VOLUME 32 · NUMBER 12 · APRIL 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

Miyako Satouchi, Yoshikazu Kotani, Taro Shibata, Masahiko Ando, Kazuhiko Nakagawa, Nobuyuki Yamamoto, Yukito Ichinose, Yuichiro Ohe, Makoto Nishio, Toyoaki Hida, Koji Takeda, Tatsuo Kimura, Koichi Minato, Akira Yokoyama, Shinji Atagi, Haruhiko Fukuda, Tomohide Tamura, and Nagahiro Saijo

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on March 17, 2014.

Written on behalf of the Japan Clinical Oncology Group.

Supported in part by Grants No. 23-A-16 and 23-A-18 from the National Cancer Center Research and Development Funds; by Grants-in-Aid for Cancer Research No. 17S-2, 17S-5, 20S-2, and 20S-6 from the Ministry of Health, Labour and Welfare of Japan; and by a contract for periodic safety reports on amrubicin from Dainippon Sumitomo Pharma.

Presented in part at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: UMIN000000720 (registered at University Hospital Medical Information Network Clinical Trials Registry).

Corresponding author: Miyako Satouchi, MD, PhD, 13-70, Kitaoji-cho, Akashi, 673-8558, Japan; e-mail: satouchi@hp.pref.hyogo.jp.

0732-183X/14/3212w-1262w/$20.00

DOI: 10.1200/JCO.2013.53.5153

ABSTRACT

Purpose
This randomized phase III trial was conducted to confirm noninferiority of amrubicin plus cisplatin (AP) compared with irinotecan plus cisplatin (IP) in terms of overall survival (OS) in chemotherapy-naive patients with extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods
Chemotherapy-naive patients with ED-SCLC were randomly assigned to receive IP, composed of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, or AP, composed of amrubicin 40 mg/m^2 on days 1, 2, and 3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks.

Results
A total of 284 patients were randomly assigned to IP (n = 142) and AP (n = 142) arms. The point estimate of OS hazard ratio (HR) for AP to IP in the second interim analysis exceeded the noninferior margin (HR, 1.31), resulting in early publication because of futility. In updated analysis, median survival time was 17.7 (IP) versus 15.0 months (AP; HR, 1.43; 95% CI, 1.10 to 1.85), median progression-free survival was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.16 to 1.73), and response rate was 72.3% (IP) versus 77.9% (AP; $P = .33$). Adverse events observed in IP and AP arms were grade 4 neutropenia (22.5% *v* 79.3%), grade 3 to 4 febrile neutropenia (10.6% *v* 32.1%), and grade 3 to 4 diarrhea (7.7% *v* 1.4%).

Conclusion
AP proved inferior to IP in this trial, perhaps because the efficacy of amrubicin as a salvage therapy was differentially beneficial to IP. IP remains the standard treatment for extensive-stage SCLC in Japan.

J Clin Oncol 32:1262-1268. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide,[1] and small-cell lung cancer (SCLC) accounts for almost 13% of all new cases.[2] More than half of these patients are diagnosed with extensive-disease (ED) SCLC.[3] SCLC refers to a rapidly proliferating tumor that is highly sensitive to chemotherapy. However, rapid emergence of clinical drug resistance has resulted in poor prognosis, with almost all such patients dead within 2 years of initial diagnosis.[3] Thus, there is a need for new and effective therapeutic options for ED-SCLC.

The combination of etoposide and cisplatin (EP) has been standard treatment for ED-SCLC for decades. In 2002, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG 9511) demonstrated the superiority of irinotecan plus cisplatin (IP) over EP for patients with ED-SCLC.[4] Median survival time (MST) and 1-year survival for the IP and EP arms were 12.8 versus 9.4 months and 58.4% versus 37.7%, respectively, but patients in the IP arm experienced a significantly higher proportion of grade 3 to 4 diarrhea. Although two randomized phase III trials have failed to confirm the superiority of IP over EP for chemotherapy-naive patients with SCLC in North America and Australia,[5-7] IP is considered equivalent to EP and one of the standard ED-SCLC regimens in Japan.

