm A and 11.3 months (CI, 9.6-14.9) in arm B (P = .735) (Fig. 3). The HR for OS was 0.87 (CI, 0.51-1.48). Thus, noninferiority of amrubicin compared with carboplatin/etoposide was not found in this study. There were 3 patients in arm A and 4 patients in arm B in whom response was not evaluable because they received only one cycle of chemotherapy owing to severe toxicity. The objective response rates were 74.2% (CI, 55.4-88.1) in arm A and 60.0% (CI, 40.6-77.3) in arm B (P = .283). The same tendency for the response was observed in patients who received amrubicin at doses of 45 mg/m^2 and 40 mg/m^2 (Table 4).

Postprotocol second-line chemotherapy was administered in 13 patients (50%) in arm A and in 19 patients (63%) in arm B (Table 5).

Quality of Life

The mean (± standard deviation) QOL scores at each time point for the 2 treatment arms are shown in Figure 4. The scores for the LCS of the FACT-L and the EQ-5D utility index in arm B indicated a better QOL than those in arm A at several time points; however, ANCOVA found no significant difference at any time

Table 4 Tumor Response

Treatment	CR	PR	SD	PD	NE	Response Rate (%) (95% CI)
Amrubicin (n = 31)	0	23	3	2	3	74.2 (55.4-88.1)
45 mg/m^2 (n = 8)	0	5	2	0	1	
40 mg/m^2 (n = 23)	0	18	1	2	2	
Carboplatin/Etoposide (n = 30)	0	18	4	4	4	60.0 (40.6-77.3)

Abbreviations: CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; SD = stable disease.

Table 5 Second-Line Chemotherapy After Disease Progression

	Arm A (n = 32) (AMR)		Arm B (n = 30) (C + E)	
Chemotherapy Regimen	**n**	**(%)**	**n**	**(%)**
Carboplatin/Etoposide	13	(41)	6	(20)
Amrubicin	2	(6)	10	(33)
Irinotecan	1	(3)	1	(3)
Topotecan	0		2	(7)
None	16	(50)	11	(37)

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.

point (LCS score: $P = .171$, .080, .112, and .371; EQ-5D utility index: $P = .171$, .080, .112, and .371 for 3 weeks and 3, 6, and 12 months after the start of chemotherapy, respectively). The repeated-measures ANOVA also found no significant difference between the arms for LCS scores ($P = .067$) and the EQ-5D utility index ($P = .865$). In the analysis of QALY, there was no significant difference between the arms by log-rank test ($P = .716$) and generalized Wilcoxon test ($P = .959$) (Table 6).

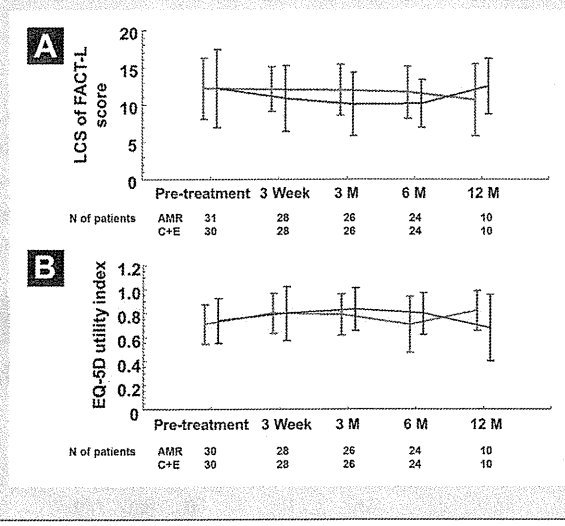
Discussion

This study was planned to test for the noninferiority of monotherapy with amrubicin compared with combination therapy with carboplatin/etoposide, in terms of overall survival. The toxicity of amrubicin was initially considered to be mild, because single-agent chemotherapy generally has toxicity milder than that of multiple-agent regimens and because a previous phase II study[7] of amrubicin monotherapy at a dose of 45 mg/m^2 for 3 days in patients with ED-SCLC found tolerable myelotoxicity. In this previous trial, 13 patients (39% of the study population) were ≥ 70 years old, and the oldest patient was 78 years old. Grade 3 to 4 leukopenia and neutropenia were noted in 52% and 85% of patients, respectively, with no febrile neutropenia or treatment-related death. One patient developed interstitial pneumonia after the second cycle, but this was resolved by steroid therapy and cessation of amrubicin treatment.[7]

For these reasons, the starting dose of 45 mg/m^2 on days 1 to 3 every 3 to 4 weeks for patients aged 70 to 74 years in the current study was considered reasonable. However, leukopenia and neutropenia in the amrubicin arm were severer than expected. The incidence of grade 3 to 4 leukopenia was as high as 80%; febrile neutropenia developed in 34% of patients; and treatment-related deaths from neutropenia-associated infection occurred in 2 patients who received amrubicin at 45 mg/m^2 for 3 days. A retrospective comparison of amrubicin chemotherapy at 30 to 40 mg/m^2 for 3 days between patients aged ≥ 70 and < 70 years found that the mean number of treatment cycles, mean dose, and mean interval of amrubicin administration, as well as hematologic toxicity, did not differ between the 2 age groups.[15] In another retrospective case series, amrubicin at 35 to 40 mg/m^2 for 3 days was also well tolerated in patients aged > 75 years, without treatment-related death.[16] Thus, the dose of amrubicin is critical for development of serious neutropenia.

In this study, 4 patients developed grade 3 to 5 interstitial lung disease in arm A, whereas no grade 3 or severe lung disease occurred in arm B. Yoh et al[17] recently summarized 7 cases of amrubicin-associated interstitial lung disease in a review of 100 cases of SCLC treated with amrubicin monotherapy. The incidences of interstitial lung disease were 3% and 33% in patients without and with pre-existing pulmonary fibrosis, respectively. These results are consistent with the present study's finding that a patient who developed fatal interstitial lung disease had pulmonary fibrosis before amrubicin chemotherapy. Preexisting pulmonary fibrosis is a risk factor for chemotherapy-associated interstitial lung disease, with odds ratios of approximately 5 and 25 for mild and severe preexisting pulmonary fibrosis, respectively.[18] Any type of anticancer agent can cause severe

Figure 4 Quality of Life (QOL) in Arm A (Amrubicin; Pink) and Arm B (Carboplatin/Etoposide; Blue) Based on the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L) (A) and Euro-QOL 5-Dimension (EQ-5D) Utility Index (B). The QOL Scores at Each Time Point are Shown as Mean ± Standard Deviation. A Lower LCS Score on the FACT-L and a Higher EQ-5D Utility Index Indicate a Better QOL



Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.

Table 6 Quality-Adjusted Life-Years (QALY)

Arm	No. of Patients	QALY, Median	P^a	P^b
A (AMR)	30	0.745	–	–
B (C + E)	30	0.714	.716	.959

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.
[a]Log-rank test.
[b]Generalized Wilcoxon test.

interstitial lung disease in patients with preexisting pulmonary fibrosis, including platinum-containing drugs and etoposide.[19] Because pulmonary fibrosis is common among elderly people, the indication of chemotherapy with amrubicin and other chemotherapeutic agents may be limited in elderly patients with SCLC.

This study was performed as a registration-directed industry-sponsored clinical trial in Japan that meets Japanese Good Clinical Practice Guidelines and the Pharmaceutical Affairs Law. However, the trial failed to provide sufficient information on the efficacy and safety of amrubicin because of early termination due to excessive toxicity in the experimental arm (arm A). Similarly, a subset analysis of a phase III trial of carboplatin and paclitaxel with or without bevacizumab in patients with advanced non–small-cell lung cancer found that bevacizumab was significantly associated with grade 3 to 5 toxicities and no overall survival benefit in elderly patients.[20] Many of the elderly patients had preexisting comorbid conditions that may have adversely affected organ function and influenced functional status. Thus, it is important to exclude patients with poor general conditions to avoid trials with inappropriate populations for evaluation of the efficacy of new anticancer agents.

