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.

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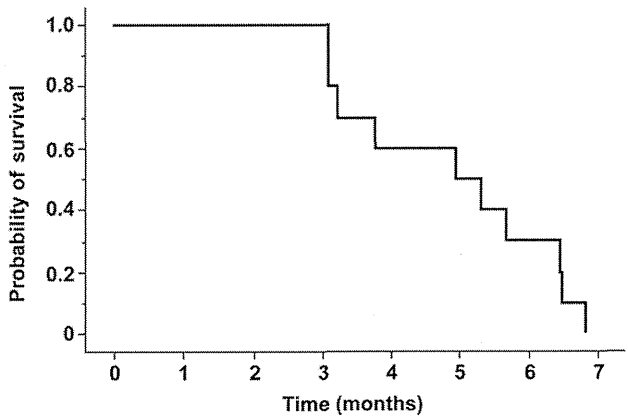

Figure 1. Progression-free survival. Median: 5.1 months (95% confidence interval [CI]: 3.9–5.8).

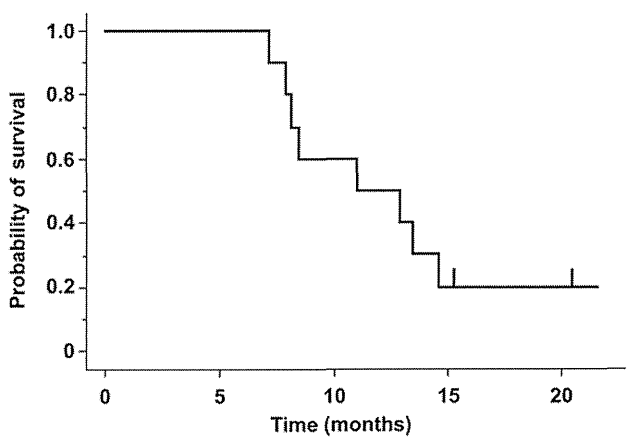

Figure 2. Overall survival. Median: 10.9 months (95% CI: 7.6–16.8).

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.

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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.

Funding

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Conflict of interest statement

None declared.

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Original Study

A Randomized Phase III Study of Single-Agent Amrubicin Vs. Carboplatin/Etoposide in Elderly Patients With Extensive-Disease Small-Cell Lung Cancer

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Abstract

This study compared amrubicin monotherapy with carboplatin/etoposide combination therapy in elderly Japanese patients with extensive-disease small-cell lung cancer (ED-SCLC). The trial was prematurely closed owing to 3 treatment-related deaths in the amrubicin arm. Overall survival in the amrubicin and carboplatin/etoposide arms was 10.9 months and 11.3 months, respectively. Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable in elderly Japanese patients with ED-SCLC.

Introduction: The efficacy and safety of amrubicin, a third-generation synthetic anthracycline, were evaluated by comparison with carboplatin/etoposide combination therapy in elderly Japanese patients with extensive-disease small-cell lung cancer (ED-SCLC). **Patients and Methods:** Eligibility included histologically or cytologically proven SCLC, no previous systemic chemotherapy, performance status of 0 to 2, and age $\geq$ 70 years. Patients received amrubicin (70-74 years old, 40-45 mg/m^2; $\geq$ 75 years old, 40 mg/m^2) intravenously on days 1 to 3 every 3 weeks for 4 to 6 cycles or carboplatin (area under the curve of 5 intravenously on day 1) and etoposide (80 mg/m^2 intravenously on days 1 to 3) every 3 weeks for 4 to 6 cycles. **Results:** The target number of patients was 130 with 65 in each arm. However, the study was terminated early owing to 3 treatment-related deaths in the amrubicin arm, and only 62 patients (median age, 76 years; range, 70-88 years) were enrolled. The characteristics of the patients in the amrubicin and carboplatin/etoposide arms did not differ significantly. Overall survival, time to progression, and objective response rate were 10.9 vs. 11.3 months (P = .7353), 4.7 vs. 4.4 months, and 74.2% (23 of 31) vs. 60.0% (18 of 30), respectively, and quality of life showed no significant difference between the 2 arms. Higher incidences of febrile neutropenia and interstitial lung disease of grade 3 or worse occurred with amrubicin (34.4% vs. 3.3% and 12.5% vs. 0%, respectively). **Conclusion:** These results indicate that amrubicin monotherapy at 40 to 45 mg/m^2 is toxic and intolerable in elderly Japanese patients with ED-SCLC.

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Keywords: Chemotherapy, Interstitial lung disease, Pulmonary disease, Pulmonary toxicity, Treatment-related death

Introduction

Small-cell lung cancer (SCLC) has an extremely poor prognosis, despite initially being highly sensitive to chemotherapy and radiotherapy.[1,2] Approximately 30% to 40% of patients with SCLC are $\geq$ 70 years old at diagnosis.[3] Cases with extensive disease (ED) spreading beyond one hemithorax account for 60% to 70% of patients with SCLC. The standard therapy for ED-SCLC is systemic chemotherapy alone, which results in tumor shrinkage and

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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

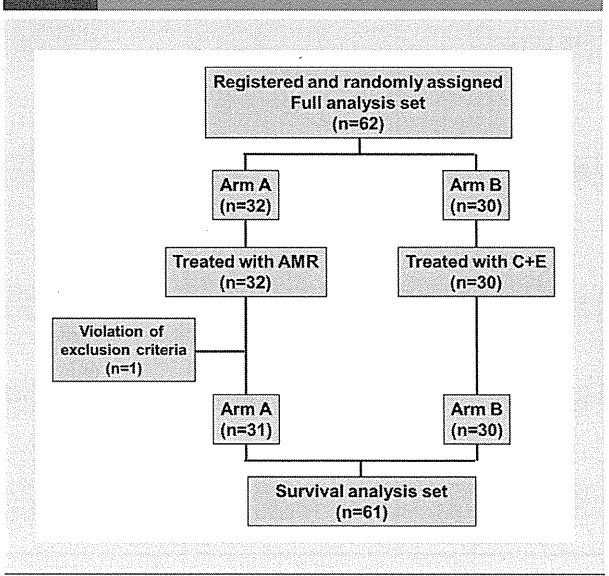
The eligibility criteria were histologically or cytologically proven SCLC; no previous chemotherapy; measurable disease; age $\geq$ 70 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; life expectancy of $\geq$ 2 months; adequate bone marrow function (white blood cell count 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 $\geq$ 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 ($\geq$ 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)		
	n	(%)	n	(%)	*P*
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)

