Original Article

Clinical impact of amrubicin monotherapy in patients with relapsed small cell lung cancer: a multicenter retrospective study

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Background: Topoisomerase is an essential enzyme for deoxyribonucleic acid replication, and its inhibitors suppress tumor progression. Amrubicin, a topoisomerase II inhibitor, is mainly used in the second-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). However, the impact of different types of topoisomerase inhibitors for first-line chemotherapy on the efficacy of amrubicin remains unclear. In the present study, we aimed to evaluate the efficacy of second-line amrubicin in patients with relapsed SCLC who were previously treated with platinum-based chemotherapy, including topoisomerase I and II inhibitors.

Methods: This study retrospectively analyzed patients with ES-SCLC who experienced recurrence and were treated with amrubicin at 22 institutions in Japan between April 2015 and November 2020. The progression-free survival of amrubicin monotherapy was investigated using the Kaplan-Meier method.

Results: A total of 320 patients were enrolled in this study, with 59 (18%) receiving platinum plus topoisomerase I inhibitor irinotecan and 261 (82%) receiving platinum plus topoisomerase II inhibitor

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etoposide as first-line treatment. The progression-free survival of amrubicin was significantly longer in the irinotecan group than in the etoposide group (3.2 *vs.* 2.5 months; P=0.034).

Conclusions: These results showed that different types of topoisomerase inhibitors could affect the efficacy of amrubicin monotherapy in the second-line treatment of patients with relapsed ES-SCLC.

Keywords: Small cell lung cancer (SCLC); amrubicin; topoisomerase inhibitor; irinotecan; etoposide

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1). Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is characterized by a rapid doubling time, a high growth fraction, and the early development of widespread metastases (2,3). Nearly 70% of patients with SCLC are diagnosed with extensive-stage SCLC (ES-SCLC), and systemic platinum-based chemotherapy has been the standard treatment for ES-SCLC for decades (4). Although first-line chemotherapy frequently results in high response rates, almost all patients with ES-SCLC experience early disease progression or recurrence, with less than 5% surviving for 2 years (4,5). Therefore, novel, effective treatments for ES-SCLC are warranted in daily clinical settings.

Recent trials have demonstrated that treatment with immune checkpoint inhibitors has greatly improved the prognosis of patients with non-SCLC (6-10). However, a phase 2 study of maintenance pembrolizumab and a phase 3 study of ipilimumab plus platinum-based chemotherapy did not show improved efficacy in the first-line treatment of ES-SCLC (5,11). In several recent phase 3 trials, the addition of immunotherapy to platinum and etoposide has resulted in significantly longer overall survival (OS) and progression-free survival (PFS) than chemotherapy alone (12,13). The main cytotoxic agents used for SCLC treatment are platinum plus topoisomerase inhibitors (e.g., etoposide, amrubicin, and irinotecan) (3,14).

Topoisomerase is an essential enzyme for DNA replication, and its inhibitors suppress tumor progression (15). Amrubicin is one of the second-line treatments for SCLC because it improved OS in patients with refractory disease in a phase 3 trial (16). Amrubicin and etoposide are type II topoisomerase inhibitors, and irinotecan is a type I topoisomerase inhibitor (15,17). However, it is unclear whether differences between their mechanisms of action affect the clinical outcomes of second-line amrubicin for relapsed ES-SCLC. Moreover, the impact of first-line immunochemotherapy on the efficacy of amrubicin monotherapy has not yet been elucidated. The present study aimed to evaluate the efficacy of second-line amrubicin in patients with relapsed SCLC who were previously treated with platinum-based chemotherapy, including topoisomerase I and II inhibitors. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-160/rc).

Methods

Patients

This study retrospectively assessed 320 patients with ES-SCLC who were refractory to first-line treatment with platinum-based chemotherapy or immunochemotherapy and received amrubicin monotherapy as second-line treatment at 22 institutions in Japan between April 2015 and November 2020. Eligible patients were aged >20 years, with histologically or cytologically confirmed SCLC and evaluable target lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1. The following clinical data were extracted from retrospective medical records: age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), history of first-line treatment, overall response rate (ORR) following amrubicin monotherapy, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, the PFS following amrubicin monotherapy, and the PFS of the first-line treatment. The relapse-free interval of the first-line treatment was also extracted and classified into sensitive or refractory relapse based on whether the period exceeded 90 days. OS was defined as the time from the first administration of platinum-based chemotherapy until any cause of death. The