Conclusion

Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable in elderly Japanese patients with ED-SCLC.

Clinical Practice Points

- SCLC has an extremely poor prognosis, and elderly patients (≥ 70 years old) account for approximately 30% to 40% of SCLC at diagnosis.
- Amrubicin, a third-generation synthetic anthracycline, has shown promising efficacy in phase II studies with patients with ED-SCLC at 45 mg/m^2/d for 3 consecutive days every 3 weeks.
- In this study, the efficacy and safety of amrubicin were evaluated by comparison with carboplatin/etoposide combination therapy in elderly Japanese patients with ED-SCLC. The trial was prematurely closed owing to 3 treatment-related deaths in the amrubicin arm. Noninferiority of OS and TTP of amrubicin compared with carboplatin/etoposide was not found in this study.
- Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable for elderly patients with ED-SCLC. More attention should be paid to the elderly patients with preexisting pulmonary fibrosis in amrubicin-containing chemotherapy.

Acknowledgments

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Disclosure

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A Feasibility Study of Carboplatin Plus Irinotecan Treatment for Elderly Patients with Extensive Disease Small-cell Lung Cancer

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Objective: The role of platinum agents plus irinotecan has been unclear for elderly patients with extensive disease small-cell lung cancer. We conducted a feasibility study to evaluate the safety and efficacy of carboplatin plus irinotecan in preparation for a planned Phase III study.
Methods: Based on another Phase I study, carboplatin area under the curve of four Day 1 plus irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks for four courses was administered. Patients aged ≥70 years with a performance status of 0–2 were eligible. The primary endpoint was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. If the feasibility was ≥60% in the first 10 patients, this endpoint would be considered to be met.
Results: Eleven patients were registered. The median age was 77 years, and nine patients had a performance status of 1. Ten patients completed four courses of treatment, and neither dose omission nor modification was required. The feasibility was 91% (10/11) and the relative dose intensity was 76.9%. Because neutropenia was frequently prolonged, the next course was delayed in 53% of all courses. Other toxicities were generally mild, and the only Grade 4 toxicity was hyponatremia. The overall response rate was 90% (9/10), and the progression-free survival and the overall survival were 5.1 and 10.9 months, respectively.
Conclusions: This regimen appears to be feasible and effective. Based on these results, a Phase II/III trial comparing carboplatin plus etoposide with carboplatin plus irinotecan for elderly patients with extensive disease small-cell lung cancer is being planned by the Japan Clinical Oncology Group.

Key words: chemo-respiratory tract – chemo-Phase I–III – clinical trials – lung medicine

INTRODUCTION

Approximately 30–40% of patients with small-cell lung cancer (SCLC) are ≥70 years old, and the proportion of elderly SCLC patients is continuously increasing in Japan (1–3). However, as elderly patients have been frequently excluded from clinical trials, no standard chemotherapeutic regimen has been established for this patient population. Moreover, standard chemotherapeutic regimens for non-elderly SCLC patients are not always suitable for older patients due to their vulnerable organ function and/or co-morbidities. Therefore, the establishment of a chemotherapeutic regimen that is well balanced between safety and efficacy for this population should be pursued.

The Japan Clinical Oncology Group (JCOG) 9702 study compared carboplatin plus etoposide (CE) versus split-dose cisplatin plus etoposide (SPE) in elderly and poor-risk patients with extensive disease (ED)-SCLC (4). Based on the results of this study, the JCOG concluded that the SPE regimen should remain as the standard treatment for elderly and poor-risk patients with ED-SCLC, the CE regimen being an alternative. However, because the CE regimen does not require hydration and can be administered in an outpatient setting, elderly patients with ED-SCLC in Japan more commonly receive this regimen.

In contrast, the Phase III JCOG 9511 study has shown that irinotecan plus cisplatin (IP) is more effective than etoposide plus cisplatin (EP) for treating non-elderly patients with ED-SCLC (5). However, elderly patients (age $\geq$71 years) were excluded from this trial. When considering the treatment plan for elderly patients with ED-SCLC, the 1-day bolus administration of this cisplatin-based regimen would be difficult because hydration is required. Until now, the carboplatin plus irinotecan (CI) regimen has been repeatedly reported. Although several studies included patients 70 years of age or older, few studies were especially designed for the elderly. Therefore, it would be meaningful to consider a CI regimen for the elderly. Two randomized trials have compared CI with CE for ED-SCLC patients. Although Schmittel et al. (6) did not show a significant survival benefit in the CI arm, survival was marginally better and fewer hematological toxicities were observed. In contrast, Hermes et al. (7) reported a significant survival advantage of CI over CE. Although these trials were not specifically designed for elderly patients and the doses used differed from Japanese standard doses, we believed it was worthwhile to investigate the efficacy of CI in elderly patients with ED-SCLC. Furthermore, a recent meta-analysis of camptothecins compared with etoposide in combination with platinum in ED-SCLC showed a survival benefit associated with camptothecins plus platinum (excluding nogitecan) over etoposide plus platinum in a subgroup analysis (8). Thus, a Phase III trial comparing CE with CI in elderly patients with ED-SCLC is being warranted in the JCOG Lung Cancer Study Group (LCSG).

In our previous study (9), we reported the 4-weekly schedule of CI regimen using prophylactic granulocyte colony-stimulating factor (G-CSF) support in elderly patients with SCLC. However, this study was not a Phase I study and had a heterogeneous patient population. In addition, because not only chemotherapy-naïve but also pretreated patients were included and the treatment drug dose was changed according to the patient's characteristics, the recommended dose could not be decided in the study. Recently, prophylactic use of G-CSF has not been preferred in clinical practice in Japan because more expensive cost and prolonged hospital stays are required. For the reason given above, we cannot apply the previous data to plan the Phase III study and we think that optimal schedule and dose of CI for elderly patients with SCLC have not been established. On the other hand, Thoracic Oncology Research Group (TORG) decided a recommended dose of 3-weekly schedule of CI regimen for elderly patients with limited disease (LD)-SCLC in a Phase I study (unpublished data). Because thoracic radiotherapy was sequentially administered after four courses of chemotherapy in this Phase I study, it might be justified that the recommended dose of CI for LD-SCLC could be used in elderly patients with ED-SCLC based on these data. Furthermore, because members of JCOG and TORG were much different, JCOG-LCSG recommended a further feasibility study by only JCOG members for elderly patients with ED-SCLC. Therefore, we conducted a feasibility study to evaluate the safety and efficacy of CI in elderly patients with ED-SCLC in preparation for a future JCOG Phase III study designed to compare CE with CI in this patient population. This study is registered with the UMIN Clinical Trials Registry as trial 000003208.

PATIENTS AND METHODS

Patient Selection

Patients with the following inclusion criteria were enrolled: age $\geq$70 years; cytologically or histologically confirmed SCLC; ED stage (defined as at least one of the following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion and pericardial effusion); no prior chest radiotherapy or chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; no other co-existing malignancy and adequate hematologic, hepatic and renal organ function (leukocyte count $\geq$4000/mm^3, absolute neutrophil count [ANC] $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3, hemoglobin level $\geq$9.0 g/dl, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels $\leq 2\times$ upper limit of normal range, total bilirubin $\leq$1.5 mg/dl, creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min and $PaO_2 \geq$ 60 mmHg). The additional criteria were: no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, no diarrhea and provision of written informed consent. The exclusion criteria included brain metastases requiring radiotherapy, superior vena cava syndrome requiring radiotherapy and serious medical or psychiatric illness. Patients with interstitial pneumonitis detected by chest computed tomography (CT) scan were excluded. All the patients had chest X-ray, CT scan of the chest and abdomen, CT scan or magnetic resonance imaging of the brain and isotope bone scanning or positron emission tomography within 28 days before registration.