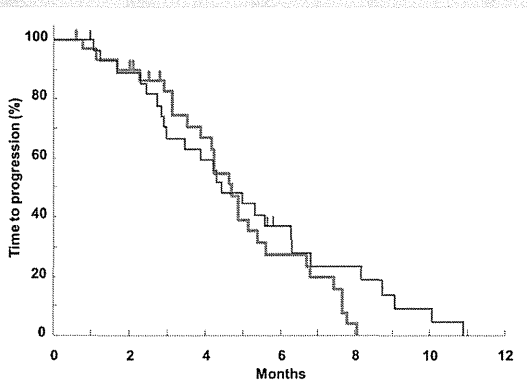
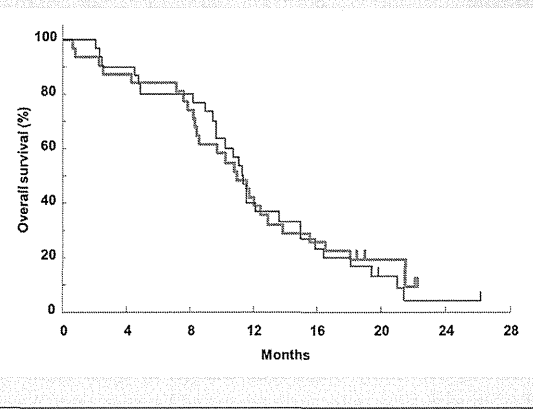


Figure 3 Overall Survival in Arm A (Amrubicin, n = 31; Pink) and Arm B (Carboplatin/Etoposide, n = 30; Blue). The Median Survival Times Were 10.9 Months and 11.3 Months for Arms A and B, Respectively (P = .74 by log-Rank Test)



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)

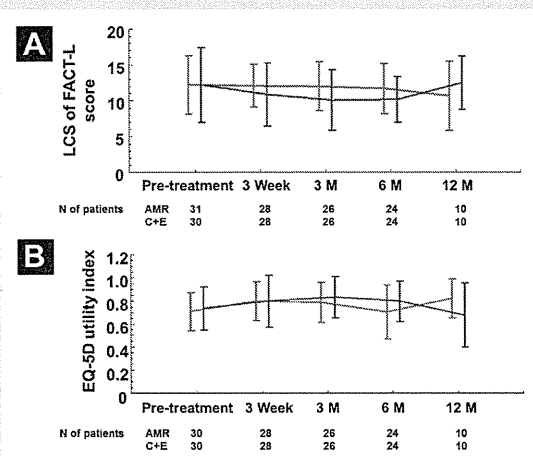
Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide.

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]

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.

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

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

The study was sponsored by Dainippon Sumitomo Pharma Co Ltd, Osaka, Japan. Dr Fukuoka received an advisory fee from Dainippon Sumitomo Pharma Co Ltd. All other authors state that they have no conflicts of interest.

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Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study

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Summary

Background Four cycles of etoposide plus cisplatin and accelerated hyperfractionated thoracic radiotherapy (AHTRT) is the standard of care for limited-stage small-cell lung cancer (SCLC). Irinotecan plus cisplatin significantly improved overall survival compared with etoposide plus cisplatin for extensive-stage SCLC. We compared these regimens for overall survival of patients with limited-stage SCLC.

Methods We did this phase 3 study in 36 institutions in Japan. Eligibility criteria included age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ functions. Eligible patients with previously untreated limited-stage SCLC received one cycle of etoposide plus cisplatin (intravenous etoposide 100 mg/m² on days 1–3; intravenous cisplatin 80 mg/m² on day 1) plus AHTRT (1·5 Gy twice daily, 5 days a week, total 45 Gy over 3 weeks). Patients without progressive disease following induction therapy were randomised (1:1 ratio, using a minimisation method with biased-coin assignment balancing on ECOG performance status [0 *vs* 1], response to induction chemoradiotherapy [complete response plus near complete response *vs* partial response and stable disease], and institution) to receive either three further cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin (intravenous irinotecan 60 mg/m² on days 1, 8, 15; intravenous cisplatin 60 mg/m² on day 1). Patients, physicians, and investigators were aware of allocation. The primary endpoint was overall survival after randomisation; primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00144989, and the UMIN Clinical Trials Registry, number C000000095.

Findings 281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. After induction etoposide plus cisplatin and AHTRT, 258 patients were randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1). In the irinotecan and cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6); overall survival did not differ between the two groups (hazard ratio 1·09 [95% CI 0·80–1·46], one-sided stratified log-rank p=0·70). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). There was one treatment-related adverse event leading to death in each group (radiation pneumonitis in the etoposide plus cisplatin group; brain infarction in the irinotecan plus cisplatin group).

Interpretation Four cycles of etoposide plus cisplatin and AHTRT should continue to be the standard of care for limited-stage SCLC.

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Introduction

The shift from non-filter to filter tobacco has resulted in a decrease in small-cell and squamous-cell lung cancer, and an increase in adenocarcinoma of the lung.[1] Currently, small-cell lung cancer (SCLC) accounts for 13% of all lung cancer, and about a third of patients with SCLC have limited-stage disease—ie, disease confined to the hemithorax.[2]

Combination chemotherapy is the cornerstone of SCLC treatment, and meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5–7] have shown that early use of concurrent thoracic radiotherapy results in improved overall survival compared with sequential or late use when etoposide and cisplatin are used as combination

chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC resulted in significantly improved overall survival compared with standard fractionation, once-daily irradiation, with 5-year survival of 26% and 16%, respectively. Thus, etoposide plus cisplatin and AHTRT is now the standard of care in patients with limited-stage SCLC. However, many patients with limited-stage SCLC experience tumour recurrence and die from the disease, showing the need for improved therapy.

The Japan Clinical Oncology Group (JCOG) previously undertook a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin with etoposide plus cisplatin in patients with extensive-stage SCLC. Response and overall survival were significantly better for patients treated with irinotecan than those treated with etoposide. The result prompted us to explore the use of irinotecan and cisplatin in limited-stage SCLC. A phase 2 study[10] showed that irinotecan and cisplatin after concurrent etoposide plus cisplatin plus AHTRT for limited-stage SCLC was safe with acceptable side-effects, and the 3-year survival of 38% of patients was encouraging.

Therefore, we did a randomised phase 3 trial to compare overall survival of patients with limited-stage SCLC given three cycles of irinotecan plus cisplatin or etoposide plus cisplatin after one cycle of induction etoposide plus cisplatin and concurrent AHTRT.