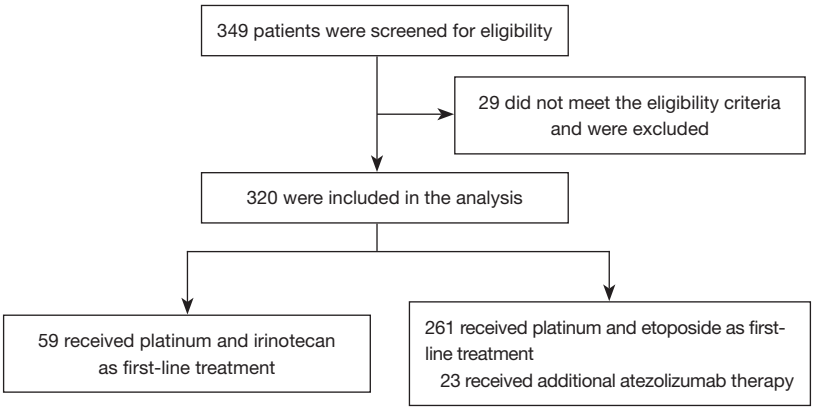

Figure 1 Consort diagram for this study.

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committees of the Kyoto Prefectural University of Medicine (No. ERB-C-1927-3) and all hospitals involved. However, the requirement for informed consent was waived because this was a retrospective study, and the official website was used as an opt-out method, which was approved by the Ethics Committee of each hospital.

Matching

Rigorous adjustment for significant differences in the baseline characteristics of patients with propensity score matching was performed using the following variables: age, sex, ECOG PS at first-line treatment initiation, and ECOG PS at amrubicin initiation. Nearest-neighbor matching was performed at a ratio of 1:1 without replacement. The caliper was set at 0.2.

Statistical analysis

PFS was analyzed using the Kaplan-Meier method and compared using the Peto-Peto-Wilcoxon test. PFS of amrubicin was defined as the time from the initiation of amrubicin to disease progression or death from any cause, while PFS of the first-line treatment was defined as the time from the initiation of the first-line treatment to disease progression. The data cut-off date was November 25, 2020. Variables related to PFS reported in previous studies and the most relevant factors identified in the results of univariable analyses were included in a multivariate Cox proportional hazards model. Hazard ratios estimated from the Cox analysis were reported with 95% confidence intervals (CIs). The pairwise deletion was used for missing data in some cases. All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P<0.05 was considered statistically significant.

Results

Patient characteristics

This study enrolled 320 patients with ES-SCLC who received amrubicin monotherapy as a second-line treatment (*Figure 1*). Among these, 59 (18%) patients received platinum plus irinotecan (irinotecan group), and the remaining 261 (82%) received platinum plus etoposide (etoposide group) as the first-line treatment. In the etoposide group, 23 patients received immunochemotherapy, including atezolizumab. The patient characteristics are shown in *Table 1*. Patients in the irinotecan group were significantly younger than those in the etoposide group (median: 67.0 *vs.* 71.0 years, P<0.001). The baseline PS was better in the irinotecan group than in the etoposide group, but there was no significant difference in PS at amrubicin initiation between the two groups.

Clinical predictive factors related to the PFS following amrubicin monotherapy in the second-line setting

The ORR following amrubicin monotherapy was not significantly different between the irinotecan and etoposide groups (P=0.16; *Table 2*). The median PFS with amrubicin monotherapy was 2.6 months in all patients with ES-SCLC (*Figure 2A*). The PFS was longer in the irinotecan group than in the etoposide group (median: 3.2 *vs.* 2.5 months,

Table 1 Clinicopathological features by regimens of first-line treatment

Variables	Platinum plus etoposide, n=261	Platinum plus irinotecan, n=59	P value
Median age, years (range)	71.0 (47.0–91.0)	67.0 (50.0–83.0)	<0.001
Age categorization, n (%)			<0.001
<75	174 (66.7)	55 (93.2)	
≥75	87 (33.3)	4 (6.8)	
Sex, n (%)			0.18
Male	200 (76.6)	40 (67.8)	
Female	61 (23.4)	19 (32.2)	
ECOG PS =0, 1, n (%)			
At first-line initiation	220 (84.3)	56 (94.9)	0.05
At AMR initiation	212 (81.2)	51 (86.4)	0.31
Combined use of atezolizumab, n (%)	23 (8.8)	0 (0.0)	–

ECOG PS, Eastern Cooperative Oncology Group performance status; AMR, amrubicin.

Table 2 Overall response rate for AMR treatment by first-line treatment regimens

Overall response rate for AMR treatment	Platinum plus etoposide, n=261	Platinum plus irinotecan, n=59	P value
Complete response, n (%)	2 (0.8)	1 (1.7)	0.161
Partial response, n (%)	51 (19.5)	17 (28.8)	
Stable disease, n (%)	86 (33.0)	23 (39.0)	
Progressive disease, n (%)	72 (27.6)	11 (18.6)	
Not evaluable, n (%)	50 (19.2)	7 (11.9)	

AMR, amrubicin.

