Correlation between the efficacy of amrubicin and the previous chemotherapy regimen for relapsed small cell lung cancer

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Abstract. Amrubicin has been demonstrated to be beneficial in the treatment of patients with relapsed small cell lung cancer (SCLC). The aim of the present study was to evaluate whether there is a significant difference in the efficacy of amrubicin between patients with relapsed SCLC who were previously treated with a platinum agent in combination with a topoisomerase I inhibitor, and those patients previously treated with a platinum agent in combination with a topoisomerase II inhibitor. The medical records of patients with SCLC, who were diagnosed as having relapsed following treatment with a platinum-based regimen and subsequently received amrubicin monotherapy, were retrospectively reviewed. Of a total of 48 patients with SCLC who were treated with amrubicin, the overall response rate, median progression-free survival (PFS) time and median survival time (MST) were determined to be 31.3%, 7.1 and 17.0 months, respectively. The response rate, PFS time and MST did not differ significantly between the patients treated previously with a platinum agent in combination with irinotecan, a topoisomerase I inhibitor, (36.4%, 5.7 and 11.4 months, respectively) and those treated previously with a platinum agent in combination with etoposide, a topoisomerase II inhibitor (30.0%, 4.7 and 14.8 months, respectively). The results indicate that amrubicin may be effective as a second-line chemotherapeutic agent for patients with SCLC, irrespective of which platinum agent and topoisomerase inhibitor-based chemotherapy regimen was previously administered.

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Introduction

Small-cell lung cancer (SCLC) is the most aggressive type of lung cancer and has a poor prognosis (1). The standard therapy for extensive SCLC is chemotherapy with a platinum compound (carboplatin or cisplatin) administered in combination with etoposide, a topoisomerase II inhibitor (2). A Japanese phase III study [Japan Clinical Oncology Group (JCOG) 9511] investigated the clinical outcomes patients who were administered cisplatin and etoposide, compared with those who received cisplatin and irinotecan, a topoisomerase I inhibitor (3). Irrespective of the regimen selected, the majority of patients experience relapse or disease progression following an initial response to chemotherapy, and second-line therapy is subsequently required (4,5).

Amrubicin is a synthetic 9-aminoanthracycline that is converted to its active metabolite, amrubicinol, through the reduction of its C-13 ketone group to a hydroxy group (6). Amrubicin and amrubicinol are topoisomerase II inhibitors, which have been demonstrated to exert antitumor activities in various human tumor xenograft models (7). The drug has been evaluated in a number of Japanese studies and reported to yield a response rate of 36-52% and a median survival time of 7-12 months when administered as a second-line treatment (8-13). The results of previous studies have indicated that amrubicin is useful for the treatment of relapsed SCLC (8-13).

Few previous studies have evaluated the efficacy of amrubicin as a second-line treatment in patients with SCLC with consideration of the previous chemotherapy regimen. The present study aimed to evaluate whether there is a significant difference in the efficacy of amrubicin in patients with SCLC when treated previously with a platinum agent combined with either the topoisomerase II inhibitor etoposide or the topoisomerase I inhibitor irinotecan.

Materials and methods

Patient selection. A retrospective study was conducted using the data of a cohort of 48 consecutive Japanese patients with

SCLC that had relapsed following treatment with a platinum-based regimen combined with etoposide or irinotecan, and subsequently received amrubicin monotherapy at Kitasato University Hospital (Tokyo, Japan) between January 2009 and November 2014. The study reviewed the medical records of the patients and excluded those who did not have at least one measurable lesion, according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (14). The patient characteristics were identified by a retrospective chart review, including age at diagnosis, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of amrubicin treatment initiation, smoking status, brain metastasis status, type of relapse (sensitive or refractory) following prior therapy and the previously administered chemotherapy regimen (platinum agent plus etoposide, or cisplatin plus irinotecan). The platinum agent was cisplatin or carboplatin. With regard to their smoking status, the patients were classified as current smokers, former light smokers (history of smoking a total of ≤10 pack-year plus smoking cessation ≥15 years previously), and non-smokers (a lifetime history of smoking <100 cigarettes). Refractory relapse was defined as the absence of response to a previous chemotherapy regimen, disease progression during chemotherapy or disease progression within 90 days of completing chemotherapy following the initial confirmation of an objective response. Sensitive relapse was defined as the absence of response to a previous chemotherapy regimen, disease progression during chemotherapy or disease progression ≥90 days after completing chemotherapy following the initial confirmation of an objective response.