Methods

Study design and participants

We did this randomised, open-label, phase 3 study in 36 institutions in Japan (appendix). We enrolled patients with histologically or cytologically confirmed limited-stage SCLC—defined as disease confined to one hemithorax, including ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases. Pleural effusion of less than 1 cm width by chest CT was defined as limited-stage disease; malignant pleural effusion was defined as extensive-stage disease and excluded from the study. Additional eligibility criteria consisted of measurable disease, age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no previous treatment for SCLC, no history of anticancer chemotherapy, 4000 leucocytes per μL or greater, 10^5 platelets per μL or greater, haemoglobin of 90 g/L or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aspartate aminotransferase of 100 IU/L or less, serum alanine aminotransferase of 100 IU/L or less, and partial pressure of oxygen of 9·33 kPa or greater. Consultation with a radiation oncologist was mandated before enrolment. We included patients aged between 20 years and 70 years because the previous JCOG trial[9] (JCOG9511) comparing irinotecan and cisplatin with etoposide plus cisplatin for extensive-stage SCLC included only patients aged 70 years or younger.

Exclusion criteria were active concomitant malignancy, active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 6 months, unstable angina, uncontrollable hypertension or diabetes mellitus, interstitial pneumonia or active lung fibrosis on chest radiograph, psychiatric disease, malignant pericardial effusion, diarrhoea, intestinal obstruction or paralysis, and concurrent administration of any oral or intravenous steroid. We excluded pregnant or lactating women.

All patients enrolled in the study underwent an induction therapy of one cycle of etoposide plus cisplatin with concurrent AHTRT, eligible patients were registered again and randomised to consolidation chemotherapy consisting of three cycles of etoposide plus cisplatin or irinotecan plus cisplatin. The second registration eligibility criteria were: within 49 days from the first registration, ECOG performance status of 0–1, 3000 leucocytes per μL or greater, 10^5 platelets per μL or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aminotransferase of 100 IU/L or less, no fever or diarrhoea within 24 h, no pulmonary infiltration beyond the radiation portal, no active infection, radiation dermatitis or oesophagitis of grade 2 or less, completion of induction chemoradiotherapy, no progressive disease, and tumour response to induction chemoradiotherapy as assessed by chest CT (complete response, near complete response, partial response, or stable disease). Because almost all patients with limited-stage SCLC are admitted to hospital during induction chemoradiotherapy in Japan, chest CT assessment within the specified timeframe was not problematic. The assessment of response to chemoradiation was done after day 23, counted from the start of induction chemoradiotherapy.

The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review boards of the participating institutions. All patients provided written informed consent.

Procedures

Induction chemotherapy consisted of intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3. AHTRT was begun on day 2 of induction chemotherapy and administered twice daily, 5 days a week, (1·5 Gy per fraction, with 6 h or more between fractions) to a total dose of 45 Gy in 3 weeks. 30 Gy was delivered with 6–10 MV photons using anterior–posterior opposed fields that included the primary tumour; metastatic lymph nodes; and regional nodes, excluding the contralateral hilar nodes. Supraclavicular lymph nodes were also included when involved. A booster dose of 15 Gy was delivered to the primary tumour and metastatic lymph nodes. Conventional two-dimensional radiograph simulation and three-dimensional CT simulation were allowed for treatment planning; PET scanning was not required. The clinical target volume was equal to the gross tumour volume, including the primary tumour and metastatic nodes (1 cm or greater in shortest dimension).

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See Online for appendix

The planned target volumes for the primary tumour, metastatic lymph nodes, and regional nodes were defined as clinical target volume plus adequate margins (typically 0·5–1·0 cm laterally and 1·0–2·0 cm craniocaudally). The volume of the lung unaffected by cancer to receive 20 Gy or more was kept to 35% or less when three-dimensional CT simulation was used. Lung heterogeneity corrections were not used. If grade 3 non-haematological side-effects (excluding hyponatraemia, nausea, vomiting, and appetite loss), performance status of 3, grade 2 pneumonitis or pulmonary infiltrates, or a fever of 38·0°C or more developed, radiotherapy was withheld until recovery. Quality assurance reviews were done and the results are reported elsewhere.[11]

In the consolidation chemotherapy stage, patients assigned to etoposide plus cisplatin received intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3, repeated every 3 weeks for three cycles. Patients assigned to irinotecan plus cisplatin were treated every 3–4 weeks for three cycles; this regimen consisted of intravenous irinotecan 60 mg/m² on days 1, 8, and 15 and intravenous cisplatin 60 mg/m² on day 1. The doses of cisplatin were the same as in the previous JCOG trial (JCOG9511) in extensive-stage SCLC.[9]

If the leucocyte count decreased to less than 3000 leucocytes per μL or the platelet count fell below 10^5 platelets per μL on the first day of etoposide plus cisplatin or irinotecan plus cisplatin, chemotherapy was withheld until the counts recovered to above these cutoffs. Administration of irinotecan was skipped on day 8 or 15, or on both days, if the leucocyte count was less than 2000 leucocytes per μL, the platelet count was below 10^5 platelets per μL, or if there was any diarrhoea irrespective of grade, or a fever of 37·5°C or more. The dose of etoposide in subsequent cycles was reduced by 20 mg/m² from the planned dose if grade 4 leucopenia, grade 4 thrombocytopenia, or grade 3 non-haematological side-effects (excluding nausea, vomiting, appetite loss, hyponatraemia, and creatinine) developed. The dose of irinotecan in subsequent cycles was reduced by 10 mg/m² from the planned dose if grade 4 leucopenia or grade 4 thrombocytopenia, grade 2 or 3 diarrhoea, or grade 3 non-haematological side-effects (excluding nausea, vomiting, hyponatraemia, and creatinine) developed. The dose of cisplatin was reduced by 10 mg/m² if serum creatinine was higher than 132·60 μmol/L but not exceeding 176·80 μmol/L. Cisplatin was not administered if creatinine was higher than 176·80 μmol/L. Treatment was stopped in patients with non-haematological side-effects of grade 4.

Administration of granulocyte colony stimulating factor (G-CSF) was prohibited on the same days as chemotherapy or radiotherapy. Primary prophylactic G-CSF was not administered. For patients who had developed grade 4 neutropenia or grade 3 febrile neutropenia during previous cycles of chemotherapy, secondary prophylactic G-CSF administration was allowed. Prophylactic antibiotics were not administered.

Prophylactic cranial irradiation (25 Gy in ten fractions) was undertaken for patients showing a complete response or near complete response, defined as a reduction of 70% or more in the sum of the longest diameters of the target lesions.

Before enrolment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest radiograph, electrocardiogram, chest CT scan and whole-brain CT or MRI, abdominal ultrasound or CT, and isotope bone scans. Data regarding the time interval between diagnosis and start of concurrent chemoradiotherapy were not collected. Blood cell counts, differential white cell counts and other laboratory data were obtained weekly during induction chemoradiotherapy. All patients were reassessed at the end of consolidation chemotherapy with the same imaging assessments as at the time of enrolment. For efficacy assessments after the end of study treatment, patients were monitored once a month for 1 year and once every 3 months after 1 year. If progression was suspected on the basis of worsening symptoms or abnormal laboratory test values, the site of suspected progression was examined. If recurrence or progression was established, restaging including chest CT, brain MRI or CT, abdominal ultrasound or CT, and bone scintigraphy were done.

Responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Response was defined as the proportion of patients whose best overall response was complete reponse or partial response according to RECIST. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 2.0. Serious adverse events were defined as grade 4 non-haematological or grade 5 adverse events.

Randomisation and masking

After induction chemoradiotherapy, eligible patients were randomly assigned in a 1:1 ratio to receive either three cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin at the JCOG Data Center. Randomisation was done using a minimisation method with biased-coin assignment balancing on ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response and stable disease) and institution. Patients, treating physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation.

Statistical analysis

The primary endpoint was overall survival after randomisation. The planned sample size for randomisation was 250 and the expected number of events was 223, with a one-sided α of 2·5% and at least 70% power to detect a difference between groups, assuming 30·0% 3-year survival with etoposide plus cisplatin versus 42·5% with

irontecan plus cisplatin. Final analysis was planned 5 years after completion of accrual. Secondary endpoints were adverse events associated with induction chemoradiotherapy, adverse events associated with consolidation chemotherapy, late radiation morbidity after thoracic irradiation, adverse events during treatment with prophylactic cranial irradiation, incidence of serious adverse events, and progression-free survival after randomisation.

Progression-free survival was calculated from the date of randomisation until the date of documented progression or death (in the absence of progression). Overall survival was calculated from the date of randomisation until the date of death from any cause. Both intervals were estimated by the Kaplan-Meier method.

Three interim analyses were scheduled. The first interim analysis was to assess the futility of the trial after half the planned sample size was randomised. The second interim analysis was planned immediately after patient accrual was completed to decide whether the preplanned follow-up was necessary in terms of efficacy. The third interim analysis was planned 2 years after completion of accrual, with the same aim as the second interim analysis. Results of the interim analyses were reviewed by the JCOG Data and Safety Monitoring Committee and investigators were masked to the results. Multiplicity for analyses of the primary endpoint was adjusted with the O'Brien-Fleming type α-spending function.[12]

The primary endpoint, overall survival after randomisation, was analysed with the log-rank test, stratified by ECOG performance status (0 *vs* 1) and response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response plus stable disease). Hazard ratios (HR) were estimated with a Cox regression model, stratified by the same factors as the log-rank test. Unstratified log-rank tests and unstratified Cox regression models were used for all other analyses. The efficacy analyses were by modified intention to treat, including all patients enrolled at the second registration who did not violate any inclusion criteria. Safety analyses included all patients enrolled at the second registration who received at least one dose of study drug. Analyses were done by the JCOG Data Center using SAS (version 9.2).

This trial was registered with ClinicalTrials.gov, number NCT00144989 and UMIN Clinical Trials Registry, number C000000095.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. Four patients were shown to be ineligible after the first registration, three did not receive study treatment because of progressive disease, and two did not receive AHTRT, one because of an inappropriate radiation field and one because of an allergy to etoposide (figure 1). After the induction etoposide plus cisplatin plus AHTRT, 258 patients were enrolled at the second registration and

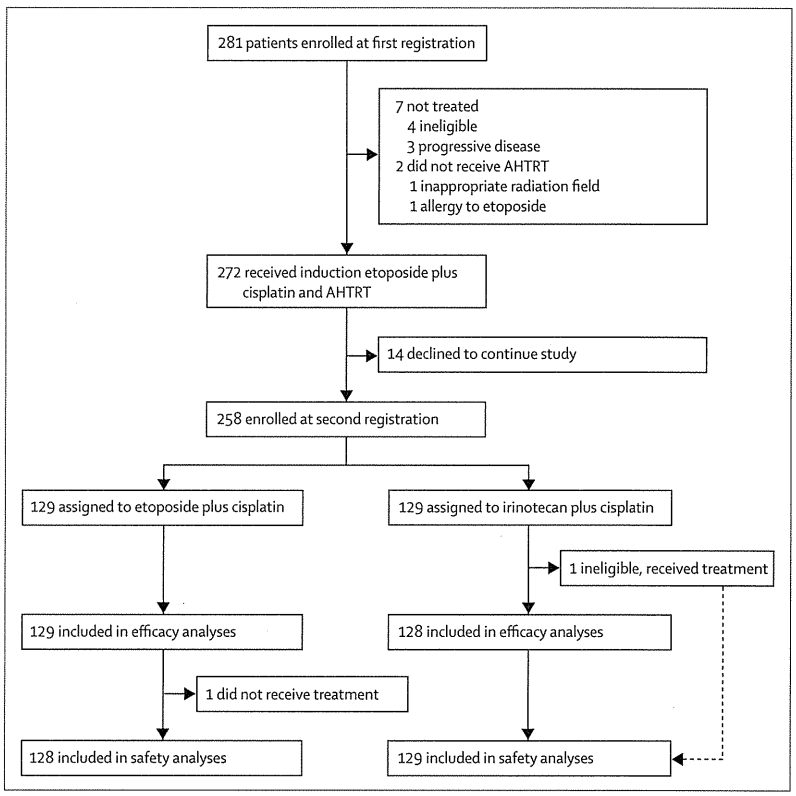

Figure 1: **Trial profile**
AHTRT=accelerated hyperfractionated thoracic radiotherapy.

	First registration (n=281)	Second registration	
		Etoposide and cisplatin (n=129)	Irinotecan and cisplatin (n=129)
Age (years)	61 (32–70)	60 (32–70)	62 (39–70)
Sex			
Men	228 (81%)	103 (80%)	106 (82%)
Women	53 (19%)	26 (20%)	23 (18%)
ECOG performance status			
0	170 (60%)	86 (67%)	85 (66%)
1	111 (40%)	43 (33%)	44 (34%)
Response to induction chemoradiotherapy*			
Complete response	..	3 (2%)	4 (3%)
Near complete response	..	28 (22%)	26 (20%)
Partial response	..	92 (71%)	87 (67%)
Stable disease	..	6 (5%)	12 (9%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *According to Response Evaluation Criteria In Solid Tumors (version 1.0).