Amrubicin is a completely synthetic anthracycline derivative that is converted to an active metabolite, amrubicinol, and it is a potent topoisomerase

II inhibitor.[7] The high degree of therapeutic activity of amrubicin is caused by the selective distribution of amrubicinol, which is 10× to 100× more cytotoxic than its parent compound, amrubicin.[8,9]

A phase II study of amrubicin as single-agent therapy for previously untreated ED-SCLC yielded a response rate (RR) of 76%, complete response (CR) rate of 9%, and MST of 11.7 months,[10] similar to outcomes for platinum-based doublets at the time. Moreover, a phase I/II study of amrubicin plus cisplatin (AP) recommended administration of amrubicin 40 mg/m^2 on days 1, 2, and 3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. An RR of 87.8% and MST of 13.6 months were demonstrated in the patients treated with the recommended dose.[11] The major toxicity of the AP regimen was hematologic, which was acceptable because of the absence of febrile neutropenia (FN). Moreover, the incidence of grade 3 to 4 diarrhea, a concern with IP, was only 4.9%. Therefore, we believed AP might be a new effective treatment option for ED-SCLC, with a more favorable toxicity profile than IP. We undertook a multicenter, randomized, phase III noninferiority trial of AP compared with IP in previously untreated patients with ED-SCLC.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically demonstrated ED-stage SCLC (defined as ≥ one of following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion, pericardial effusion), chemotherapy naive, age 20 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to1, no prior chemotherapy or radiotherapy for any cancers, and adequate organ function, defined as leukocyte count ≥ 4,000/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, AST ≤ 100 IU/L, ALT ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL, and partial pressure of arterial blood gas without oxygen inhalation ≥ 70 torr. Patients had normal ECG and were asked to respond to a quality-of-life (QOL) questionnaire before enrollment. Patients were excluded if they had other unrelated invasive malignancies requiring ongoing therapy, serious tumor-related complication, active bacterial or fungal infection, diarrhea, intestinal paralysis or obstruction, evidence of interstitial pneumonia or pulmonary fibrosis on chest x-ray, received or expected to receive long-term treatment (≥ 50 days) with nonsteroidal anti-inflammatory drugs or steroids, serious cardiac disease, serious psychiatric disorder, pregnancy, active gastroduodenal ulcer, or history of myocardial infarction within 12 months. All enrolled patients provided written informed consent to participate in the study.

Treatment Plan

Patients were randomly assigned at a one-to-one ratio to receive either AP or IP. Random assignment was adjusted according to the following stratification factors: ECOG PS, institution, and sex. The IP regimen consisted of four cycles of irinotecan 60 mg/m^2 intravenously (IV) on days 1, 8, and 15 and cisplatin 60 mg/m^2 IV on day 1. Cycle length for this arm was 4 weeks. The AP regimen initially consisted of four cycles of amrubicin 40 mg/m^2 IV on days 1, 2, and 3 and cisplatin 60 mg/m^2 IV on day 1 every 3 weeks. However, because of the high incidence of severe hematologic toxicities, the protocol was revised to reduce the initial dose of amrubicin to 35 mg/m^2 in the AP group after 66% of patients (94 of 142) in the AP arm had been enrolled. The subsequent cycles of both arms were begun if absolute leukocyte count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum creatinine ≤ 1.5 mg/dL, and treatment-related nonhematologic toxicities (excluding alopecia, weight loss, and hyponatremia) had been resolved to grade ≤ 1. In regard to dose modification, if during the previous course the patient presented with thrombocytopenia (platelet count < 20,000/mm^3) and/or grade 3 nonhematologic toxicity including FN and diarrhea, the dose of irinotecan was reduced by 10 mg/m^2 and the dose of amrubicin by 5 mg/m^2 in the next cycle. The dose of cisplatin was reduced by 20 mg/m^2 for subsequent courses in the event of any of the following toxicities: creatinine > 1.5 to ≤ 2.0 mg/dL, grade 3 nonhematologic toxicity, grade ≥ 2 neuropathy (sensory or motor), and grade ≥ 2 muscle or joint pain. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in the first cycle. After the fourth cycle, initially prophylactic cranial irradiation (PCI) was conducted as per institutional policy. However, because of the report at the 2007 Annual Meeting of the American Society of Clinical Oncology stating that addition of PCI for ED-SCLC responders significantly extended survival,[12] the protocol was revised just 4 months after the start of patient enrollment so that patients with CR or tumor elimination would additionally receive PCI.