Treatment. The patients received infusion of amrubicin at 40 mg/m^2/day for 3 consecutive days every 21 days; the treatment was repeated until the appearance of disease progression, intolerable toxicity or the patient's refusal to continue the treatment. Prior to the start of treatment, patients were required to have an absolute neutrophil count of ≥1,500/mm^3, a platelet count of ≥100,000/mm^3, serum aspartate aminotransferase and alanine aminotransferase levels <3-times the maximum normal value, and serum total bilirubin and creatinine levels of <1.5-times the maximum normal values. The doses of amrubicin were modified as required on the basis of hematological and non-hematological toxicities.

Evaluation of response and toxicities. Tumor response to treatment was classified according to the RECIST (version 1.1). Patients were evaluated for progression or regression of the disease by a physical examination and complete medical history, chest radiography, computed tomography of the chest and abdomen, magnetic resonance imaging of the head and positron emission tomography. Patient medical records were reviewed to identify toxicities, which were graded according to the National Cancer Institute Common Toxicity Criteria (version 4) grading system (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

Statistical analysis. The distributions of the categorical characteristics between patient groups, divided according to the previous chemotherapy regimen, were analyzed using the χ^2 test. Progression-free survival (PFS) time was measured as the duration from the start of amrubicin therapy to the determination of treatment failure (mortality or documentation of disease progression) or the date of censoring at the final follow-up examination. Overall survival (OS) time was defined as the duration from the start of amrubicin therapy to patient mortality, or the date of censoring at the final follow-up examination. The survival curves were generated using the Kaplan-Meier method and variations in survival were analyzed by the log-rank test. The variables of age, gender, PS, prior chemotherapy regimen, status of brain metastasis and type of relapse were fitted into a Cox proportional-hazards model to predict the hazard ratios for the PFS and OS. All statistical analyses were performed using SPSS software, version 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows. The data are presented as the median and range, unless otherwise stated. $P<0.05$ was considered to indicate a statistically significant result.

Results

Patient characteristics. The clinical characteristics of the patients are presented in Table I. A total of 48 patients treated with amrubicin were included in the final analysis. The median age of the patients was 67 years; 36 patients (75%) had a PS of 0 or 1 (a PS of 1 or 2 was considered to be good) and 8 patients (17%) had brain metastasis. Of the 48 patients, 37 (77%) had been previously treated with platinum, including cisplatin or carboplatin, and etoposide, and 11 patients (23%) had been treated with cisplatin and irinotecan. A total of 33 patients (69%) presented with sensitive relapse and 15 patients (31%) with refractory relapse. There were no significant differences observed in the clinical characteristics between those patients who had received platinum and etoposide, compared with patients who had received cisplatin and irinotecan.

Tumor response. Of a total of 48 patients, an objective response (as determined using RECIST version 1.1) to a first-line platinum doublet chemotherapy regimen had been identified in 35 patients, corresponding to an overall response rate of 72.9%. The response rates following treatment with platinum plus etoposide or cisplatin plus irinotecan were 73.0 and 72.7%, respectively (P=0.99). An objective response to the subsequent amrubicin therapy was identified in 15 patients, equating to a response rate of 31.3%. The response rate was 36.4% for patients previously treated with cisplatin and irinotecan, and 30.0% for patients previously treated with a platinum agent and etoposide; no significant differences were observed between the two groups (P=0.68). The tumor responses are presented in Table II.

Toxicities of amrubicin. A comparison of toxicities between the patients who had received platinum and etoposide and patients who had received cisplatin and irinotecan is presented in Table III. There were no significant differences identified in the frequencies of each type of toxicity between the two groups.

PFS and OS. The survival data update was completed by January 2015 and the median follow-up period was determined

Table I. Characteristics of the patients involved in the present study.

Category	Total (n=48)	EP (n=37)	IP (n=11)	P-value[a]
Age, median (range)	67 (34-82)	67 (34-82)	67 (56-75)	
Gender, n				0.52
Male	42	33	9	
Female	6	4	2	
Smoking status, n				
Current	48	37	11	
Non or former light	0	0	0	
ECOG performance status, n				0.84
0-1	36	28	8	
2-3	12	9	3	
Clinical stage prior to receiving the previous therapy, n				0.15
LD	6	6	0	
ED	42	31	11	
Brain metastasis, n				0.05
Positive	8	4	4	
Negative	40	33	7	
Type of relapse, n				0.68
Sensitive	33	26	7	
Refractory	15	11	4	

[a]χ^2 test. IP, irinotecan plus platinum group; EP, etoposide plus platinum group; ECOG, Eastern Cooperative Oncology Group; LD, limited disease; ED, extensive disease.