Treatment Plan

Based on our previous feasibility study using CI for elderly patients with SCLC (9), the TORG conducted a Phase I study of the CI regimen and sequential thoracic radiotherapy for elderly patients with LD-SCLC. In that study, the recommended dose was carboplatin area under the curve (AUC) of four Day 1 and irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks (unpublished data). Although the TORG study

included only elderly patients with LD-SCLC, we elected to use the recommended dose from this study in the current study of elderly patients with ED-SCLC. Thus, all the patients were assigned to carboplatin AUC 4 intravenously (IV) on Day 1 plus irinotecan 50 mg/m^2 IV on Days 1 and 8 every 21 days. Irinotecan on Day 8 was withdrawn if leukocyte counts were $<3000/mm^3$, platelet counts were $<100\,000/mm^3$ or if diarrhea Grade ≥ 1 occurred. Treatment was repeated for up to four cycles. Subsequent cycles were permitted only if the ANC was $\geq 1500/mm^3$, the leukocyte count was $\geq 3000/mm^3$, the platelet count was $\geq 100\,000/mm^3$, serum creatinine was ≤ 1.57 mg/dl, AST/ALT levels were $\leq 2.5\times$ upper limit of normal range, PS was 0–2, neither infection nor fever was present and treatment-related non-hematologic toxicities (excluding alopecia) had resolved to Grade ≤ 2 after Day 21. A treatment delay of ≤ 2 weeks was permitted. Use of G-CSFs was recommended in accordance with their package inserts or clinical recommendations. If G-CSF therapy was administered, the criteria for the next cycle had to be satisfied both after Day 21 and ≥ 2 days after discontinuation of G-CSF. Antiemetic prophylaxis with 5-HT_3 antagonists plus dexamethasone was routinely administered. Dose modifications were allowed only once if Grade 4 leukopenia or neutropenia lasting ≥ 4 days, Grade 4 thrombocytopenia or Grade 3 non-hematological toxicities, except for nausea/vomiting, constipation, hyponatremia and creatinine, occurred. When dose modification was needed, the next treatment course was started with carboplatin AUC 4 on Day 1 plus irinotecan 40 mg/m^2 on Days 1 and 8 every 21 days.

The protocol treatment was terminated if any of the following occurred: disease progression, a treatment delay ≥ 2 weeks, need for dose modification two times, Grade 2–4 pneumonitis and Grade 4 non-hematological toxicities. Because this was a feasibility study, post-protocol treatments were left to the discretion of the treating physicians.

Study Design

This trial was designed as a multicenter prospective feasibility study. The study protocol was approved by the institutional review board at each institution prior to study initiation. The primary objective was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. Patients showing disease progression prior to receiving three courses of chemotherapy were excluded from the feasibility evaluation. In addition, even if irinotecan was not administered on Day 8 due to toxicity, the chemotherapy course was judged as being complete. In the JCOG9702 (4), the percentages of patients who have received three and four courses of CE regimen were 69 and 63%, respectively. In this study, we considered that the completion rate of three or more courses of chemotherapy was a more appropriate endpoint than that of four courses because CI regimen might be more toxic than the CE regimen. Therefore, we concluded that the study treatment was feasible when the completion rate of three or more courses of chemotherapy was $\geq 60\%$. Ten patients were initially registered into this study. If the feasibility (completion rate) was $>60\%$, the study would be considered to have yielded positive results and to be finished. If the completion rate was 30 to $<60\%$, we planned to enroll 10 more patients to confirm whether the low rate was due to the treatment regimen or to chance. If the feasibility remained at $<60\%$ in a total of 20 patients, the study would be considered to have yielded negative results. The secondary objectives were toxicity status, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.0. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have a stable disease (SD) if it was confirmed and sustained for 6 weeks or longer.

The relative dose intensity (RDI) of irinotecan was calculated by dividing the actual received dose of the agent among all chemotherapy courses (mg/m^2/week) by the total projected dose of the four treatment courses (mg/m^2/week).When chemotherapy was completed without any delays or skipping of agents, the RDI was 100%.

Table 1. Patient characteristics

Median age, years (range)	77.5 (70–82)
Gender	
Male/female	10/0
ECOG PS 0/1	1/9
TNM classification	
T 4/3/2/1	4/2/1/3
N 0/1/2/3	1/1/2/6
M 0/1	1/9
Brinkman index	
Median (range)	1110 (840–3000)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

RESULTS

Patient Characteristics

From March 2010 through March 2011, 11 patients were registered in three institutions. One patient withdrew consent after Day1 of the first course. Because this patient did not experience acute toxicities and the reason seemed to be related to other personal problems, we thought one more additional patient to the previously scheduled 10 patients were appropriate for this study. The median age was 77 (range, 70–82) years and nine patients had a PS of 1, all of whom were male (Table 1). The median Brinkman Index was 1110 (range,

840–3000). A patient with M0 had a contralateral hilar lymph node metastasis.

Drug Delivery and Dose Intensity

Except for the one patient who withdrew consent, all the patients completed four courses of treatment and no omission of irinotecan on Day 8 occurred (Table 2). Furthermore, no patients required dose modifications. Because the completion rate was 91% (10/11), the primary endpoint of a ≥60% completion rate was met. The RDI of irinotecan was 76.9%. The median course delays between the first and second courses, second and third courses and third and fourth courses were 8.5 (range, 2–11) days, 5.5 (range, 0–10) days and 6.5 (range, 0–17) days, respectively. Of a total of 30 courses, the reasons for chemotherapy delay of ≥4 days were leukopenia or neutropenia in 15 patients (50%) and thrombocytopenia and leukopenia in one patient (3%). Delays caused by bed scheduling at participating institutions occurred in six cases (20%).

Toxicities

Toxicity profiles are shown in Table 3. Both hematological and non-hematological toxicities were generally mild. The only Grade 4 toxicity was hyponatremia in one patient. Grade 3 ANC, hemoglobin and thrombocytopenia occurred in six (60%), one (10%) and two (20%) patients, respectively. G-CSF was administered to three patients. No treatment-related deaths occurred during the study.

One patient suffered from pneumonia during his first course of chemotherapy. He received antibiotic therapy for 7 days and fully recovered. He did not experience infection in subsequent protocol treatment cycles.

Another patient suffered from Grade 4 hyponatremia (117 mEq/l) during his first course of chemotherapy. He did not have any history of renal dysfunction and was considered to have syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a paraneoplastic syndrome. Appropriate intravenous crystalloid infusion facilitated full recovery, and he was able to continue chemotherapy. Severe hyponatremia was not observed in his subsequent protocol treatment cycles.

Table 2. Additional days required in each course and the reasons for delays

Patient no.	Courses 1 and 2	Courses 2 and 3	Courses 3 and 4
1	+7[a]	+10[a]	+11[a]
3	+8[a]	+4[a]	+8[a]
4	+7[b]	+7[b]	+6[b]
5	+11[b]	+7[b]	0[d]
6	+11[a]	+4[a]	+7[a]
7	+8[c]	+9[b]	+2[d]
8	+9[a]	0[d]	+13[a]
9	+2[d]	0[d]	0[d]
10	+11[a]	+2[d]	+1[d]
11	+11[a]	+8[a]	+17[a]
Median delays (range)	8.5 (2–11)	5.5 (0–10)	6.5 (0–17)

Relative dose intensity = 76.9%.
[a]Leukocytopenia.
[b]No available bed.
[c]Leukocytopenia/thrombocytopenia.
[d]No delay or delay within 2 days.

Efficacy

Nine patients achieved PR and one patient experienced SD, yielding an ORR of 90%. The median PFS was 5.1 months (95% confidence interval [CI]: 3.9–5.8; Fig. 1), and the median OS was 10.9 months (95% CI: 7.6–16.8; Fig. 2).

