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Retrospective analysis of Japanese patients with relapse or refractory small-cell lung cancer treated with amrubicin hydrochloride

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Abstract. Amrubicin (AMR) is one of the most active chemotherapeutic agents for small-cell lung cancer (SCLC). Previous phase II studies reported on its effectiveness and severe hematological toxicities. However, AMR has yet to be approved outside Japan. Subsequently, no extensive evidence of its effects exist. Between January 2004 and October 2009, 69 patients received AMR for relapsed SCLC at our hospital. We reviewed these patients, and analyzed the efficacy and hematological toxicities of AMR. There were 27 sensitive relapses (S) and 42 refractory relapses (R). Patients received platinum agents, and 43 and 71% of the patients received etoposide and irinotecan, respectively. The median number of treatment cycles was 3 (range 1-14), and the response rate was 51% (70% in the S and 38% in the R cases, respectively). In patients administered with AMR as second-line therapy, the response rate was 55% and as third-line therapy, 39%. Median progression-free survival time was 3.2 months in the S and 1.9 months in the R patients (p=0.1071). Median survival time from the start of AMR was 6.2 months in the S and 4.8 months in the R cases (p=0.0045). The frequency of grade ≥3 hematological toxicities was leukopenia (41%), neutropenia (51%), anemia (14%), thrombocytopenia (17%) and febrile neutropenia (12%). No treatment-related death was observed. Although hematological toxicities, particularly neutropenia, were severe, AMR showed excellent anti-tumor activity, not only in the S, but also in the R cases, as shown in previous phase II studies. These results warrant further evaluation of AMR in the second-line setting, and also in the first-line setting in both limited- and extensive-stage disease. We conducted a phase II study to assess the efficacy of consolidation chemotherapy with AMR after standard chemoradiation in limited-stage SCLC.

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Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15% of all types of lung cancer (1). Despite the high sensitivity to chemotherapy, the majority of patients develop relapse. Second-line chemotherapy is considered for cases of relapsed SCLC; however, the prognosis of such patients is usually poor. Topotecan has shown a survival benefit against best supportive care and also a comparable response rate and survival with combination chemotherapy of cyclophosphamide, doxorubicin and vincristine (CAV) in relapsed SCLC (2,3). Currently, topotecan is the only drug approved by the US Food and Drug Administration for relapsed SCLC.

Amrubicin (AMR), a totally synthetic 9-aminoanthracycline, is converted to an active metabolite, amrubicinol, by reduction of its C-13 ketone group to a hydroxyl group (4). In a phase I/II study of patients with non-small-cell lung cancer, the recommended dose was determined to be 45 mg/m^2/day for 3 consecutive days every 3 weeks (5). In a phase II study of SCLC, 35 patients with extensive disease (ED) were treated at the recommended dose, and a response rate of 75.8% and median survival time (MST) of 11.7 months were reported (6).

In a phase II study evaluating the activity of AMR in relapsed SCLC, the response rate and MST were 52%, 11.6 months and 50%, 10.3 months in sensitive and refractory relapse, respectively (7,8). In addition, AMR was compared with topotecan in a randomized phase II study. In sensitive relapse (n=36), response rates were 53% for AMR and 21% for topotecan, and in refractory relapse, 17% for AMR and 0% for topotecan. Overall survival (OS) was not significantly different between the two arms; however, multivariate analysis showed that AMR had more influence than topotecan on OS. Although the dose of AMR was 40 mg/m^2/day, lower than the recommended dose, hematological toxicity was severe in the AMR arm, and one treatment-related death resulting from infection was observed in the AMR arm (9).

AMR is one of the most active chemotherapeutic agents for SCLC. However, currently it is not approved outside Japan, and no extensive evidence of its effects exist. This study examined relapsed SCLC patients treated with AMR in our hospital and analyzed its efficacy and hematological toxicities.

Table I. Patient characteristics.

Characteristic	S (n=27)	R (n=42)	Total (n=69)
Age (years)			
Median	70	62	66
Range	50-80	33-82	33-82
Gender (%)			
Male	23 (85)	32 (76)	55 (80)
Female	4 (15)	10 (24)	14 (20)
Disease extent (%)			
LD	10 (37)	5 (12)	15 (22)
ED	17 (63)	37 (88)	54 (78)
Response to first-line treatment (%)			
CR	8 (30)	5 (12)	13 (19)
PR	19 (70)	28 (67)	47 (68)
SD	0 (0)	5 (12)	5 (7)
PD	0 (0)	4 (9)	4 (6)
PS at the timing of AMR (%)			
0-1	21 (78)	27 (64)	48 (70)
2-4	6 (22)	15 (36)	21 (30)
No. of prior chemotherapy regimens (%)			
1	19 (70)	32 (76)	51 (74)
2	8 (30)	10 (24)	18 (26)
Previous chemotherapy (%)			
Platinum	27 (100)	42 (100)	69 (100)
Etoposide	13 (48)	17 (40)	30 (43)
Irinotecan	20 (74)	29 (69)	49 (71)
Topotecan	1 (4)	3 (7)	4 (6)

S, sensitive relapse; R, refractory relapse; LD, limited disease; ED, extensive disease; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PS, performance status and AMR, amrubicin.