P=0.034; *Figure 2B*). A propensity score matching analysis was performed to compare the topoisomerase inhibitors in the first-line treatment to minimize the impact of treatment allocation bias, as described in section 2.2. Clinicopathological features by regimens of first-line treatment after matching are shown in *Table 3*. A significant difference in the PFS following amrubicin monotherapy was observed between the irinotecan and etoposide groups in the propensity score matching analysis (median: 3.4 *vs.* 2.1 months, P=0.03; *Figure 3*).

In the univariate analysis, the PFS with amrubicin monotherapy was significantly longer in patients with good PS at amrubicin initiation [0, 1] than in those with poor PS [2, 3] [2.8 months (95% CI: 2.6–3.4 months) *vs.* 1.4 months (95% CI: 0.93–1.8 months), P<0.001; *Table 4*]. Thus, the multivariate analysis demonstrated that platinum plus etoposide at the first-line treatment and poor PS at amrubicin initiation were independent prognostic factors for prolonged PFS following amrubicin monotherapy (*Table 5*). In this study, PFS with amrubicin was evaluated in the aging of patients ≥70 and those ≥75 years. The results of ≥70 years old patients were similar to those of ≥75 years, compared with the younger patients (Figure S1).

Correlation between the PFS times following first-line treatment and amrubicin monotherapy in the second-line setting

The impact of first-line treatment on the clinical outcomes of amrubicin monotherapy in a second-line setting was evaluated. The irinotecan and etoposide groups were classified into two groups based on the median PFS following first-line treatment. The PFS following amrubicin monotherapy was significantly longer in the PFS

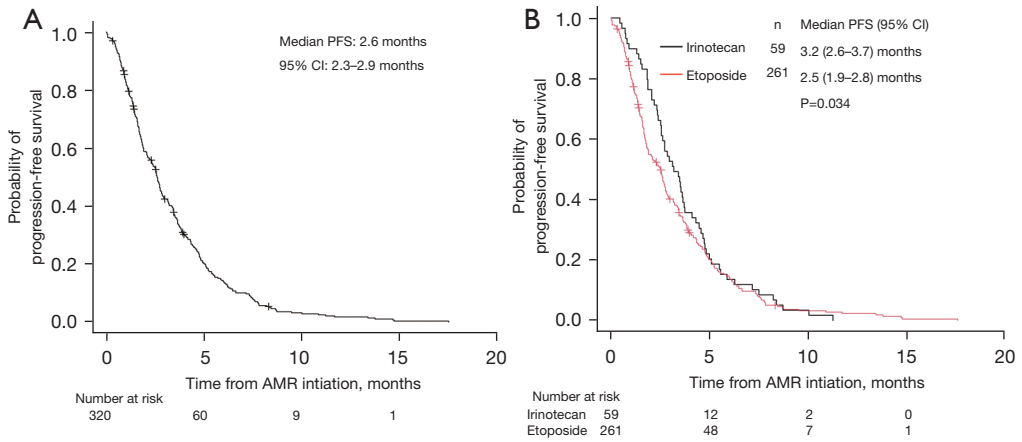

Figure 2 Kaplan-Meier curve for PFS following AMR monotherapy in all patients. (A) The median PFS following AMR in all patients was 2.6 months. (B) The median PFS following AMR was significantly longer in the platinum plus irinotecan group than in the platinum plus etoposide group (3.2 *vs.* 2.5 months, P=0.034). PFS, progression-free survival; CI, confidence interval; AMR, amrubicin.

Table 3 Clinicopathological features by first-line treatment regimens after matching

Variables	Platinum plus etoposide, n=57	Platinum plus irinotecan, n=57	P value
Median age, years (range)	68.0 (53.0–80.0)	67.0 (50.0–83.0)	0.025
Age categorization, years, n (%)			1
<75	53 (93.0)	53 (93.0)	
≥75	4 (7.0)	4 (7.0)	
Sex			1
Male	38 (66.7)	38 (66.7)	
Female	19 (33.3)	19 (33.3)	
ECOG PS =0, 1, n (%)			
At first-line treatment initiation	54 (94.7)	54 (94.7)	1
At AMR initiation	51 (89.5)	51 (89.5)	1

ECOG PS, Eastern Cooperative Oncology Group performance status; AMR, amrubicin.

≥4.8 months group than in the PFS <4.8 months group (3.4 *vs.* 1.6 months, Peto-Peto-Wilcoxon test, P<0.001) in the etoposide group (*Figure 4A*). In contrast, there was no significant difference in the PFS following amrubicin monotherapy between the PFS ≥4.9 months group and the PFS <4.9 months group (2.9 *vs.* 3.5 months, Peto-Peto-Wilcoxon test, P=0.373) in the irinotecan group (*Figure 4B*). The subgroup analyses based on various clinicopathological factors are shown in *Figure 5*. Compared with chemotherapy with platinum and etoposide, the additional use of atezolizumab in the first-line treatment had no significant effect on the PFS following amrubicin monotherapy (Figure S2).