Second-Line Therapy

A total of 9 patients received second-line chemotherapy. The most commonly administered agent was amrubicin ($n = 7$). Other regimens included nogitecan ($n = 1$) and CI ($n = 1$). Palliative chest radiotherapy was administered to one patient. Only one patient did not receive second-line chemotherapy, due to poor PS.

Table 3. Toxicity (worst of any course)

	Grade		
	2	3	4
Hematological			
Leukopenia	3	3	0
Neutropenia	2	6	0
Anemia	5	1	0
Thrombocytopenia	2	2	0
Non-hematological			
High AST/ALT	1	0	0
Creatinine	0	0	0
Nausea	2	0	0
Vomiting	0	0	0
Diarrhea	3	0	0
Constipation	1	0	0
Pneumonitis	0	0	0
Bleeding	0	0	0
Infection	0	1	0
Hyponatremia	0	0	1
Peripheral neuropathy	1	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

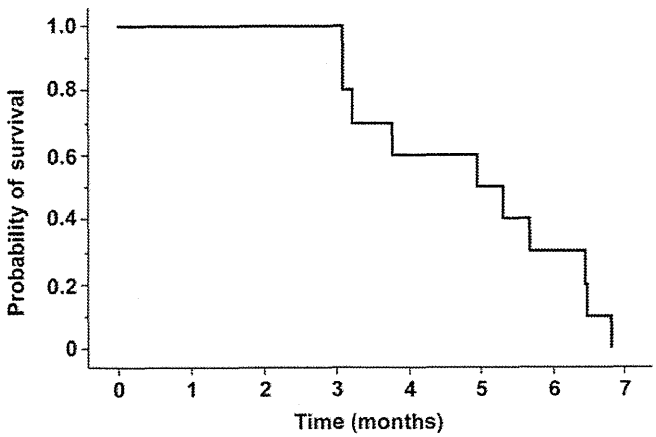

Figure 1. Progression-free survival. Median: 5.1 months (95% confidence interval [CI]: 3.9–5.8).

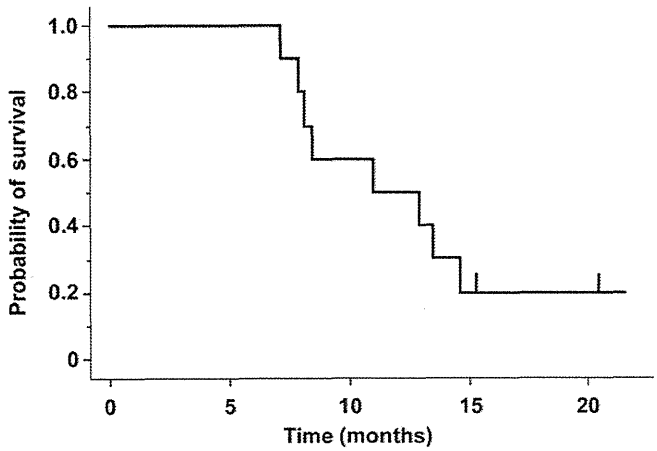

Figure 2. Overall survival. Median: 10.9 months (95% CI: 7.6–16.8).

DISCUSSION

Standard treatment for elderly patients with ED-SCLC has been controversial until now. Moreover, no global treatment consensus for these elderly patients has yet been reached. Because the median age of lung cancer patients is increasing in Japan, the need to formulate a strategy for treating this population is urgent. Some trials have shown that irinotecan might be a key drug for SCLC, particularly among Asian individuals (5,9); therefore, we conducted this feasibility study of CI in elderly SCLC patients. In this study, except for one patient who withdrew consent for chemotherapy, all other patients completed four courses of protocol treatment and the primary endpoint was met, with a feasibility of 91% (10/11). The toxicities were tolerable in this study. In general, Grade 4 hematologic toxicities are commonly experienced in association with chemotherapy for SCLC, even in patients with a good PS and adequate organ function (4–9). Only one patient in the present study experienced Grade 4 hyponatremia, and no Grade 4 hematologic toxicities were observed. The low frequency of diarrhea is particularly interesting. While the JCOG 9511 study comparing IP with EP (5) showed that the frequency of diarrhea associated with the IP regimen was relatively high (16%), no Grade 3 or 4 diarrhea was observed in the present study. Although the reason for this low frequency of diarrhea remains unclear, the low dose of irinotecan used (50 mg/m^2, Days 1 and 8) might have been a contributing factor.

While no CRs were observed, the 90% (9/10) response rate was satisfactory. Moreover, both OS and PFS were slightly longer than those observed in both treatment arms of JCOG 9702, which had almost the identical eligibility criteria (4). These data suggest that the CI regimen might improve outcomes of elderly patients with ED-SCLC. Two possible reasons may explain the promising efficacy observed in this trial. First, amrubicin was administered to 70% of patients as second-line chemotherapy. This agent was not administered at the time of the JCOG 9702 study. Because some investigators reported that second-line amrubicin was effective in relapsed SCLC (10–13), the use of this agent might have positively impacted on survival in this study. Secondly, all of the patients PS of 0–1, even though the eligibility criteria also allowed a PS of 2. In contrast, 26% of patients in the JCOG9702 study had a PS of 2–3 (4). Therefore, patient selection may have also contributed to the prolonged survival and reduced toxicities observed in this study.

This study has several limitations. First, we could have conducted more dose escalation due to the mild toxicity. However, chemotherapy delays occurred frequently, primarily due to neutropenia. Because dose escalation could have potentially caused more severe myelosuppression or delays of chemotherapy administration, we believe that it would have been difficult to escalate the dose in this trial. Secondly, our regimen included relatively low doses compared with the regimens used in non-elderly patients. Administration of irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks yields a dose intensity of 33 mg/m^2/week. In contrast, the dose intensity of irinotecan (60 mg/m^2, Days 1, 8 and 15, every 4 weeks) was 45 mg/m^2/week in JCOG9511. However, the omission of Day 15 irinotecan occurred in 50% of the courses in JCOG9511 (5). As no omission of Day 8 irinotecan occurred in the present study and course delays only occurred occasionally, the actual difference in dose intensity between the present trial and JCOG9511 may be relatively small. Thirdly, this feasibility study had a small sample size. Further investigation with a larger number of patients is warranted to verify the current results. Fourthly, this trial was not designed based upon an appropriate statistical method. However, if this study was done as a Phase II study using a Simon Minimax design, ~30–40 patients were required. At the time of study initiation, we felt that CI regimen became a promising experimental arm for a future Phase III trial based on our previous study. In addition, many JCOG members hesitated to perform a time-consuming Phase II trial of CI regimen. Therefore, we evaluated the feasibility of this regimen using a small sample size of 10 patients. If a marginal result for feasibility was obtained in the first 10 patients, additional 10 patients were required to avoid a negative result by chance.

In conclusion, treatment with CI in elderly ED-SCLC patients is feasible and appears to provide less toxicities and more efficacy than other regimens. Based on the current study, a Phase II/III trial comparing CE with CI in elderly patients with ED-SCLC is being scheduled by the JCOG LCSG.

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Conflict of interest statement

None declared.

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Efficacy of Rechallenge Chemotherapy in Patients With Sensitive Relapsed Small Cell Lung Cancer

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Objectives: To evaluate the efficacy of rechallenge with current induction regimens for sensitive-relapse small cell lung cancer (SCLC) patients.

Methods: We defined sensitive relapse as treatment-free interval (TFI ≥ 90 d). Sensitive-relapse SCLC patients who received second-line chemotherapy were separated into those treated with rechallenge chemotherapy (rechallenge group) and those treated with other regimens (other group). The endpoints were overall survival (OS), progression-free survival, and toxicity.