Table II. Response and treatment delivery.

	S	R	Total
CR	1	1	2
PR	18	15	33
SD	5	8	13
PD	3	18	21
Response rate (%)	70	38	51
No. of treatment cycles			
Median	4	2	3
Range	1-8	1-14	1-14
Dose (mg/m²/day)			
25	0	1	1
30	6	11	17
35	6	19	25
40	9	8	17
45	6	3	9

S, sensitive relapse; R, refractory relapse; CR, complete response; PR, partial response; SD, stable disease and PD, progressive disease.
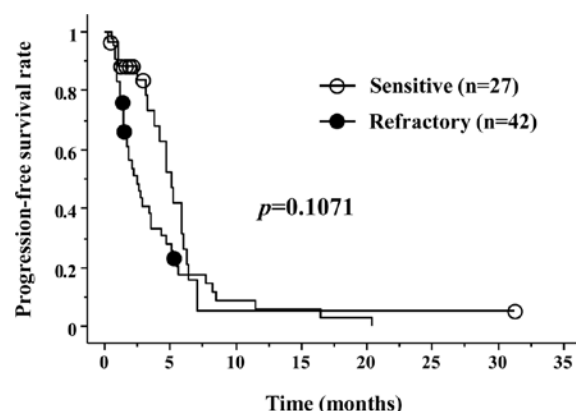

Figure 1. Progression-free survival (PFS) of sensitive and refractory relapse patients. Median PFS was 3.2 months in the sensitive group and 1.9 months in the refractory group, respectively (p=0.1071).

Patients and methods

Patients. Between January 2002 and January 2009, 164 SCLC patients were admitted to Kyoto University Hospital. Among them, 112 patients received chemotherapy alone, 36 chemoradiotherapy, 6 surgical resection with adjuvant chemotherapy and 10 best supportive care. As a consequence, 92 patients received second-line chemotherapy, including 69 that received AMR. In this study, patients who responded to initial chemotherapy and relapsed >3 months after chemotherapy were defined as sensitive relapse (S), while patients who did not respond to initial chemotherapy or relapsed within 3 months were defined as refractory relapse (R) patients. Patient data were obtained from our database. Consent was obtained form all patients. The study was approved by the Institutional Review Board.

Tumor evaluation and statistical analysis. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (10). Hematological toxicity was evaluated
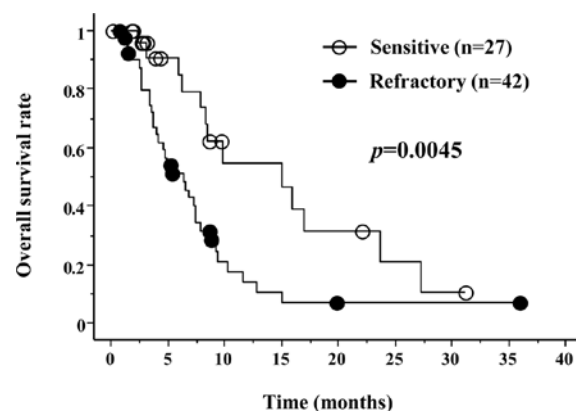

Figure 2. Overall survival (OS) of sensitive and refractory relapse patients. Median OS was 6.2 months in the sensitive group and 4.8 months in the refractory group, respectively (p=0.0045).

Table III. Univariate and multivariate analyses for overall survival.

Variables	MST (months)	Univariate	Multivariate		
		p-value	Risk ratio	95% CI	p-value
Age					
<70	5.3	0.9299	0.544	0.277-1.069	0.0775
≥70	4.9				
Gender					
Male	5.4	0.3841	2.148	0.942-4.901	0.0691
Female	5.0				
PS					
0-1	6.4	0.0039	0.388	0.197-0.763	0.0060
2-4	2.5				
Relapse pattern					
Sensitive	6.2	0.0045	3.533	1.656-7.540	0.0011
Refractory	4.8				

MST, median survival time; CI, confidence interval and PS, performance status.

Table IV. Hematological toxicities.

Event	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukopenia	12	16	18	10	28 (41)
Neutropenia	10	18	17	18	35 (51)
Anemia	19	32	6	4	10 (14)
Thrombocytopenia	18	8	8	4	12 (17)
Febrile neutropenia	0	0	8	0	8 (12)

according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). Survival time was measured from the start of chemotherapy to either the time of the patient succumbing to the disease due to any cause or the date when patients were last known to be alive. The survival curve was estimated using the Kaplan-Meier method and compared using the log-rank test. Individual clinical factors were compared using the χ^2 test. Multivariate analysis was conducted according to the Cox proportional hazards model. P<0.05 was considered to be significant. Statistical analyses were performed using StatView, version 5.0 (Abacus Concepts, Berkeley, CA, USA).