Table 1: **Characteristics of patients**

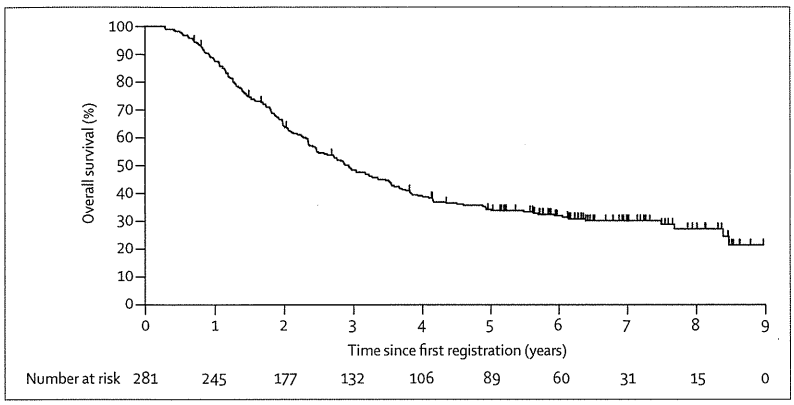

Figure 2: **Overall survival after first registration**
*One-sided p value from stratified log-rank test, with Eastern Cooperative Oncology Group performance status and response to induction chemoradiotherapy as strata.

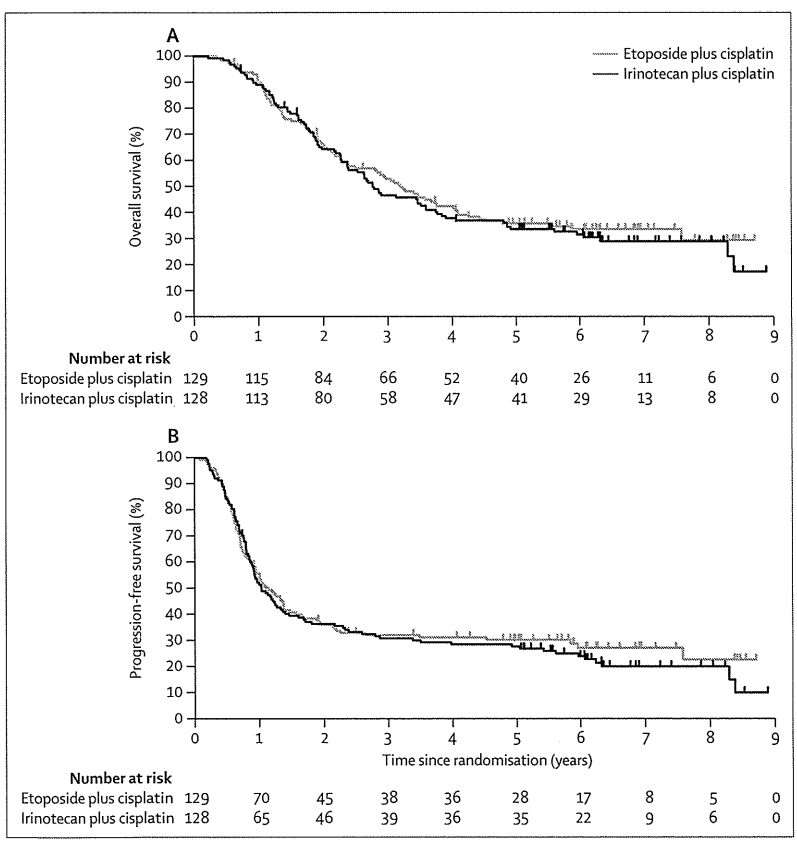

Figure 3: **Overall survival (A) and progression-free survival (B) after randomisation**
*p value from unstratified log-rank test.

randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). One patient in the irinotecan plus cisplatin group was shown to be ineligible after the second registration because of contralateral hilar node metastasis, this patient was excluded from the efficacy analyses, but included in the safety analyses. Table 1 shows the characteristics of the patients.

Of 129 patients who were randomised to the etoposide plus cisplatin group, 116 patients (90%) received three cycles of consolidation chemotherapy, four (3%) received two cycles, eight (6%) received one cycle, and one (1%) had no consolidation therapy. In the irinotecan plus cisplatin group, 110 of 128 (86%) patients received three cycles of consolidation chemotherapy, six (5%) received two cycles, 12 (9%) received one cycle. The main reasons for non-completion of three cycles of consolidation chemotherapy in the both groups were adverse events (eight patients in the etoposide plus cisplatin group, 12 patients in the irinotecan plus cisplatin group) and patient refusal because of adverse events (nine patients in the etoposide plus cisplatin group, 14 patients in the irinotecan plus cisplatin group); one patient in each group did not complete consolidation chemotherapy because of progressive disease. In the etoposide plus cisplatin group, 115 (89%) of 129 patients received at least 70% of the planned of dose of etoposide, and 116 (90%) of 129 received at least 70% of the planned dose of cisplatin; in the irinotecan plus cisplatin group, 88 (69%) of 128 received at least 70% of the planned dose of irinotecan and 110 (86%) of 128 received at least 70% of the planned dose of cisplatin. Prophylactic cranial irradiation was administered to 76 patients in the etoposide plus cisplatin group and 73 in the irinotecan plus cisplatin group.

Of 281 patients who entered into the first registration, median follow-up for the 88 censored patients was 6·3 years (IQR 5·6–7·2); median overall survival was 2·9 years (95% CI 2·5–3·5), 3-year overall survival was 48·4% (95% CI 42·4–54·1), and 5-year overall survival was 34·3% (28·7–39·9; figure 2). Of 257 patients included in the final analysis of the primary outcome, median follow-up for the 84 censored patients was 6·2 years (IQR 5·4–7·0); there were 173 events. In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1), 3-year overall survival was 52·9% (95% CI 43·9–61·1), and 5-year overall survival was 35·8% (27·4–44·1). In the irinotecan plus cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6), 3-year overall survival was 46·6% (37·7–55·1) and 5-year overall survival was 33·7% (25·5–42·0; HR 1·09 [95% CI 0·80–1·46]; p=0·70 from one sided stratified log-rank test; figure 3A). The results of the unstratified analysis did not differ from those of the stratified analysis (data not shown).

Figure 3B shows the Kaplan-Meier curves for progression-free survival in the two groups. Median progression-free survival was 1·1 years (95% CI 0·9–1·4) in the etoposide plus cisplatin group and 1·0 years (0·9–1·4) in the irinotecan plus cisplatin group (HR 1·10; 95% CI 0·83–1·45; p=0·74 from one sided unstratified log-rank test). In the etoposide group, 3-year progression-free survival was 32·0% (95% CI 24·1–40·1) and 5-year progression-free survival was 30·2% (22·4–38·3). In the irinotecan plus cisplatin group, these were 30·8% (23·0–38·9) and 27·7% (20·2–35·6), respectively.