Results: Sixty-five patients (19 rechallenge group and 46 other group) were assessable for efficacy and safety evaluation. No significant differences in age, sex, ECOG performance status at relapse, disease extent at diagnosis, or response to first-line treatment were found between the 2 groups, but TFI was significantly longer in the rechallenge group. Twenty-one patients of the other group received amrubicin. There was no significant difference in OS between the 2 groups [median survival time (MST): rechallenge group, 14.4 mo; other group, 13.1 mo; $P=0.51$]. In the patients treated with amrubicin, MST was 12.6 months. Comparing the rechallenge group with the patients treated with amrubicin, there was also no significant difference in OS ($P=0.38$). Both the rechallenge and other group included 11 patients with ex-sensitive relapse (TFI ≥ 180 d). There was no significant difference in OS between the 2 groups (MST 15.7 vs. 26.9 mo, $P=0.46$).

Conclusions: Rechallenge chemotherapy did not prove superior to other chemotherapies, suggesting that monotherapy, such as amrubicin, might be reasonable as second-line chemotherapy for sensitive-relapse SCLC patients.

Key Words: small cell lung cancer, rechallenge chemotherapy, second-line, sensitive relapse, amrubicin

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Lung cancer is the most common cause of cancer-related death. Small cell lung cancer (SCLC) accounts for approximately 12% of lung cancers.[1] SCLC has a very aggressive course, with approximately 60% to 70% of patients having disseminated disease at diagnosis. Although SCLC shows high sensitivity to chemotherapy and radiotherapy, about 80% of limited-disease patients and virtually all patients with extensive disease will develop disease relapse or progression.[2] The prognosis of relapsed SCLC patients is 2 to 4 months without treatment.[3]

Second-line chemotherapy may produce tumor regression, but the evidence of a clinical benefit is limited. In a phase III trial comparing oral topotecan with best supportive care, the median survival time (MST) was 25.9 weeks for patients receiving topotecan and 13.9 weeks for those receiving best supportive care (HR, 0.64; 95% CI, 0.45-0.90; $P=0.0104$).[4] Thus the efficacy of second-line chemotherapy for relapsed SCLC was demonstrated. However, selectable drugs are limited and topotecan is currently the only drug approved for the treatment of relapsed SCLC patients in the United States.[4–6]

Previous reports have shown that sensitive-relapse SCLC patients have a good chance of responding to the same induction chemotherapy (rechallenge chemotherapy).[7,8] Giaccone and colleagues reported the efficacy of rechallenge chemotherapy in 13 relapsed SCLC patients for whom the median treatment-free interval (TFI) was 30 weeks and the overall response rate (ORR) was 50%. Postmus and colleagues analyzed 37 relapsed SCLC patients and reported that the ORR of rechallenge chemotherapy was 62% (median TFI was 34 wk). Although these results suggest the effectiveness of rechallenge, the reported induction regimens were CAV (cyclophosphamide, doxorubicin, vincristine) or CDE (cyclophosphamide, doxorubicin, etoposide), which are not standard regimens at this time. It is unclear whether rechallenge with the currently standard regimens is effective. Therefore, to evaluate the efficacy of rechallenge with current induction regimens, we performed a retrospective analysis of second-line chemotherapy for sensitive-relapse SCLC patients.

MATERIALS AND METHODS

Patients

We collected data between September 2002 and May 2011 from the medical records of the Shizuoka Cancer Center. In this study, we defined TFI as the period from the date of completion of first-line treatment to the first relapse. When sequential radiotherapy or prophylactic cranial irradiation (PCI) was performed as first-line treatment, the date of completion of first-line treatment was defined as the last day of these treatments. We defined sensitive relapse as TFI ≥ 90 days, based on the definition in several previous trials.[9–11] Patients with TFI ≥ 180 days were considered as "ex-sensitive relapse," based on the NCCN guideline recommendation for rechallenge chemotherapy.

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We divided the sensitive-relapse SCLC patients into 2 groups according to the second-line chemotherapy regimen. The "rechallenge" group comprised patients who received rechallenge chemotherapy, which is defined in this study as retreatment with the same induction regimen. The "other" group comprised patients who received regimens other than rechallenge chemotherapy, including monotherapy such as amrubicin or irinotecan.

Evaluation and Statistical Analysis

We evaluated tumors according to the Response Evaluation Criteria in Solid Tumors by performing computed tomography of the chest and abdomen, and magnetic resonance imaging of the head and a bone scintiscan.[12] All patients were evaluated every 2 cycles or every 2 months. All categorical variables were analyzed by χ^2 test or the Fisher exact test, as appropriate. Clinical evaluation of progression-free survival (PFS) and overall survival (OS) after the start of second-line chemotherapy was conducted by the Kaplan-Meier method to assess the time of recurrence or death. The log-rank test was used to compare cumulative survival in each group. We assessed toxicity by National Cancer Institute Common Toxicity Criteria, version 2.0. All P values were reported as 2 sided, and values <0.05 were considered statistically significant. All statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC).

The study protocol was approved by the Institutional Review Board of the Shizuoka Cancer Center.

TABLE 1. Sensitive-Relapse* SCLC Patient Characteristics for Rechallenge Group and Other Group

	Rechallenge Group (n = 19)	Other Group (n = 46)	P
Age at second-line chemotherapy (y)			0.24
Median	69	65.5	
Range	51-83	43-80	
Sex [n (%)]			0.14
Male	17 (89)	34 (74)	
Female	2 (11)	12 (26)	
PS at recurrence [n (%)]			0.33
0-1	18 (95)	40 (87)	
2-4	1 (5)	6 (13)	
Disease extent at diagnosis [n (%)]			0.20
LD	12 (63)	21 (46)	
ED	7 (37)	25 (54)	
Chemoradiation [n (%)]			0.77
Yes	9 (47)	20 (43)	
No	10 (53)	26 (57)	
Prophylactic cranial irradiation [n (%)]			0.09
Yes	7 (37)	8 (17)	
No	12 (63)	38 (83)	
Response to first-line therapy [n (%)]			0.88
CR/PR	18 (95)	44 (96)	
SD/PD	1 (5)	2 (4)	
Treatment-free interval (mo)			0.01
Median	7.1	4.8	
Range	3.1-39.2	3.0-8.7	

*Defined as TFI ≥ 90 days.

CR indicates complete response; ED, extended disease; LD, limited disease; PD, progressive disease; PR, partial response; PS, performance status; SCLC, small cell lung cancer; SD, stable disease; TFI, treatment-free interval.

RESULTS

Patient Characteristics

Of the 65 sensitive-relapse SCLC patients who received second-line chemotherapy, 19 were placed in the rechallenge group and 46 in the other group, including 21 patients treated with amrubicin. The sensitive-relapse patient characteristics are listed in Table 1. No significant differences in age, sex, ECOG performance status at relapse, disease extent at diagnosis, or response to first-line treatment were found between the 2 groups. PCI was more frequent in the rechallenge group. TFI was significantly longer in the rechallenge group than in the other group. In the rechallenge group, etoposide and platinum were used in 68% of the patients as second-line chemotherapy. In the other group, 46% of the patients were treated with amrubicin, and 11% were treated with topotecan (Table 2).

Both groups included 11 ex-sensitive-relapse patients; their characteristics are listed in Table 3. There were also no significant differences in patient characteristics and response to first-line treatment.

Response

Response to second-line chemotherapy in sensitive-relapse and ex-sensitive-relapse SCLC patients is shown in Table 4. In the sensitive-relapse patients, there was no significant difference in response between the rechallenge group and the other group (ORR: rechallenge group 37% vs. other group 44%, $P = 0.62$). ORR in patients treated with amrubicin was 38% and was not significantly different compared with the rechallenge group ($P = 0.93$). In the ex-sensitive-relapse patients, there was also no significant difference in ORR between the 2 groups (rechallenge group 46% vs. other group 55%, $P = 0.67$).

PFS and OS

In the sensitive-relapse patients, there was no significant difference in OS from the start of second-line chemotherapy between the 2 groups (MST: rechallenge group 14.4 mo vs.