Results

Patient characteristics. Patient characteristics are listed in Table I. There were 27 S and 42 R cases. The median age was 70 years for sensitive patients and 62 for refractory patients. Most patients (~80%) were male in the two groups. The proportion of ED cases was 63% in sensitive patients and 88% in refractory patients. The proportion of performance status (PS) 2-4 was higher in the R group. Patients had previously received platinum agents, and ~40 and 70% had received etoposide and irinotecan, respectively. AMR as second-line

treatment was received by 74% of patients and as third-line treatment by the remaining patients.

Response and treatment delivery. Table II shows results of the response and treatment delivery. There were 1 complete response (CR), 18 partial response (PR), 5 stable disease (SD) and 3 progressive disease (PD) cases in the S group (response rate 70%) and 1 CR, 15 PR, 8 SD and 18 PD cases in the R group (response rate 38%). The median number of treatment cycles was 4 (range 1-8) in the S group and 2 (range 1-14) in the R group. The median dose of AMR was 40 mg/m^2 in the S group and 35 mg/m^2 in the R group, respectively.

Survival. Progression-free survival (PFS) is shown in Fig. 1. Median PFS was 3.2 months in the S group and 1.9 months in the R group, respectively (p=0.1071). OS was significantly better in the S group (Fig. 2). Median OS was 6.2 months in the S group and 4.8 months in the R group, respectively (p=0.0045). Univariate and multivariate analyses showed that PS of 0-1 or 2-4 for AMR, and the relapse pattern (sensitive or refractory) were both independent prognostic factors for OS (Table III).

Hematological toxicities. Results of the hematological toxicities are listed in Table IV. The frequency of grade ≥3

hematological toxicities was leukopenia (41%), neutropenia (51%), anemia (14%), thrombocytopenia (17%) and febrile neutropenia (12%). The number of patients requiring the administration of granulocyte-stimulating factor (G-CSF), red blood cell transfusion and platelet transfusion were 34 (50%), 7 (10%) and 2 (3%), respectively. No treatment-related death was noted.

Discussion

SCLC is highly sensitive to chemotherapy. Therefore, the main treatment strategy for SCLC is systemic chemotherapy. Currently, both cisplatin + etoposide and cisplatin + irinotecan are considered to be standard chemotherapeutic regimens for SCLC (11). Despite the high initial sensitivity to chemotherapy, the majority of patients develop relapse, and the prognosis of patients with relapsed SCLC is usually poor. The effects of topotecan, a DNA topoisomerase-I inhibitor, are extensively evaluated in patients with relapsed SCLC. Currently, topotecan is the only drug approved by the US Food and Drug Administration for relapsed SCLC. AMR has shown promising anti-tumor activity in previous phase II studies for relapsed SCLC, as well as superiority in a randomized phase II study compared to topotecan (7-9). AMR is at present being examined for SCLC worldwide. However, it has yet to be approved outside Japan. Therefore, clinical data regarding AMR is limited.

In a randomized phase II study comparing AMR with topotecan, the response rate in the AMR arm was better in S with 53% in S and 17% in R cases, respectively (9). However, in previous single-arm phase II studies of AMR, a comparable response rate was noted between S and R cases [52 and 50% in Onoda *et al* (7); 40 and 50% in Kato *et al* (8)]. Considering that R is extremely chemo-resistant, the anti-tumor activity of AMR is considerably promising. Although inferior to S, a response rate of 38% was observed in the R group in our study.

PFS was not significantly different between S and R patients. However, OS was significantly more favorable in the S patients (6.2 vs. 4.8 months, p=0.0045). Multivariate analysis demonstrated that PS of 0-1 or 2-4 for AMR, and the relapse pattern (sensitive or refractory) were both independent prognostic factors for OS. The results were consistent with our previous study (12).

Hematological toxicities, particularly neutropenia, were found to be severe, as shown in previous studies. Although the majority of patients received AMR under the recommended dose, 50% required G-CSF support in our study. In previous single-arm phase II studies of AMR, the frequency of grade ≥3 neutropenia and G-CSF support were 83.3 and 70%, respectively, at a dose of 40 mg/m^2, and 97 and 71%, respectively, at a dose of 45 mg/m^2 (7,8). Since the recommended dose of 45 mg/m^2 was determined in chemo-naïve patients, it may be too high for previously treated patients. Igawa *et al* evaluated the recommended dose of AMR in previously treated SCLC patients and determined the dose to be 40 mg/m^2 for second-line and 35 mg/m^2 for third-line treatment (13).

In conclusion, in this retrospective study, we confirmed that AMR has excellent anti-tumor activity, not only in sensitive relapse, but also in refractory relapse, as shown in previous phase II studies. These results warrant further evaluation of AMR in both the second and first-line setting in limited- and extensive-stage disease. We are currently conducting a phase II study to assess the efficacy of consolidation chemotherapy following AMR following standard chemoradiation in limited-stage SCLC.

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