Response and Toxicity Evaluations

Baseline evaluation consisted of complete medical history and physical examination, ECG, ECOG PS, complete blood count, blood chemistry, blood gas analysis, computed tomography (CT) scan of the chest, CT or ultrasound of the abdomen, magnetic resonance imaging or CT of the brain, and bone scan or positron emission tomography. During treatment within the study, complete blood count, blood chemistry, and complete physical examination with clinical assessment were performed at least every week. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3). Chest x-ray was performed every cycle during protocol treatment, whether or not there was evidence of progression. All responses were defined according to RECIST (version 1.0). We evaluated patient QOL twice—once at baseline and once after completion of the second course (8 weeks in IP arm, 6 weeks in AP arm after treatment initiation)—using a QOL questionnaire for patients with cancer treated with anticancer drugs (QOL-ACD) and QOL Questionnaire Core 30 (QLQ-C30; diarrhea score). The primary metric used to analyze QOL was a comparison between arms in terms of improvement of physical status score over baseline QOL questionnaire.

End Points

The objective of this randomized phase III study was to establish the noninferiority of AP compared with IP as first-line therapy in patients with ED-SCLC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), RR, adverse events (AEs), grade 3 to 4 diarrhea, and QOL.

Study Design and Statistical Analysis

This trial was a multicenter randomized trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution.

The trial was designed to achieve at least 70% power to confirm noninferiority of AP compared with IP, with a noninferiority margin of 1.31 in terms of hazard ratio (HR), MST of 12.8 months in both arms, and one-sided α = 0.05. We believed 3 months would be the maximum allowable noninferiority margin in the case of a less-toxic regimen with a different toxicity profile—a profile that we had expected from the phase I/II study. An MST 3 months shorter than that of the IP arm would correspond to an HR of 1.31. The planned sample size was 282 patients, determined by the methods of Schoenfeld and Richter,[13] with 3 years of accrual and 3 years of follow-up. Because of an insufficient accrual rate during the study, the accrual period was revised to 4 years.

An interim analysis was scheduled because of the futility of the trial at the halfway mark of registration. The results from the interim analysis were reviewed by the JCOG Data and Safety Monitoring Committee, and investigators were blinded for the results. After the first interim analysis, the protocol was revised to add second interim analysis after all patients had been registered. Multiplicity for the primary end point was adjusted using O'Brien-Fleming–type alpha spending function.[14] The primary end point—OS—was analyzed using stratified Cox regression analysis with PS (0 *v* 1) and sex (male *v* female) as strata for all eligible patients. Except for the primary analysis, OS and PFS were analyzed using unstratified Cox regression analysis. OS and PFS were estimated using the Kaplan-Meier method. RRs were compared using Fisher's exact test. QOL scores were analyzed using logistic regression with covariate, treatment arm, and QOL scores at baseline. All *P* values are two sided, except for the primary analysis of the noninferiority hypothesis. Statistical analyses were conducted using SAS software (version 9.1 or 9.2; SAS Institute, Cary, NC).