TABLE 2. First-Line and Second-Line Chemotherapy of Sensitive-Relapse* SCLC Patients in Rechallenge Group and Other Group

	Rechallenge Group (n = 19)	Other Group (n = 46)
First-line chemotherapy [n (%)]		
Cisplatin and etoposide	7 (36)	20 (43)
Carboplatin and etoposide	6 (32)	10 (22)
Cisplatin and irinotecan	6 (32)	14 (30)
Other	0	2 (5)
Second-line chemotherapy [n (%)]		
Cisplatin and etoposide	7 (36)	1 (2)
Carboplatin and etoposide	6 (32)	2 (4)
Cisplatin and irinotecan	6 (32)	0 (0)
Amrubicin	0	21 (46)
Irinotecan	0	10 (22)
Topotecan	0	5 (11)
Other	0	7 (15)

*Defined as TFI ≥ 90 days.

SCLC indicates small cell lung cancer; TFI, treatment-free interval.

TABLE 3. Ex-Sensitive Relapse SCLC Patient Characteristics in Rechallenge Group and Other Group

	Rechallenge Group (n = 11)	Other Group (n = 11)	P
Age at second-line chemotherapy (y)			0.72
Median	69	69	
Range	52-79	48-79	
Sex [n (%)]			0.26
Male	10 (91)	8 (73)	
Female	1 (9)	4 (27)	
PS at recurrence [n (%)]			0.26
0-1	10 (91)	8 (73)	
2-4	1 (9)	3 (27)	
Disease extent at diagnosis [n (%)]			0.65
LD	8 (73)	7 (64)	
ED	3 (27)	4 (36)	
Chemoradiation [n (%)]			0.37
Yes	8 (73)	6 (55)	
No	3 (27)	5 (45)	
Prophylactic cranial irradiation [n (%)]			0.19
Yes	5 (45)	3 (27)	
No	6 (55)	8 (73)	
Response to first-line therapy [n (%)]			0.23
CR/PR	11 (100)	10 (91)	
SD/PD	0 (0)	1 (9)	
Treatment-free interval (mo)			0.02
Median	268	207	
Range	182-1176	6.0-262	

*Defined as TFI ≥ 180 days.

CR indicates complete response; ED, extended disease; LD, limited disease; PD, progressive disease; PR, partial response; PS, performance status; SCLC, small cell lung cancer; SD, stable disease; TFI, treatment-free interval.

other group 13.1 mo, $P=0.51$) (Fig. 1A). There was also no significant difference in PFS (median PFS 5.6 vs. 4.9 mo, $P=0.15$) (Fig. 1B). In the patients treated with amrubicin, MST was 12.6 months and median PFS was 4.6 months. Comparing the rechallenge group with the patients treated with amrubicin, there were also no significant differences in OS and PFS (Figs. 2A, B).

In the ex-sensitive-relapse patients, there was no significant difference in OS from the start of second-line chemotherapy between the 2 groups (MST 15.7 vs. 26.9 mo, $P=0.46$) (Fig. 3A). There was also no significant difference in PFS (median PFS 7.8 vs. 4.9 mo, $P=0.63$) (Fig. 3B).

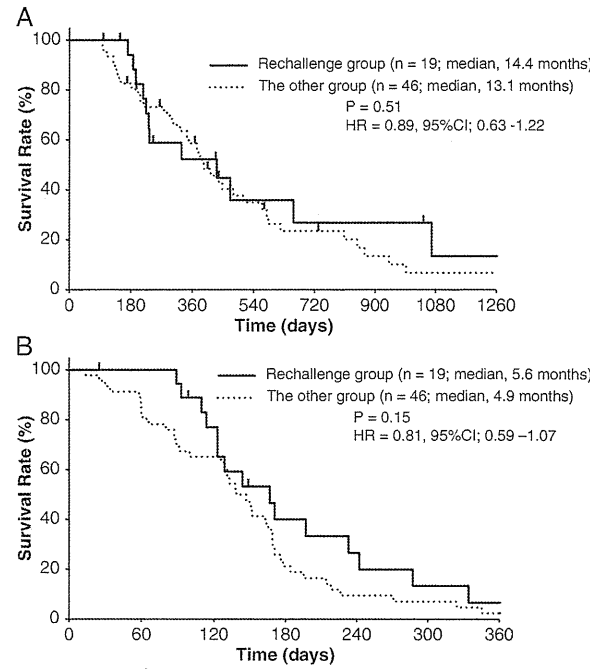

FIGURE 1. (A) Overall survival and (B) progression-free survival in sensitive-relapse SCLC patients in the rechallenge chemotherapy group and other regimen group. SCLC indicates small cell lung cancer.

Safety

Toxicity was evaluated in both group patients. The most common grade 3 or worse adverse events were hematologic toxicity and included neutropenia (rechallenge group 94% vs. other group 61%, $P=0.02$), thrombocytopenia (rechallenge group 26% vs. other group 22%, $P=0.76$), and anemia (rechallenge group 10% vs. other group 26%, $P=0.29$). Febrile neutropenia was noted in 3 rechallenge group patients (16%) and 2 other group patients (4%). No patients experienced nonhematologic toxicities worse than grade 3.

DISCUSSION

This study could not show the superiority of rechallenge chemotherapy over other regimens in sensitive-relapse SCLC patients. As TFI is a prognostic factor,[13,14] we analyzed treatment efficacy after adjusting the value. Although TFI was

TABLE 4. Response to Second-Line Chemotherapy in Sensitive-Relapse and Ex-Sensitive-Relapse SCLC Patients

	Sensitive Relapse (TFI ≥ 90 d) [n (%)]			Ex-Sensitive Relapse (TFI ≥ 180 d) [n (%)]	
	Rechallenge Group	Other group	Amrubicin	Rechallenge Group	Other Group
CR	1 (5)	0 (0)	0 (0)	1 (9)	0 (0)
PR	6 (32)	20 (44)	8 (38)	4 (37)	6 (55)
SD	9 (47)	17 (37)	7 (33)	3 (27)	3 (27)
PD	0 (0)	9 (19)	6 (29)	0 (0)	2 (18)
NE	3 (16)	0 (0)	0 (0)	3 (27)	0 (0)
ORR (%)	37	44	38	46	55
95% CI	19—59	30-57	20-59	21-72	28-78
P	—	0.62*	0.93*	—	0.67*

*Compared with the rechallenge group.

95% CI indicates 95% confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; TFI, treatment-free interval.

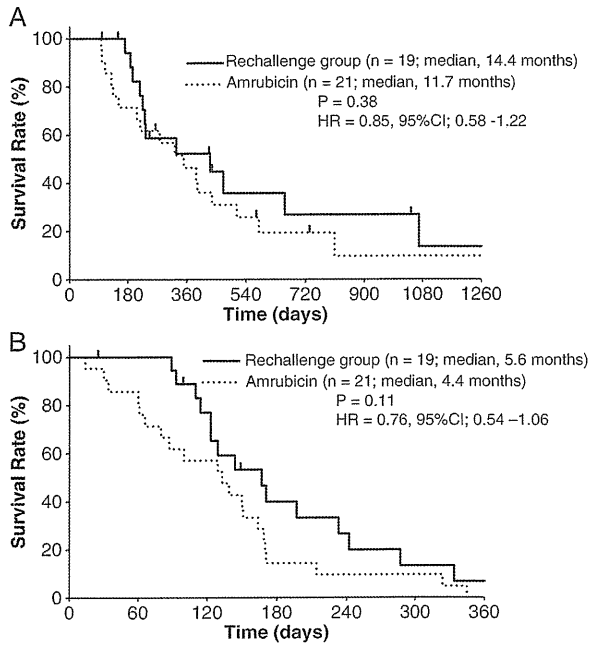

Figure 2. (A) Overall survival and (B) progression-free survival in sensitive-relapse SCLC patients in the rechallenge group and those taking amrubicin in the other group. SCLC indicates small cell lung cancer.

significantly longer in the rechallenge group than in the other group, rechallenge chemotherapy did not show significant differences in ORR, PFS, or OS compared with the other chemotherapies. In our study, neutropenia was more frequently observed in rechallenge group. Because a cure cannot be expected in relapsed SCLC, the purpose of second-line chemotherapy is improvement of prognosis and quality of life.[15] When quality of life and treatment results are taken into account, less toxic monotherapy may be reasonable.