Table II. Clinical response in patients treated previously with cisplatin and irinotecan, and patients treated previously with a platinum agent and etoposide.

Groups	Total, n	Number of responders	RR, %	P-value
Platinum agent+etoposide	37	11	30.0	0.68[a]
Cisplatin+irinotecan	11	4	36.4	
Total	48	15	31.3	

[a]χ^2 test (platinum agent + etoposide vs. cisplatin+irinotecan). RR, response rate.

to be 12.7 months. The amrubicin treatment results for all patients indicated that the median PFS and OS times were 7.1 months [95% confidence interval (CI), 4.6-9.5 months; Fig. 1A] and 17.0 months (95% CI, 11.5-22.5 months; Fig. 1B), respectively.

With regard to the previous chemotherapy regimen, the median PFS times were 5.7 months (95% CI, 3.5-5.9 months) in the cisplatin and irinotecan group, and 4.7 months (95% CI, 2.7-8.7 months) in the platinum and etoposide group (P=0.43; Fig. 2A). The median OS times were 11.4 months (95% CI, 3.4-19.4 months) in the cisplatin and irinotecan group, and 14.8 months (95% CI, 6.9-22.7 months) in the platinum agent and etoposide group (P=0.23; Fig. 2B).

Multivariate analysis identified the PS, status of brain metastasis and type of relapse following the previous regimen as significant predictors of PFS. The PS and type of relapse following previous chemotherapy were also determined to be significant predictors of OS (Table IV).

Discussion

Few previous studies have evaluated the efficacy of amrubicin monotherapy in patients with SCLC with regard to the previously administered chemotherapy regimen. Following the evaluation of the objective response, PFS and OS, the present study revealed no significant differences in the clinical efficacy of amrubicin monotherapy in patients treated with cisplatin and irinotecan (a topoisomerase I inhibitor) compared with patients treated with a platinum agent and etoposide (a topoisomerase II inhibitor).

Table III. Toxicities of amrubicin in patients who had received platinum and etoposide and patients who had received cisplatin and irinotecan.

	All toxicity grades, n (%)			Toxicity grade ≥3, n (%)		
Toxicity	IP	EP	[a]P-value	IP	EP	[a]P-value
Nausea	2 (18.2)	5 (13.5)	NS	0 (0)	0 (0)	-
Fatigue	3 (27.3)	5 (13.5)	NS	0 (0)	0 (0)	-
Anorexia	3 (27.3)	8 (21.6)	NS	0 (0)	1 (2.7)	NS
Constipation	3 (27.3)	3 (8.1)	NS	0 (0)	0 (0)	NS
Anemia	3 (27.3)	9 (24.3)	NS	0 (0)	3 (8.1)	NS
Thrombocytopenia	7 (63.6)	17 (45.9)	NS	1 (9.1)	5 (13.5)	NS
Leukopenia	10 (90.9)	33 (89.2)	NS	3 (27.3)	16 (43.2)	NS
Neutropenia	10 (90.9)	32 (86.5)	NS	3 (27.3)	16 (43.2)	NS
Neutropenic fever	0 (0)	4 (10.8)	NS	0 (0)	4 (10.8)	NS
AST	1 (9.1)	4 (10.8)	NS	1 (9.1)	1 (2.7)	NS
ALT	1 (9.1)	4 (10.8)	NS	0 (0)	0 (0)	-
Creatinine increased	2 (18.2)	1 (2.7)	NS	1 (9.1)	1 (2.7)	NS
Pneumonitis	0 (0)	1 (2.7)	NS	0 (0)	1 (2.7)	NS