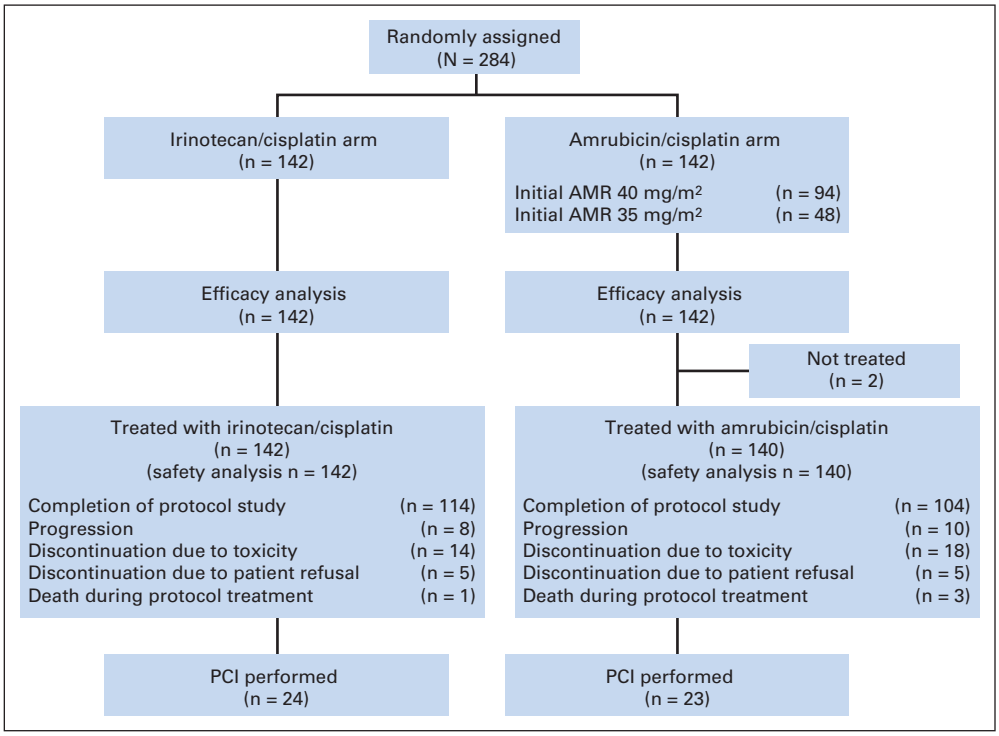

Fig 1. CONSORT diagram. AMR, amrubicin; PCI, prophylactic cranial irradiation.

RESULTS

From May 2007 to December 2010, 284 patients from 35 institutions were enrolled onto the study. All patients were deemed eligible; 142 patients were randomly assigned to the IP arm and 142 to the AP arm (Fig 1). Baseline characteristics were well balanced between the arms (Table 1). All 284 patients were included in the analysis for OS, PFS, and response. Patients who received at least one cycle of study treatment (n = 282) were assessable for toxicity analysis.

Treatment Delivery

Table 2 lists the number of cycles delivered. There were no significant differences between the two arms in treatment delivery. Two patients in the AP arm did not receive any protocol treatment. For the remaining 142 and 140 patients, the proportions receiving the planned four cycles of chemotherapy were 81% and 73.2% in the IP and AP arms, respectively. In the AP arm, 67% (63 of 94) of those who received an initial dose of 40 mg/m^2 completed four cycles, whereas in the AP arm, 85.4% of those who received 35 mg/m^2 completed four cycles; 4.9% (seven of 142) in the IP group and 7% (10 of 142) in the AP group received < two thirds of the planned dose of cisplatin. The interruption rates before protocol completion in the IP and AP arms were 19.7% and 26.8%, respectively; 13.4% and 16.2% of the patients in the IP and AP arms, respectively, had their treatment interrupted because of toxicity. In the IP and AP arms, 24 and 23 patients underwent PCI, respectively.

Toxicity

Table 3 lists grade ≥ 3 major toxicities. The most common grade ≥ 3 AEs in the AP arm were myelosuppression and FN. Diarrhea represented the predominant type of grade ≥ 3 toxicity in the IP arm. Myelosuppression was improved by reducing the initial dose of amrubicin: grade 3 to 4 leukopenia (from 77.2% to 62.5%), neutropenia (from 96.7% to 93.8%), anemia (from 43.5% to 22.9%), thrombocytopenia (from 35.9% to 10.4%), and FN (from 37% to 22.9%).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
Sex				
Male	120	84.5	119	83.8
Female	22	15.5	23	16.2
Age, years				
Median	63		63	
Range	39-70		29-70	
ECOG PS				
0	78	54.9	80	56.3
1	64	45.1	62	43.7
Measurable lesions				
None	1	0.7	2	1.4
Yes	141	99.3	140	98.6
Smoking status				
Nonsmoker	3	2.1	3	2.1
Smoker	139	97.9	139	97.9
Metastasis (overlapped)				
Lung	9	6.3	14	9.9
Bone	25	17.6	31	21.8
Brain	32	22.5	41	28.9
Liver	35	24.6	45	31.7
Others	68	47.9	64	45.1

Abbreviations: AP, amrubicin plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; IP, irinotecan plus cisplatin.

Table 2. Delivered Cycles

No. of Cycles	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
0	0	0.0	2	1.4
1	7	4.9	8	5.6
2	10	7.0	14	9.9
3	10	7.0	14	9.9
4	115	81.0	104	73.2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

One treatment-related death occurred in the IP arm (resulting from infection), and two occurred in the AP arm (one resulting from infection, and other resulting from pulmonary hemorrhage).

