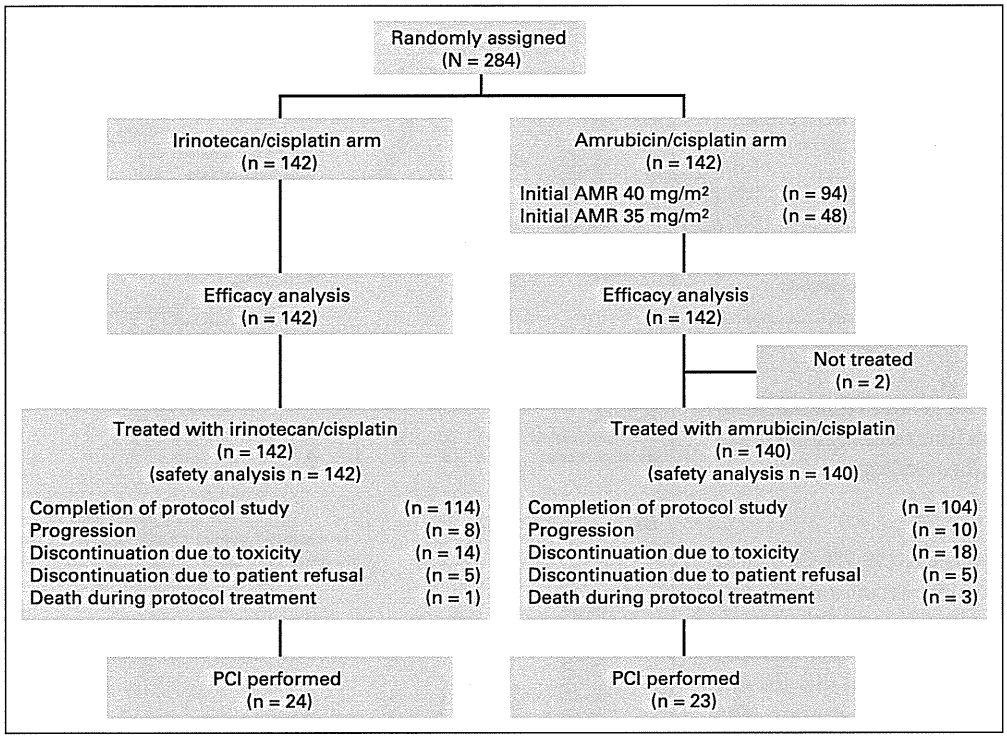

Fig 1. CONSORT diagram. AMR, amrubicin; PCI, prophylactic cranial irradiation.

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).

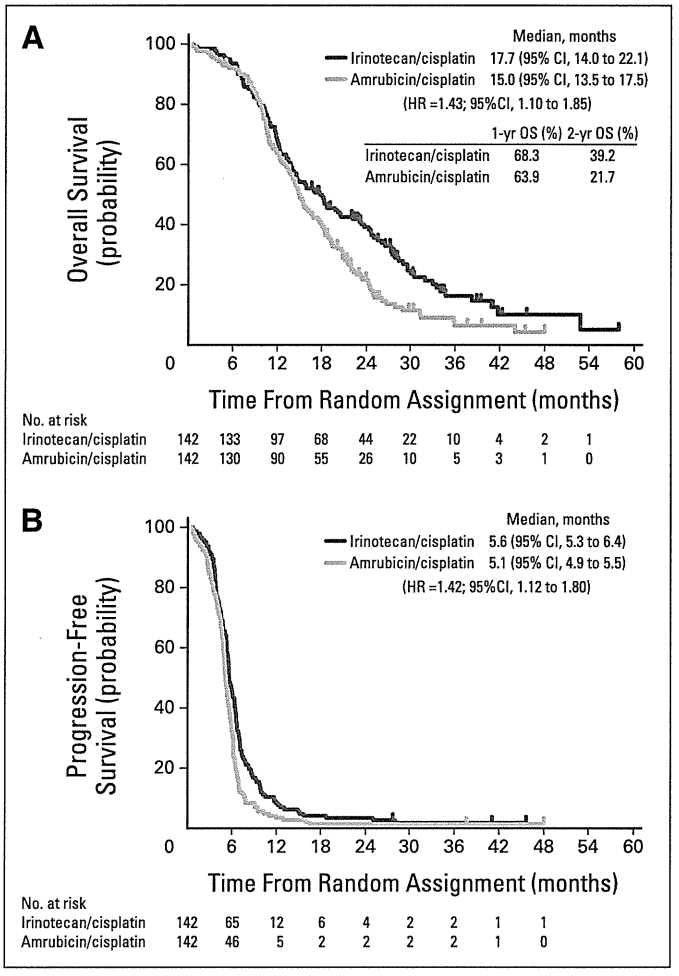

Fig 2. (A) Overall and (B) progression-free survival for intent-to-treat population (n = 284). HR, hazard ratio.

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

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Manuscript writing: All authors
Final approval of manuscript: All authors

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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.

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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.