	Etoposide plus cisplatin plus AHTRT*				Consolidation chemotherapy							
	Grade 1–2	Grade 3	Grade 4	N	Etoposide plus cisplatin				Irinotecan plus cisplatin			
					Grade 1–2	Grade 3	Grade 4	N	Grade 1–2	Grade 3	Grade 4	N
Leucopenia	16 (6%)	148 (54%)	109 (40%)	273	12 (9%)	81 (63%)	34 (27%)	128	28 (22%)	76 (59%)	25 (19%)	129
Anaemia	86 (32%)	1 (<1%)	0	273	76 (59%)	33 (26%)	11 (9%)	128	72 (56%)	42 (33%)	8 (6%)	129
Thrombocytopenia	108 (40%)	20 (7%)	0	273	56 (44%)	22 (17%)	4 (3%)	128	28 (22%)	6 (5%)	0	129
Neutropenia	12 (4%)	57 (21%)	203 (74%)	273	6 (5%)	33 (26%)	87 (68%)	128	28 (22%)	62 (48%)	39 (30%)	129
Hypoalbuminaemia	194 (72%)	0	..	271	102 (80%)	0	..	127	109 (84%)	0	..	129
Bilirubin	72 (26%)	1 (<1%)	0	272	20 (16%)	0	0	128	21 (16%)	0	0	129
Aspartate aminotransferase	54 (20%)	1 (<1%)	0	273	19 (15%)	1 (1%)	0	128	29 (22%)	0	0	129
Alanine aminotransferase	91 (33%)	4 (1%)	0	273	38 (30%)	1 (1%)	0	128	47 (36%)	0	0	129
Creatinine	67 (25%)	0	0	273	55 (43%)	0	0	128	35 (27%)	0	0	129
Fever	75 (27%)	0	0	274	28 (22%)	1 (1%)	0	128	33 (26%)	0	0	129
Alopecia	207 (77%)	..	..	270	94 (76%)	..	..	123	93 (74%)	..	..	126
Weight loss	43 (16%)	0	..	274	17 (13%)	0	..	128	20 (16%)	1 (1%)	..	129
Anorexia	158 (58%)	22 (8%)	1 (<1%)	274	82 (64%)	12 (9%)	0	128	78 (60%)	16 (12%)	0	129
Diarrhoea	28 (10%)	3 (1%)	0	274	10 (8%)	2 (2%)	0	128	68 (53%)	13 (10%)	0	129
Dysphagia-oesophageal†	229 (84%)	5 (2%)	0	274	34 (27%)	0	0	128	34 (26%)	1 (1%)	0	129
Nausea	139 (51%)	17 (6%)	..	274	82 (64%)	7 (5%)	..	128	82 (64%)	7 (5%)	..	129
Stomatitis or pharyngitis	38 (14%)	1 (<1%)	0	274	16 (13%)	0	0	128	15 (12%)	0	0	129
Vomiting	53 (19%)	3 (1%)	0	274	26 (20%)	3 (2%)	0	128	21 (16%)	5 (4%)	0	129
Febrile neutropenia	..	67 (25%)	0	271	..	21 (16%)	0	128	..	18 (14%)	0	129
Infection with grade 3 or 4 neutropenia	0	37 (14%)	0	272	0	15 (12%)	0	128	0	8 (6%)	0	129
Infection without neutropenia	7 (3%)	11 (4%)	1 (<1%)	274	11 (9%)	4 (3%)	0	128	16 (12%)	8 (6%)	0	129
Pneumonitis or pulmonary infiltrates	2 (1%)	1 (<1%)	0	274	9 (7%)	1 (1%)	0	128	16 (12%)	0	0	129

Data were missing for some patients. AHTRT=accelerated hyperfractionated thoracic radiotherapy. *Including two patients who did not undergo radiotherapy. †Related to radiation.

Table 2: **Adverse events**

The two groups did not differ in terms of sites of primary failure. Of 175 patients who had disease progression, in the etoposide plus cisplatin group, 30 had local progression within the radiation field, seven had local progression outside of the radiation field, 26 had progression to the brain, and 35 had systemic progression to other sites; in the irinotecan plus cisplatin group, 27 had local progression within the radiation field, six had local progression outside of the radiation field, 33 had progression to the brain, and 38 had systemic progression to other sites (some patients had progression to more than one site).

In a planned subgroup analysis, women in the etoposide plus cisplatin group had improved overall survival compared with those in the irinotecan plus cisplatin group (median overall survival not reached, 5-year overall survival 55·3% [95% CI 33·8–72·3] *vs* median overall survival 2·4 years [1·6–3·4], 5-year overall survival 26·1% [10·6–44·7] in the irinotecan group; unstratified HR 2·56; 95% CI 1·20–5·44, one-sided p=0·99) whereas outcomes for men did not differ between the groups (0·90; 0·65–1·24, one-sided p=0·25). Other prespecified subgroup analyses, including age (≤60 years old *vs* >60 years old), stage by UICC-TNM 7th edition (≤IIIA *vs* ≥IIIB), ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial repsonse plus stable disease), bodyweight loss during 6 months (≤5% *vs* >5%), and smoking history (<20 packs per year *vs* ≥20 packs per year) did not differ between the two groups (data not shown).

Of 129 eligible patients randomised to the etoposide plus cisplatin group, 128 (99·2%) had an overall response (24 complete response; 54 near complete response; 50 partial response); of 128 patients in the irinotecan plus cisplatin group, 123 (96·1%) had an overall response (30 complete response; 57 near complete response; 36 partial response).

Table 2 shows side-effects associated with concurrent chemoradiotherapy and consolidation chemotherapy. During consolidation chemotherapy, the most common adverse events of grade 1 or 2 were hypoalbuminaemia (102 [80%] in the etoposide plus cisplatin group *vs* 109 [84%] in the irinotecan plus cisplatin group) and alopecia (94 [76%] *vs* 93 [74%]). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). 12% of patients in the in the etoposide plus cisplantin group and 6% in the irinotecan plus cisplatin group had infection with grade 3 or 4 neutropenia. However, grade 3 febrile neutropenia did not differ between the two groups. Grade 3 or 4 leucopenia was less frequent in the

Panel: Research in context

Systematic review

Combination chemotherapy is the cornerstone of treatment of small-cell lung cancer (SCLC). We searched PubMed for reports of randomised clinical trials published in English up to Sept 30, 2013, using the terms "lung neoplasms", "small-cell lung cancer", "radiotherapy", and "not non-small-cell lung cancer". We also searched the reference lists of retrieved articles. The quality of evidence was assessed mainly on the basis of whether the standard chemotherapy regimen, etoposide plus cisplatin, was used as the reference group. Meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5-7] have shown that early use of concurrent thoracic radiotherapy is better than sequential or late use, when etoposide and cisplatin are used as combination chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC was better than standard fractionation, once-daily irradiation.