Efficacy

In the first interim analysis, the HR was 1.25 (99.9% CI, 0.28 to 5.59; information time, 0.16). The second interim analysis was conducted after completion of patient accrual based on the data as of May 2011. It showed that the median OS for AP (15.0 months) was much worse than that for IP (18.3 months) and that the HR was 1.41 (96.3% CI, 1.03 to 1.93) in stratified Cox regression. The point estimate of HR in OS for AP to IP exceeded the noninferiority margin (HR, 1.31); therefore, the Data Safety Monitoring Committee recommended early publication because of futility according to the preplanned decision rule that a point estimate of HR of AP to IP exceed the noninferiority margin (HR > 1.31). The Bayesian predictive probability that noninferiority would be shown with statistical significance at the end of this trial was 16.2%. Median PFS was 5.7 (IP) versus 5.2 months (AP; HR, 1.43; 95% CI, 1.13 to 1.82). RR was 72.3% (IP) versus 77.9% (AP; $P = .33$). Even updated analysis, as of May 2012, showed OS to be inferior in the AP arm (17.7 *v* 15.0 months; HR, 1.43; 95% CI, 1.10 to 1.85; Fig 2A). Median PFS was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.12 to 1.80; Fig 2B). The initial dose reduction in amrubicin had no impact on any efficacy results when the dose was reduced to 35 mg (Table 4).

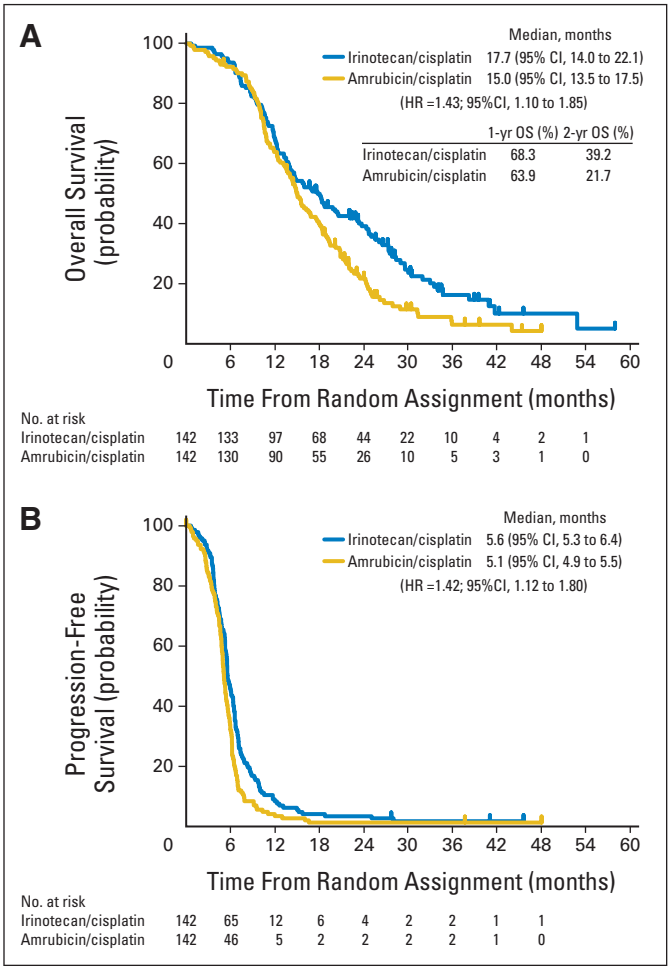

Fig 2. (A) Overall and (B) progression-free survival for intent-to-treat population (n = 284). HR, hazard ratio.

Table 3. Toxicities

Toxicity	Regimen by Grade (%) IP Arm (n = 142)* All	3	4	AP Arm (n = 140)† All	3	4
Hematologic						
Leukopenia	88.7	20.4	2.1	98.6	46.4	25.7
Neutropenia	95.8	35.9	22.5	99.3	16.4	79.3
Anemia	85.9	16.9	6.3	91.4	23.6	12.9
Thrombocytopenia	12.0	1.4	0.7	59.3	15.7	11.4
Nonhematologic						
FN	10.6	9.9	0.7	32.1	31.4	0.7
Fatigue	61.3	3.5	0.7	64.3	3.6	0.0
Nausea	78.9	6.3	0.0	79.3	4.3	0.0
Vomiting	37.3	3.5	0.0	34.3	2.1	0.0
Diarrhea	63.4	7.7	0.0	26.4	1.4	0.0
Hyponatremia	74.6	14.8	4.9	79.3	15.7	6.4
Cardiovascular events	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: AP, amrubicin plus cisplatin; FN, febrile neutropenia; IP, irinotecan plus cisplatin.
*One treatment-related death (0.7%).
†Two treatment-related deaths (1.4%).