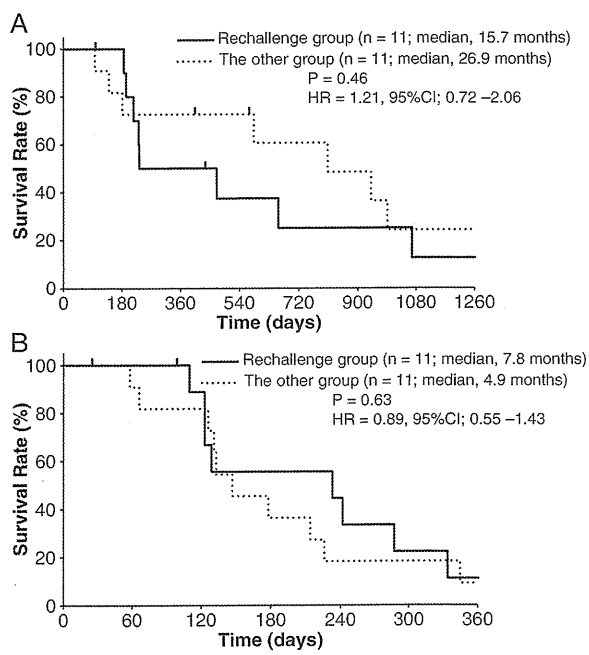

Figure 3. (A) Overall survival and (B) progression-free survival in ex-sensitive-relapse SCLC patients in the rechallenge group and other group. SCLC indicates small cell lung cancer.

Moreover, in comparing amrubicin with rechallenge chemotherapy, similar results were obtained. In the rechallenge group in this study, ORR was 37% whereas in previous reports it was 50% to 62%.[7,8] In this study, median TFI in rechallenge chemotherapy was 20 weeks, but in previous reports it was 30 to 34 weeks. These results suggest that the difference in TFI might have led to the difference in ORR.

At this time, clinical evidence of second-line chemotherapy for relapsed SCLC patients is limited. The number of randomized trials is small, and topotecan is the only established drug.[4–6] Amrubicin is a synthetic 9-amino-anthracycline, which showed response rates of 50% to 53% in 2 phase II trials.[16,17] In phase II trials comparing topotecan with amrubicin, the efficacy of amrubicin was promising.[9,10] On the basis of the results, a phase III trial was conducted.[11] However, this trial was unable to show the superiority of amrubicin over topotecan. MST with amrubicin was 9.2 months compared with 9.9 months with topotecan ($P=0.62$; HR, 0.88).

Although several guidelines recommend rechallenge chemotherapy for sensitive-relapse SCLC patients, the recommendation is not based on randomized trials. In addition, the reported induction chemotherapy regimens were not platinum based. Garassino et al[18] evaluated the clinical outcomes of SCLC patients who received second-line chemotherapy after platinum-etoposide chemotherapy. In their report, platinum-based rechallenge showed significant better results in ORR and OS than other chemotherapy regimens for sensitive-relapse and refractory-relapse SCLC patients. A platinum-containing regimen showed better results independently of the time to second-line therapy. However, there is a difference in subjects between our study and Garassino's report. We evaluated only sensitive-relapse SCLC patients. In addition, 46% of the patients received amrubicin in our study, whereas 44.8% of the patients received anthracycline-based regimens such as CAV in Garassino's report.

Our study had several limitations. First, the sample size was small and the timing of response assessment was decided by each physician, which might have resulted in variance of ORR and PFS. Second, we did not assess the influence of PCI, which is known to improve the prognosis.[19] Although the patients in the rechallenge group received more frequent PCI, there was no significant difference in ORR, PFS, or OS between the 2 groups. However, there are a few reports that evaluated the rechallenge chemotherapy for sensitive-relapse SCLC patients with the currently standard regimen.

In conclusion, superiority of rechallenge chemotherapy over other chemotherapies could not be demonstrated. The results suggest that monotherapy, such as amrubicin, may be reasonable as second-line chemotherapy for sensitive-relapse SCLC patients.

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A phase II study of S-1 in relapsed small cell lung cancer

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Abstract. S-1 is a new oral fluoropyrimidine derivative designed to enhance anticancer activity and reduce gastrointestinal toxicity. This phase II trial aimed to evaluate S-1 in patients with relapsed small cell lung cancer (SCLC). SCLC patients who had experienced treatment failure with ≥1 prior chemotherapies were eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 and adequate organ function. Treatment consisted of oral S-1 at 40 mg/m^2 twice/day for 28 days every 6 weeks. Twenty-six patients were enrolled, 85% of whom were males. The median age was 68 years (range, 33-79) and 81% of the patients had a performance status of 0-1, and 46% of the patients had relapse-sensitive SCLC. An objective response was obtained in only 1 patient (3.8%), and the median progression-free survival (PFS) was 1.1 months. The median overall survival was 5.3 months, and the 1-year survival rate was 23%. The most common grade 3/4 toxicities included neutropenia (7.7%), leukopenia (7.7%), anemia (7.7%), hyponatremia (7.7%), rash (7.7%), infection (7.7%) and diarrhoea (3.8%). None of the patients developed febrile neutropenia and no deaths were attributed to treatment. In conclusion, S-1 has minimal single-agent activity in relapsed SCLC.

Introduction

Lung cancer is the leading cause of mortality in Japan, and small cell lung cancer (SCLC) accounts for 15-20% of all the types of lung cancer (1). Although SCLC is an extremely chemosensitive disease, it is ultimately fatal in the majority of patients. Several anticancer agents tested over the last three decades have demonstrated some activity, but there have been only minimal improvements in the treatment of extensive SCLC (2).

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Key words: lung cancer, small cell lung cancer, S-1, relapse

Based on the findings of a randomized trial comparing topotecan with cyclophosphamide, doxorubicin and vincristine in patients with relapse-sensitive SCLC, topotecan was considered to be a standard treatment in the second-line setting (3). However, the response rate ranged from 7 to 21%, with a median survival time of only 6 months (3). Therefore, additional options are needed for patients with relapsed SCLC.

S-1 is a novel oral fluoropyrimidine anticancer agent designed to enhance anticancer activity and reduce gastrointestinal toxicity. It is a combination of an oral fluoropyrimidine (tegafur), a dihydropyrimidine dehydrogenase (DPD) inhibitor (5-chloro-2,4-dihydroxypyridine), and an orotate phosphoribosyl transferase inhibitor (potassium oxonate) (4). Although 5-fluorouracil (5-FU) was thought to be inactive against non-small cell lung cancer (NSCLC) and SCLC (5,6), single-agent S-1 has been shown to provide one of the highest response rates against metastatic NSCLC and previously treated NSCLC (7). In addition, the combination of S-1 and cisplatin or carboplatin has been evaluated in Japanese phase III studies. The results of a phase III trial demonstrated the non-inferiority of carboplatin/S-1 compared to carboplatin/paclitaxel in terms of overall survival time (OS) (8). Most of the agents that are active against NSCLC have been tested and have also exhibited activity against SCLC. However, the activity of S-1 against SCLC has not been determined. Therefore, this study aimed to examine the activity of S-1 in patients with relapsed SCLC.

Materials and methods

Study subject criteria. Eligible patients had histologically or cytologically confirmed SCLC. The patients were ≥20 years, had measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, and adequate bone marrow, kidney and liver functions. Patients were required to have received at least 1 prior chemotherapy regimen (including 1 regimen containing a platinum agent). Relapse-refractory and -sensitive patients were eligible. Patients who had undergone radiation therapy were required to have had their last treatment at least 14 days prior to registration in the protocol.