Interpretation

At present, standard treatment for patients with limited-stage SCLC is etoposide plus cisplatin with thoracic radiotherapy. AHTRT is recommended when logistically acceptable. As far as we are aware, JCOG0202 is the first randomised trial investigating the efficacy of irinotecan plus cisplatin in patients with limited-stage disease. The hypothesis that irinotecan plus cisplatin could improve overall survial for these patients compared with etoposide plus cisplatin was refuted. Four cycles of etoposide plus cisplatin and concurrent AHTRT should be the standard of care in patients with limited-stage SCLC, and discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.

irinotecan plus cisplatin group than in the etoposide plus cisplatin group; grade 3 or 4 diarrhoea was more frequent in the irinotecan plus cisplatin group than in the etoposide plus cisplatin group (table 2).

Late radiation morbidity after thoracic irradiation did not differ between the two groups (two [1·6%] grade 3 and two [1·6%] grade 4 events in the etoposide plus cisplatin group *vs* two [1·6%] grade 3 events in the irinotecan plus cisplatin group). Only one event [1·3%] of nausea of grade 3 due to prophylactic cranial irradiation was reported in the etoposide and cisplatin group.

Study treatment was terminated because of side-effects in 17 patients (13%) in the etoposide plus cisplantin group and in 26 patients (20%) in the irinotecan plus cisplatin group. There were three treatment-related deaths. One treatment-related death from pneumonitis occurred 86 days after induction chemoradiotherapy (induction etoposide plus cisplantin plus AHTRT). The patient was not randomised because a diffuse interstitial shadow occurred after 28·5 Gy of AHTRT. One patient in the etoposide plus cisplantin group died of radiation pneumonitis 116 days after completion of study treatment. One patient in the irinotecan plus cisplatin group died of brain infarction during the third course of consolidation chemotherapy.

Discussion

In this study of 258 patients with limited-stage SCLC, three cycles of irinotecan plus cisplatin did not improve overall survival compared with three cycles of etoposide plus cisplatin, after one cycle of etoposide plus cisplatin with concurrent AHTRT (panel). Randomisation was done after completion of induction chemoradiotherapy, thus the findings are unlikely to be biased by induction chemoradiotherapy.

JCOG previously reported the results of a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin versus etoposide plus cisplatin for extensive-stage SCLC. Median overall survival was 12·8 months and 19·5% patients were alive at 2 years in the irinotecan plus cisplatin group, whereas in the etoposide plus cisplatin group, median overall survival was 9·4 months only 5·2% of patients were alive after 2 years (p=0·002 from unadjusted log-rank test). Similar trials[13–15] done mainly in white patients with extensive-stage SCLC, including the Southwest Oncology Group trial[13] (S0124) using almost the same eligibility criteria and identical treatment regimens as JCOG9511, did not confirm the JCOG results. These results suggest pharmacogenomic differences between Japanese and non-Japanese patients.[16] Despite several negative trials, two meta-analyses[17,18] using non-individual-patient data showed a significant survival improvement with irinotecan compared with etoposide in patients with extensive-stage SCLC. However, the efficacy of irinotecan plus cisplatin shown in extensive-stage SCLC was not observed in the Japanese patients with limited-stage SCLC in our current study.

Side-effects were as expected. Severe non-haematological adverse events were much the same between the two groups, except for grade 3 or 4 diarrhoea which occurred in 10% of patients in the irinotecan plus cisplatin group and only 2% of patients in the etoposide plus cisplatin group. Late radiation reactions were not increased in the irinotecan plus cisplatin group. 86% of patients in the irinotecan plus cisplatin group received the planned three cycles of consolidation chemotherapy, and 90% received three cycles in the etoposide plus cisplatin group. Thus, compliance does not explain the negative results in the present study.

5-year overall survival in patients who received standard etoposide plus cisplatin plus concurrent AHTRT has been reported to be 24–26% in two phase 3 studies[7,8] in limited-stage SCLC. Although we failed to show an improvement in survival with our investigational regimen, the 5-year overall survival of 34·3% for all patients in the present study would be the best outcome reported so far. The 5-year overall survival of 55·3% in women who received standard etoposide plus cisplatin consolidation therapy is encouraging. This favourable result might be attributable to selection of patients, such as inclusion of patients with ECOG performance status of 0 or 1, and aged 70 years or younger. However, this selection bias does not fully explain the difference because the proportion of patients with ECOG performance status of 2 in other trials was only about 5%.[7,8] Radiotherapy quality control undertaken in the present study might have contributed to the improved

outcome, because radiotherapy protocol deviations are associated with overall mortality.[11,19] Optimum care of patients, including full disclosure of prognosis in the consent form for the study, might be another factor related to the favourable outcome.[20,21]

Full dose irinotecan cannot be combined with radiotherapy.[22] Thus, it is unlikely that the addition of irinotecan to radiotherapy improves the outcome of patients with limited-stage SCLC who receive combined chemotherapy and radiotherapy treatment. In future trials, new active agents with radiosensitising potential are needed. Testing of different radiotherapy regimens would be another option to improve outcomes in limited-stage SCLC. A randomised trial to establish whether administration of high-dose thoracic radiotherapy, 70 Gy (2 Gy once daily over 7 weeks) or 61·2 Gy (1·8 Gy once daily for 16 days followed by 1·8 Gy twice daily for 9 days), will improve survival compared with 45 Gy (1·5 Gy twice daily over 3 weeks) is underway in the USA (NCT00632853).

At the present time, the results of our study indicate that four cycles of etoposide plus cisplatin plus concurrent AHTRT should continue to be the standard of care in patients with limited-stage SCLC. Because SCLC is strongly smoking-related, discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.[23]

Contributors

TT was the chief investigator of the trial. KK, TH, SI, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, NS, and TT designed the trial and wrote the protocol. KK, TH, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, and TT enrolled patients. JM and TShib were responsible for data management, statistical analysis, and data interpretation. KK drafted the report. All authors were involved in writing the report and approved the final version.

Conflicts of interest

KK has received honoraria and a research grant from Daiichi-Sankyo. TT has received honoraria from Daiichi-Sankyo and Bristol-Myers Squibb. KN has received honoraria from Bristol-Myers Squib, Nippon Kayaku, and Daiichi-Sankyo. All other authors declare that they have no conflicts of interest.