The QOL questionnaire was completed in most cases: 282 of 284 patients at baseline and 272 patients at the end of the second course. The proportion of improvement in physical status in terms of QOL—the primary metric used to analyze QOL—was 37.1% in the IP arm versus 31.7% in the AP arm (odds ratio, 0.72; 95% CI, 0.43 to 1.22; $P = .23$). There was no significant difference in QOL improvement.

Poststudy Treatment

Table 5 summarizes poststudy treatment. Overall, 93.7% of IP-arm patients and 92.1% of AP-arm patients received additional therapy; 89.4% of patients in the IP arm and 87.1% of those in the AP arm received second-line chemotherapy, whereas 59.2% of those in the IP arm and 62.1% of those in the AP arm received third-line chemotherapy, indicating no substantial difference in the percentage receiving poststudy treatment. Nonetheless, 61 and 34 patients in the IP arm were administered single-agent amrubicin in their second- or third-line therapy, respectively. These figures are higher than those observed in the AP arm.

Table 4. Summary of Survival and Response

Survival/ Response	Before Amrubicin Dose Revision		After Amrubicin Dose Revision	
	IP Arm (n = 97)	AP Arm (n = 94)	IP Arm (n = 45)	AP Arm (n = 48)
ORR				
No.	72 of 97	70 of 93*	30 of 44*	39 of 47*
%	74.2	75.3	68.2	83.0
PFS				
Median	6.0	5.3	5.4	5.0
95% CI	5.5 to 6.6	4.9 to 5.7	4.8 to 6.4	4.7 to 5.7
OS				
Median	17.7	14.9	18.0	15.6
95% CI	13.9 to 22.1	13.1 to 16.8	12.2 to NE	12.4 to 20.7

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*One patient excluded because of no measurable lesions.

DISCUSSION

The outcomes in our study did not satisfy the primary end point, showing OS in the AP arm to be significantly inferior to that in the IP arm. The MST for AP was favorable (15 months), reproducing the outcomes obtained in the phase I/II study. The MST for IP was approximately 5 months beyond that shown in JCOG 9511. AP may simply be inferior to IP in the first line in that the platinum–topoisomerase I inhibitor partnership between cisplatin and irinotecan may be more synergistic. Although there was only a 0.5-month difference in median PFS, the IP arm displayed a much longer MST (ie, postprogression survival of IP arm was longer); two conceivable reasons for this are the advancements in support therapy and the influence of poststudy treatment.

Table 5. Poststudy Therapy

Chemotherapy	Second Line		Third Line	
	IP Arm (n = 127)	AP Arm (n = 122)	IP Arm (n = 84)	AP Arm (n = 87)
IP	7	10	0	3
Irinotecan	3	24	7	19
Cisplatin, irinotecan, and etoposide	10	13	2	2
Carboplatin plus irinotecan	1	4	0	9
Irinotecan plus other	0	1	3	4
Amrubicin	61	2	34	12
AP	0	4	0	1
Carboplatin plus amrubicin	1	0	0	0
Cisplatin plus etoposide	9	11	4	1
Carboplatin plus etoposide	22	29	25	24
Etoposide	1	0	0	0
Carboplatin, etoposide, and other	0	1	0	0
Topotecan	12	23	6	5
Carboplatin	0	0	0	1
Carboplatin plus other	0	0	1	4
Other	0	0	2	2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

The incidence of the greatest toxicity concern in JCOG 9511, grade 3 to 4 diarrhea, was 7.7% in this study (16.0% in JCOG 9511). The incidence of diarrhea was lower, which was most likely the result of advances in support therapy. That said, the impact of poststudy treatment should garner the most attention as a reason for the inability to demonstrate survival extension or noninferiority in our study.

Analysis of subsequent therapies administered in this study revealed that ultimately, two thirds of all patients in the IP arm received single-agent amrubicin as a subsequent therapy. There was no difference between the two arms in terms of the percentage of patients who received subsequent therapies, suggesting that amrubicin, used in a large percentage of patients in the IP arm as postprotocol therapy, contributed to an extension in OS.