Patients were excluded due to symptomatic central nervous system metastasis, uncontrolled pleural effusion, pregnancy or lactation, the use of phenytoin, warfarin or flucytosine,

or medical problems of marked severity. Patients previously treated with S-1 were not eligible. The treatment protocol was approved by the Investigational Review Board of the Cancer Institute Hospital (Tokyo, Japan). Patients provided written informed consent.

Study design and sample size. This study was an open-label, single-institution, phase II study of the single-agent S-1 for patients with previously treated SCLC. Simon's two-stage optimal design was chosen to determine the total number of patients required for this phase II study. A response rate of 25% was set for the target activity level, with 5% as the lowest response rate [objective response rate (ORR)] of interest. The study was designed to have 90% power to accept and 10% significance to reject the hypothesis. The planned sample size was fixed at 26 patients without test power consideration. If >2 responses were observed by the end of the study, further investigation of the drug was considered necessary.

Treatment plan. Treatment consisted of oral administration of S-1 at 40 mg/m^2 twice/day for 28 days, every 6 weeks. The actual dose of S-1 was selected as follows: for a patient with body surface area (BSA) <1.25 m^2, 40 mg twice/day; for BSA of 1.25 m^2 but <1.5 m^2, 50 mg twice/day; and for BSA 1.5 m^2, 60 mg twice/day.

Statistical analysis. Intention-to-treat analysis considering the patients was performed. The safety analysis was based on the patients that had received any dose of study treatment. The primary endpoint was best ORR according to the Response Evaluation Criteria in Solid Tumors. Secondary efficacy endpoints were overall survival time (OS), progression-free survival time (PFS) and toxicity profile. OS and PFS were estimated using the Kaplan-Meier method. Toxicities were graded according to the Common Toxicity Criteria version 3.0.

Results

Patient characteristics. Between September, 2006 and May, 2008, 26 patients were enrolled in this study. Patient characteristics are summarized in Table I. The median age was 68 years (range, 33-79), and 81% of the patients had an ECOG PS of 0-1. The median number of previous chemotherapy treatment regimens was 2 (range, 1-3) and 54% of the patients received ≥2 regimens. There were 12 relapse-sensitive patients (46%) and 14 relapse-refractory patients (54%).

Treatment administration. The median number of S-1 cycles administered was 2 (range, 1-5). Twenty patients received 1 cycle due to disease progression (16 patients) or treatment-related toxicities (dermatitis and infection in 2 patients, respectively). No dose delays or modifications were required. The patients were included in the efficacy analyses.

Response and survival. Response to treatment and survival of patients is shown in Table II. Among the relapse-sensitive patients, partial response was achieved in 1 (8.3%) and stable disease in 4 patients (33.3%). Among the relapse-refractory patients, no patient (0%) had a partial response and 6 patients (42.8%) achieved stable disease. Progressive disease as the best response was noted in 7 (58.3%) of the relapse-sensitive patients and in 8 (57.1%) of the relapse-refractory patients. The median time to disease progression was 1.1 months [95% confidence interval (CI), 0.9-1.2 months]. The median overall survival was 5.3 months (95% CI, 2.9-7.7 months), while the 1-year survival rate was 23%.

Table I. Patient characteristics.

Characteristics	Value
No. of patients	26
Median age (years), n (range)	68 (33-79)
Gender, n (%)	
Male	22 (85)
Female	4 (15)
Performance status, n (%)	
0	16 (62)
1	5 (19)
2	5 (19)
Prior chemotherapy regimens, n (%)	
1	12 (46)
2	9 (35)
3	5 (19)
Relapse-sensitive cases, n (%)	12 (46)
Relapse-refractory cases, n (%)	14 (54)

Toxicity. Treatment-related toxicity is shown in Table III. In general, S-1 was well-tolerated. No patient developed febrile neutropenia or died due to the treatment.

Discussion

This phase II study was the first study to evaluate the activity of single-agent S-1 against relapsed SCLC. However, poor response rates were detected, and the majority of patients had early progressive disease. Single-agent S-1 has minimal activity in patients with previously treated SCLC, including those with a previous chemotherapy-sensitive disease.

Results similar to S-1 have been reported for another agent, pemetrexed. Since several clinical studies on NSCLC demonstrated positive findings, pemetrexed has also been thought to act against NSCLC (9). The efficacy of pemetrexed against SCLC has been examined in several studies (10-12). However, the results of those studies have been negative.

S-1 and pemetrexed have common characteristics. The primary cytotoxic mechanism of both S-1 and pemetrexed is the inhibition of thymidylate synthase (TS) (13,14). Recent clinical trials have demonstrated that pemetrexed efficacy varied according to the histologic types of lung cancer (9,11,12).

A possible explanation may involve TS expression levels in different histologic types of lung cancer, since preclinical data have shown that overexpression of TS correlates with reduced sensitivity to pemetrexed and 5-FU derivatives (15,16). The baseline expression of TS is markedly higher in squamous cell carcinoma compared to adenocarcinoma (15,16). In addition,

Table II. Response to treatment, time to progression and overall survival of patients.

Response	Patients, n (%)		
	Relapse-sensitive (n=12)	Relapse-refractory (n=14)	Total (n=26)
Best response to treatment			
Complete	0 (0)	0 (0)	0 (0)
Partial	1 (8.3)	0 (0)	1 (3.8)
Stable disease	4 (33.3)	6 (42.8)	10 (38)
Progressive disease	7 (58.3)	8 (57.1)	15 (58)
Objective response rate	1 (8.3)	0 (0)	1 (3.8)
Disease control rate	5 (41.6)	6 (42.8)	11 (42.3)
Median time to progression (days)	34	32	33
Median overall survival (months)	8.4	4.0	5.3

Table III. Haematological and non-haematological toxicities.

Toxicity	Grade				
	1	2	3	4	3/4 (%)
Haematological					
Leukopenia	9	6	2	0	7.7
Neutropenia	9	2	1	1	7.7
Febrile neutropenia	0	0	0	0	0
Anaemia	13	5	1	1	7.7
Thrombopenia	2	0	2	0	7.7
Non-haematological					
Aspartate aminotransferase	8	0	1	0	3.8
Alanine aminotransferase	3	2	1	0	3.8
Hyponatremia	16	-	0	2	7.7
Hypokalemia	0	0	2	0	7.7
Anorexia	20	6	0	0	0
Nausea	6	4	0	0	0
Diarrhoea	5	3	1	0	3.8
Rash	4	3	2	0	7.7
Malaise	15	2	0	0	0
Infection without neutropenia	0	2	2	0	7.7

TS expression in neuroendocrine tumors has been examined, and higher TS expression was observed in SCLC and large cell neuroendocrine carcinoma compared to other types of lung cancer (17,18).

However, in contrast with pemetrexed, findings of phase II and III trials of S-1 against NSCLC did not demonstrate any obvious differences in the efficacy of S-1 against squamous and non-squamous NSCLC (7).

The reason for this discrepancy between pemetrexed and S-1 is unclear. S-1 may be able to inhibit higher levels of TS compared to pemetrexed. However, TS activity in SCLC may be considerably higher than S-1 can inhibit, since expression of TS in SCLC was shown to be markedly higher compared to TS expression in squamous cell carcinoma (17).

In addition, DPD inhibition may play an important role in NSCLC compared to SCLC. Several studies have demonstrated that 5-FU sensitivity is affected by DPD expression, which is an enzyme in NSCLC affecting 5-FU catabolism (19-22).

In conclusion, S-1 monotherapy is well-tolerated but has low activity in patients with relapsed previously treated SCLC patients, including those with a previous chemotherapy-sensitive disease. Findings of this study have shown that S-1 has minimal single-agent activity in relapsed SCLC.

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