[a]χ^2 test. NS, not significant; IP, irinotecan platinum group; EP, etoposide platinum group; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table IV. Progression-free survival and overall survival analysis by the Cox regression model.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
PFS				
Age (<75 vs. >75)	0.99 (0.44-2.24)	0.98	0.97 (0.34-2.54)	0.96
Gender	0.73 (0.30-1.75)	0.48	0.61 (0.24-1.58)	0.31
Performance status (0-1 vs. 2-3)	3.27 (1.63-6.55)	0.0009	4.21 (1.86-9.57)	0.001
Clinical stage (LD vs. ED)	0.77 (0.32-1.82)	0.55	0.91 (0.32-2.54)	0.85
Previous regimen (EP vs. IP)	1.32 (0.66-2.64)	0.44	1.43 (0.63-3.24)	0.40
Brain metastasis	0.72 (0.32-1.62)	0.43	0.35 (0.13-0.95)	0.04
Type of relapse (sensitive vs. refractory)	2.59 (1.33-5.07)	0.005	3.19 (1.54-6.61)	0.002
OS				
Age (<75 vs. >75)	0.86 (0.33-2.23)	0.76	1.09 (0.35-3.39)	0.88
Gender	0.52 (0.20-1.38)	0.19	0.43 (0.15-1.21)	0.11
Performance status (0-1 vs. 2-3)	4.10 (1.93-8.73)	0.0003	4.49 (1.88-10.73)	0.001
Clinical stage (LD vs. ED)	0.73 (0.26-2.06)	0.55	0.97 (0.28-3.40)	0.97
Previous regimen (EP vs. IP)	1.21 (0.56-2.58)	0.63	0.90 (0.35-2.30)	0.83
Brain metastasis	1.35 (0.55-3.32)	0.51	1.14 (0.37-3.47)	0.82
Type of relapse (sensitive vs. refractory)	3.55 (1.58-8.00)	0.002	4.00 (1.66-9.60)	0.002

HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; LD, limited disease; ED, extensive disease; IP, irinotecan plus platinum group; EP, etoposide plus platinum group.

However, preclinical studies (15-18) have indicated that treatment with topoisomerase I inhibitors induces downregulation of topoisomerase I and upregulation of topoisomerase II, increasing cell sensitivity to topoisomerase II inhibitors. Similarly, treatment with topoisomerase II inhibitors has been reported to induce the downregulation of topoisomerase II and upregulation of topoisomerase I. A phase II study conducted by Murakami *et al* (19) reported

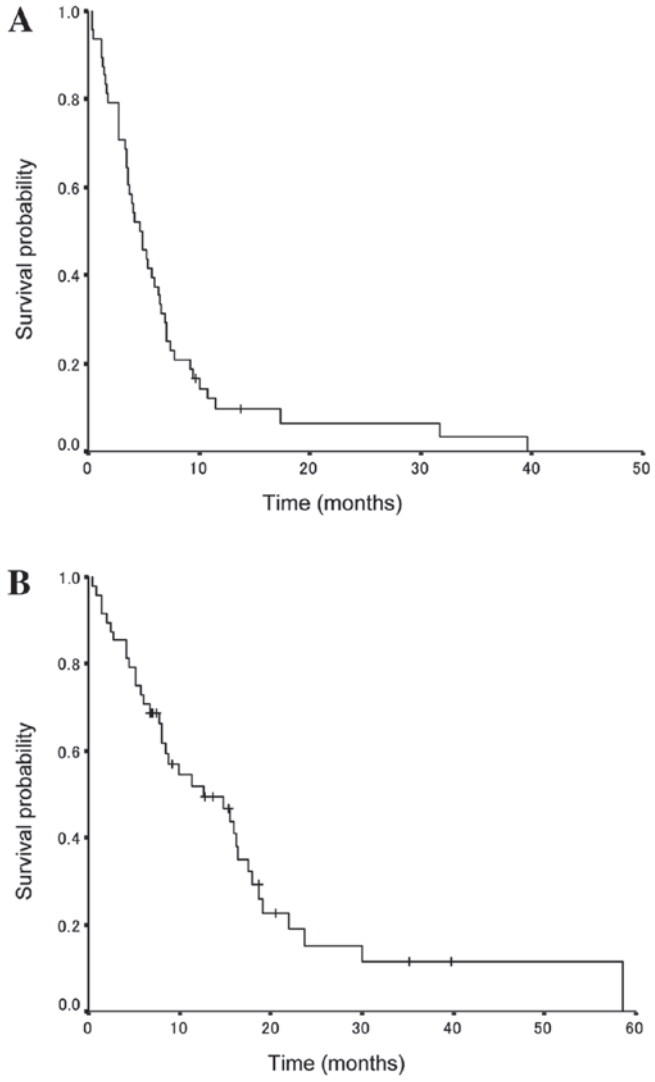

Figure 1. Kaplan-Meier survival plots of all included patients. (A) Progression-free survival. (B) Overall survival. The amrubicin treatment results for all patients indicated that the median PFS and OS times were 7.1 and 17.0 months, respectively.