Several studies have examined the use of amrubicin as secondary treatment for SCLC.[15-18] A phase II study by Inoue et al[15] comparing amrubicin with topotecan, considered to be standard secondary treatment, indicated the possibility that amrubicin might be superior to topotecan. A phase III study conducted by Jotte et al[16] did not show any significant difference between topotecan and amrubicin as second-line chemotherapy in terms of OS (MST: amrubicin, 9.2 months; topotecan, 9.9 months; HR, 0.89; 95% CI, 0.73 to 1.06); however, outcomes with amrubicin were significantly better in terms of RR and PFS, and OS was better in subanalysis only among patients experiencing refractory relapse (MST: amrubicin, 6.2 months; topotecan, 5.7 months; HR, 0.77; 95% CI, 0.79 to 1.0; $P = .047$). Although topotecan is the most evidence-based second-line therapy for SCLC,[19,20] amrubicin has come into widespread use in Japan as a result of many reports on its use among Japanese patients (ie, RR and PFS compare favorably, and survival is quite respectable).

Amrubicin is a topoisomerase II inhibitor, suggesting that it may not be effective in patients for whom etoposide (also topisomerase II inhibitor) or EP has failed. Irinotecan is a topoisomerase I inhibitor, and amrubicin may be effective in those for whom IP has failed (unlike in those for whom EP has failed). Accordingly, the possibility remains that the frequent use of amrubicin in poststudy treatment may have extended survival even beyond that expected. This may be a reason why IP therapy showed significantly better survival than AP therapy in our study. In this phase III trial, AP proved to be inferior to IP, but the results seen here do not negate the activity of this agent in SCLC and perhaps underscore the particular value of amrubicin as second- or third-line therapy in this setting.

The AP arm showed reproducible, favorable survival in the form of 15-month MST and noninferiority to EP in a phase III study conducted in China (MST: AP, 11.79 months; EP, 10.28 months),[21] suggesting that AP is rather effective. However, considering that hematotoxicity and FN, even after reduction of the dose to 35 mg/m^2, were relatively serious, and considering the excellent effect of amrubicin monotherapy in relapse treatment, we are unable to recommend AP as standard first-line therapy for ED-SCLC. Therefore, IP therapy showed favorable OS and toxicity profile, indicating, as expected, its continuing presence as one of the standard first-line therapies for ED-SCLC in Japan.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Miyako Satouchi, Nippon Kayaku; Tomohide Tamura, Daiichi Sankyo, Bristol-Myers Squibb **Research Funding:** Toyoaki Hida, Nippon Kayaku **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Miyako Satouchi, Yoshikazu Kotani, Taro Shibata, Nobuyuki Yamamoto, Yuichiro Ohe, Koichi Minato, Akira Yokoyama, Haruhiko Fukuda, Tomohide Tamura, Nagahiro Saijo
Provision of study materials or patients: Miyako Satouchi, Yuichiro Ohe, Makoto Nishio, Koji Takeda, Shinji Atagi
Collection and assembly of data: Miyako Satouchi, Masahiko Ando, Nobuyuki Yamamoto, Yukito Ichinose, Makoto Nishio, Toyoaki Hida, Koji Takeda, Tatsuo Kimura, Shinji Atagi
Data analysis and interpretation: Miyako Satouchi, Taro Shibata, Kazuhiko Nakagawa, Tomohide Tamura
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012. CA Cancer J Clin 62:10-29, 2012
2. Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24:4539-4544, 2006
3. Shepherd FA, Crowley J, Van Houtte P, et al: The International Association for the Study of Lung Cancer lung cancer staging project: Proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol 2:1067-1077, 2007
4. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85-91, 2002
5. Lara PN Jr, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: Clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530-2535, 2009
6. Hanna N, Bunn PA Jr, Langer C, et al: Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 24:2038-2043, 2006
7. Lara PN Jr, Chansky K, Shibata T, et al: Common arm comparative outcomes analysis of phase 3 trials of cisplatin + irinotecan versus cisplatin + etoposide in extensive stage small cell lung cancer: Final patient-level results from Japan Clinical Oncology Group 9511 and Southwest Oncology Group 0124. Cancer 116:5710-5715, 2010
8. Noguchi T, Ichii S, Morisada S, et al: Tumor-selective distribution of an active metabolite of the 9-aminoanthracycline amrubicin. Jpn J Cancer Res 89:1061-1066, 1998
9. Morisada S, Yanagi Y, Noguchi T, et al: Antitumor activities of a novel 9-aminoanthracycline (SM-5887) against mouse experimental tumors and human tumor xenografts. Jpn J Cancer Res 80:69-76, 1989
10. Yana T, Negoro S, Takada M, et al: Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. Invest New Drugs 25:253-258, 2007
11. Ohe Y, Negoro S, Matsui K, et al: Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 16:430-436, 2005
12. Slotman B, Faivre-Finn C, Kramer G, et al: Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357:664-672, 2007
13. Schoenfeld DA, Richter JR: Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 38:163-170, 1982
14. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983
15. Inoue A, Sugawara S, Yamazaki K, et al: Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 26:5401-5406, 2008
16. Jotte R, Von Pawel J, Spigel DR, et al: Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment foer small cell lung cancer. J Clin Oncol 29:453s, 2011 (suppl; abstr 7000)
17. Onoda S, Masuda N, Seto T, et al: Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol 24:5448-5453, 2006
18. Jotte R, Conkling P, Reynolds C, et al: Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. J Clin Oncol 29:287-293, 2011
19. O'Brien ME, Ciuleanu TE, Tsekov H, et al: Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 24:5441-5447, 2006
20. von Pawel J, Schiller JH, Shepherd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658-667, 1999
21. Sun Y, Cheng Y, Hao X: Result of phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small cell lung cancer. J Clin Oncol 31:459s, 2013 (suppl 15; abstr 7507)