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Portal Vein Thrombosis After Hepatectomy

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Abstract
Background Although various complications after hepatectomy have been reported, there have been no large studies on postoperative portal vein thrombosis (PVT) as a complication. This study evaluated the incidence, risk factors, and clinical outcomes of PVT after hepatectomy.
Methods The preoperative and postoperative clinical characteristics of patients who underwent hepatectomy were retrospectively analyzed.
Results A total of 208 patients were reviewed. The incidence of PVT after hepatectomy was 9.1 % ($n = 19$), including main portal vein (MPV) thrombosis ($n = 7$) and peripheral portal vein (PPV) thrombosis ($n = 12$). Patients with MPV thrombosis had a significantly higher incidence of right hepatectomy ($p < 0.001$), larger resection volume ($p = 0.003$), and longer operation time ($p = 0.021$) than patients without PVT ($n = 189$). Multivariate analysis identified right hepatectomy as a significant independent risk factor for MPV thrombosis (odds ratio 108.9; $p < 0.001$). Patients with PPV thrombosis had a significantly longer duration of Pringle maneuver than patients without PVT ($p = 0.002$). Among patients who underwent right hepatectomy, those with PVT ($n = 6$) had a significantly lower early liver regeneration rate than those without PVT ($n = 13$; $p = 0.040$), and those with PVT had deterioration of liver function on postoperative day 7. In all patients with MPV thrombosis who received anticoagulation therapy, PVT subsequently resolved.
Conclusions Postoperative PVT after hepatectomy is not rare. It is closely related to delayed recovery of liver function and delayed liver regeneration.

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Introduction

Hepatectomy is a widely accepted treatment for patients with primary liver tumors and well-preserved liver function [1]. It is the only curative treatment for patients with resectable metastatic liver tumors [2]. Despite the developments in surgical techniques and postoperative management, hepatectomy remains an invasive procedure with a relatively high postoperative complication rate, which has a negative impact on postoperative mortality [3].

Portal vein thrombosis (PVT) is a common complication of liver cirrhosis and is associated with decreased liver function and aggravated portal hypertension. The reported prevalence of PVT in individuals with liver cirrhosis ranges from 10 to 25 % [4]. It is generally accepted that decreased portal venous flow is the primary factor leading to PVT in patients with cirrhosis [5]. Although PVT is often overlooked, it is potentially life-threatening and may lead to mesenteric ischemia and sepsis [6]. Various postoperative complications after hepatectomy have been reported including liver failure [7], bile leakage [8], pulmonary complications [9], ascites [10], and venous thromboembolism [11], but no large studies have reported postoperative PVT as a complication.

The aim of this study was to clarify the incidence, risk factors, and clinical outcomes of postoperative PVT after hepatectomy.

Methods

Patients with primary or metastatic liver tumors who underwent hepatectomy without simultaneous splenectomy between January 2009 and June 2012 at Kyushu University Hospital (Fukuoka, Japan), and underwent contrast-enhanced computed tomography (CT) on postoperative day (POD) 7, were eligible for review.

Surgical procedures

The surgical procedure was selected according to the following criteria. The extent of resection was determined based on the expectation of an R0 resection. Patients did not undergo trisectionectomy if the indocyanine green retention rate at 15 min ($ICGR_{15}$) was >15 %, bisectionectomy if the $ICGR_{15}$ was >25 %, monosectionectomy if the $ICGR_{15}$ was >35 %, or subsectionectomy if the $ICGR_{15}$ was >45 %. Laparoscopic hepatectomy was performed if the tumor measured <3 cm.

Hepatic parenchymal transection was performed using an ultrasonic dissector (CUSA; Integra Lifesciences, Plainsboro, NJ, USA) and a TissueLink Monopolar Sealer (TissueLink Medical, Dover, NH, USA). For laparoscopic hepatectomy, although we had performed parenchymal division with laparoscopic CUSA and TissueLink Monopolar Sealer, we recently started using an EnSeal (Ethicon Endo-Surgery, Cincinnati, OH, USA) and water-dripping bipolar forceps [12, 13]. Small vessels were sealed with EnSeal, and large vessels, including Glissonian pedicles, were sealed with Hem-o-lok clips. The Pringle maneuver and/or the hanging maneuver were occasionally performed to increase the safety of the operation. The Pringle maneuver was performed as follows: The entire hepaticoduodenal ligament was encircled and tightened with a rubber tourniquet. It was then subjected to 15 min of hepatic inflow occlusion followed by 5 min of reperfusion, repeated as needed. Sectionectomy and subsectionectomy were performed with the Glissonian approach. All operations were performed under low central venous pressure conditions.

Diagnosis of PVT

Contrast-enhanced CT was routinely performed on POD 7 as one of the examinations to detect complications such as small bilomas and parenchymal congestion. Radiologists reviewed the CT images, diagnosed cases of PVT, and identified the location of the PVT. After discharge, asymptomatic patients with PVT were followed up with monthly contrast-enhanced CT scans. Main portal vein (MPV) thrombosis was defined as thrombus only in the MPV or in the MPV and superior mesenteric vein. Peripheral portal vein (PPV) thrombosis was defined as thrombus in the portal vein stump or branches of the portal vein.

Anticoagulation therapy for PVT

As hepatectomy can result in coagulopathy and increased postoperative bleeding, patients were not given routine postoperative anticoagulation therapy. In patients with MPV thrombosis, anticoagulation therapy was initiated when the thrombus extended to the superior mesenteric vein or reduced portal venous flow. In patients with PPV thrombosis, anticoagulation therapy was initiated when the thrombus was localized in the umbilical portion and reduced portal venous flow, or if the portal vein stump thrombus extended into a major branch of the portal vein. All patients with MPV or PPV thrombus, stump thrombus, or prolonged coagulopathy were carefully observed, and anticoagulation therapy was initiated if extension of the thrombus was detected.

Anticoagulation therapy consisted of low-molecular-weight heparin followed by oral warfarin, targeting a prothrombin time-international normalized ratio (PT-INR) between 2 and 3. Patients were followed up with monthly contrast-enhanced CT scans until resolution of the PVT.

Three-dimensional volumetry and estimation of liver regeneration rate

Three-dimensional volumetry has been described elsewhere [14, 15]. Briefly, multidetector helical CT (MDCT) images were obtained using 2 mm thick slices. Enhancement was achieved using an intravenous bolus injection of nonionic contrast medium. Three-dimensional reconstruction of the liver and tumor were obtained from the MDCT data using Zio M900 software (Zio Software, Tokyo, Japan), which allowed manual adjustment of the cutoff line. The liver regeneration rate was calculated as postoperative liver volume on POD 7 divided by the preoperative functional liver volume. Preoperative functional liver volume was calculated by subtracting the tumor volume from the preoperative total liver volume.

Statistical analysis

All statistical analyses were performed using SAS software (JMP 9.0.1; SAS Institute, Cary, NC, USA). All variables are expressed as the mean ± standard error. Categoric