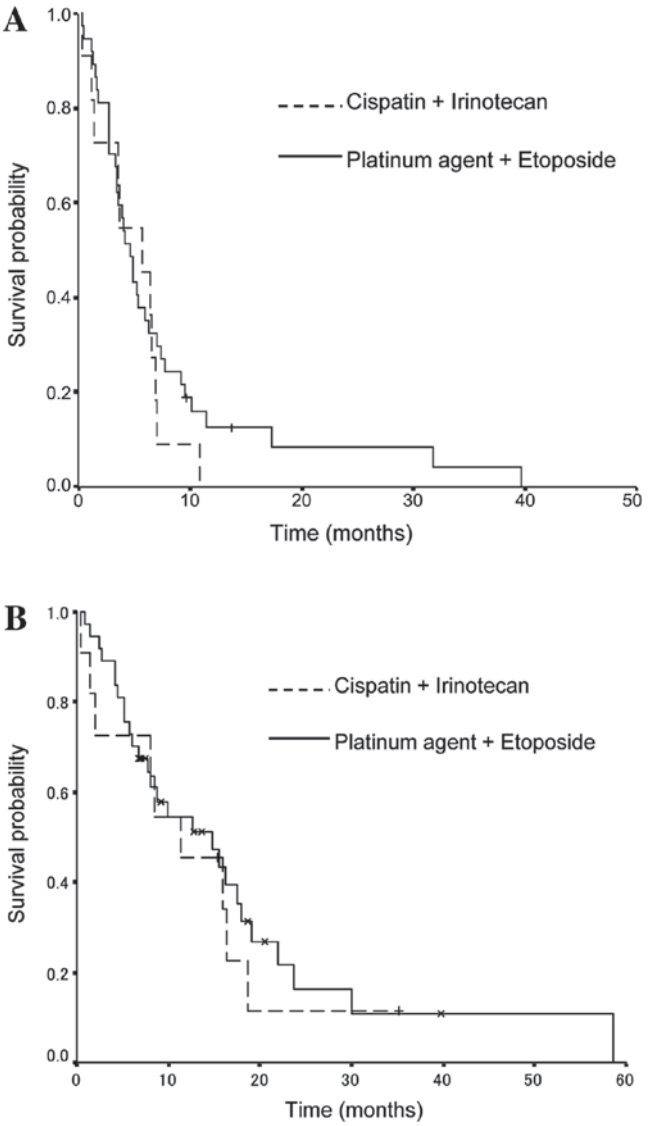

Figure 2. Kaplan-Meier plots of survival for patients treated previously with cisplatin and irinotecan, compared with patients treated previously with platinum and etoposide. There were no differences in PFS and OS according to the type of previous chemotherapy regimen. (A) PFS according to the prior regimen. (B) OS, according to the prior chemotherapy regimen. With regard to the previous chemotherapy regimen, the median PFS times were 5.7 months (95% CI, 3.5-5.9 months) in the cisplatin and irinotecan group, and 4.7 months in the platinum and etoposide group (P=0.43). The median OS times were 11.4 months in the cisplatin and irinotecan group, and 14.8 months in the platinum agent and etoposide group (P=0.23). PFS, progression-free survival; OS, overall survival.

that amrubicin monotherapy is effective against refractory SCLC; a subset analysis of this study revealed that the response to amrubicin was less pronounced and the survival rate was lower in patients who were previously treated with etoposide, a topoisomerase II inhibitor, compared with patients previously treated with irinotecan. By contrast, the results of a phase II study that evaluated the efficacy of amrubicin monotherapy for relapsed SCLC suggested that the absence of any significant difference in the PFS following amrubicin therapy was dependent on the previous platinum and topoisomerase inhibitor-based therapy (11). Furthermore, two retrospective studies also demonstrated an equivalent amrubicin efficacy against relapsed SCLC, irrespective of the prior platinum and topoisomerase inhibitor therapy (20,21).

To the best of our knowledge, this study is the first to evaluate the effectiveness of amrubicin in terms of the response rate, PFS and OS with respect to the type of chemotherapy previously administered, and to subsequently demonstrate the equivalent efficacy of the drug, regardless of the first-line chemotherapy regimen used. There were a number of limitations in the current study; as it was retrospective the results cannot be regarded as definitive. Additionally, the small sample size may not have been sufficient to be fully representative, and no pharmacokinetic validation of the efficacy of amrubicin was conducted.

In conclusion, amrubicin may be a valid choice as a second-line chemotherapeutic agent for patients with SCLC, irrespective of the type of platinum agent and topoisomerase inhibitor-based chemotherapy regimen previously administered.

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