Affiliations

Miyako Satouchi, Hyogo Cancer Center, Akashi; Yoshikazu Kotani, Kobe University Graduate School of Medicine, Kobe; Taro Shibata and Haruhiko Fukuda, Japan Clinical Oncology Group Data Center, Multi-Institutional Clinical Trial Support Center, National Cancer Center; Yuichiro Ohe, National Cancer Center Hospital East; Makoto Nishio, Cancer Institute Hospital, Japanese Foundation For Cancer Research; Tomohide Tamura, National Cancer Center Hospital; Nagahiro Saijo, Japanese Society of Medical Oncology, Tokyo; Masahiko Ando, Kyoto University School of Public Health, Kyoto; Kazuhiko Nakagawa, Kinki University School of Medicine; Koji Takeda, Osaka City General Hospital; Tatsuo Kimura, Graduate School of Medicine, Osaka City University; Shinji Atagi, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka; Nobuyuki Yamamoto, Shizuoka Cancer Center, Shizuoka; Yukito Ichinose, National Hospital Organization Kyushu Cancer Center, Fukuoka; Toyoaki Hida, Aichi Cancer Center, Nagoya; Koichi Minato, Gunma Cancer Center, Gunma; and Akira Yokoyama, Niigata Cancer Center Hospital, Niigata, Japan.

GLOSSARY TERMS

Topoisomerase I: An enzyme that acts on the topology of native DNA by changing the supercoiled structure of DNA. Topoisomerase I makes a nick in one DNA strand, twists it around the other, and religates the nicked strand.

Topoisomerase II: An enzyme that catalyzes the ATP-dependent transport of one segment of DNA duplex through another DNA duplex. Topoisomerases change the topology of DNA by controlling the essential functions of separating intertwined daughter chromosomes.

Acknowledgment

We thank the patients and their families for participating in this trial; Shunichi Negoro, MD, for encouraging and supporting this trial; Tomoko Kazato and Mieko Imai for data management; and Junki Mizusawa for statistical analysis support from the Japan Clinical Oncology Group Data Center.

Appendix

Overall survival (OS) was defined as the time from random assignment to death resulting from any cause and censored at the last follow-up date. Progression-free survival (PFS) was defined as the interval from random assignment to diagnosis of progression or death resulting from any cause and censored at the last date on which progression-free status was evaluated.

The response rate was the proportion of patients evaluated as having a complete or partial response as overall response among all eligible patients with evaluable lesions. Proportion of grade 3 to 4 diarrhea was defined the number of patients who experienced at least one grade 3 to 4 diarrhea event by Common Terminology Criteria for Adverse Events (version 3) from the first day of protocol treatment to 30 days after protocol treatment. Quality of life was compared in terms of a proportion of patients whose quality-of-life scores improved during protocol treatment.

CIs for OS and PFS proportions were estimated using Greenwood's formula, and those of median OS and median PFS were estimated using the method of Brookmeyer and Crowley. Hazard ratios were estimated using Cox regression.