Correlation between the efficacies following first-line treatment and amrubicin monotherapy

The impact of the recurrence on the clinical outcomes of amrubicin monotherapy was evaluated by classifying both the irinotecan and etoposide groups into two groups based on the period from the last administration of the first-line treatment to recurrence. The PFS following amrubicin monotherapy was significantly longer in sensitive-relapsed patients than in refractory-relapsed patients (4.1 *vs.*

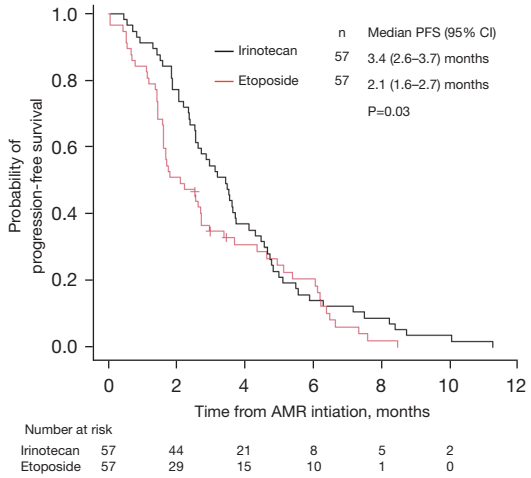

Figure 3 Kaplan-Meier curve for PFS following AMR monotherapy, classified by the first-line treatment regimen. Propensity score matching analysis was performed to minimize the impact of treatment allocation bias. The median PFS was longer in patients who had previously received platinum plus irinotecan therapy than others (3.4 *vs.* 2.1 months, P=0.03). PFS, progression-free survival; CI, confidence interval; AMR, amrubicin.

Table 4 Univariate analysis for PFS

Variables	No. of patients	Median PFS (95% CI)	P value
Age categorization, years			0.210
<75	229	2.6 (2.3–2.9)	
≥75	91	2.6 (1.7–3.2)	
Sex			0.647
Male	240	2.7 (2.3–3.1)	
Female	80	2.5 (1.8–2.8)	
ECOG PS at first-line treatment initiation			0.030
0, 1	276	2.7 (2.4–3.0)	
2, 3	42	1.8 (1.2–2.7)	
ECOG PS at AMR initiation			<0.001
0, 1	263	2.8 (2.6–3.4)	
2, 3	48	1.4 (0.93–1.8)	
First-line regimen			0.030
Platinum plus etoposide	261	2.6 (1.9–2.8)	
Platinum plus irinotecan	59	3.2 (2.6–3.8)	

PFS, progression-free survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; AMR, amrubicin.

Table 5 Multivariate analysis for PFS

Variables	HR (95% CI)	P value
Age ≥75 years	1.15 (0.78–1.68)	0.490
Female	1.01 (0.75–1.35)	0.960
Poor ECOG PS at first-line initiation	1.04 (0.71–1.53)	0.840
Poor ECOG PS at AMR initiation	1.79 (1.26–2.54)	0.001
Use of platinum plus etoposide at the first-line treatment	1.41 (1.00–1.98)	0.048

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; AMR, amrubicin.

1.8 months, Peto-Peto-Wilcoxon test, P<0.001) in the etoposide group (*Figure 6A*). In contrast, no significant difference in the PFS following amrubicin monotherapy between sensitive-relapsed and refractory-relapsed patients (4.3 *vs.* 3.0 months, Peto-Peto-Wilcoxon test, P=0.19) in the irinotecan group (*Figure 6B*).

OS analysis

At the date of data cut-off, the median follow-up was 13.6 months. No significant differences were observed between the OS of the irinotecan and etoposide groups (14.0 *vs.* 13.6 months, Peto-Peto-Wilcoxon test, P=0.35) (*Figure 7*).

Safety

Fifty patients in the irinotecan group and 241 in the etoposide group were evaluated for the safety of amrubicin monotherapy. Grade ≥3 CTCAEs were observed in 78% and 64.3% of patients in the irinotecan and etoposide groups, respectively (P=0.07). Grade ≥3 neutropenia was more frequently reported in the irinotecan group than in the etoposide group (78% *vs.* 57.9%, P=0.01). However, the incidence of febrile neutropenia was not of significance (P=1). Grade ≥3 pneumonitis were observed in both groups (4% *vs.* 7%, P=0.75). Discontinuation due to adverse events caused by pneumonitis and neutropenia occurred in both groups (10.5% *vs.* 13%, P=0.82) and treatment-related deaths were observed in 6 patients (2.5%) of the etoposide group (Table S1).

Discussion

The standard first-line treatment for ES-SCLC was

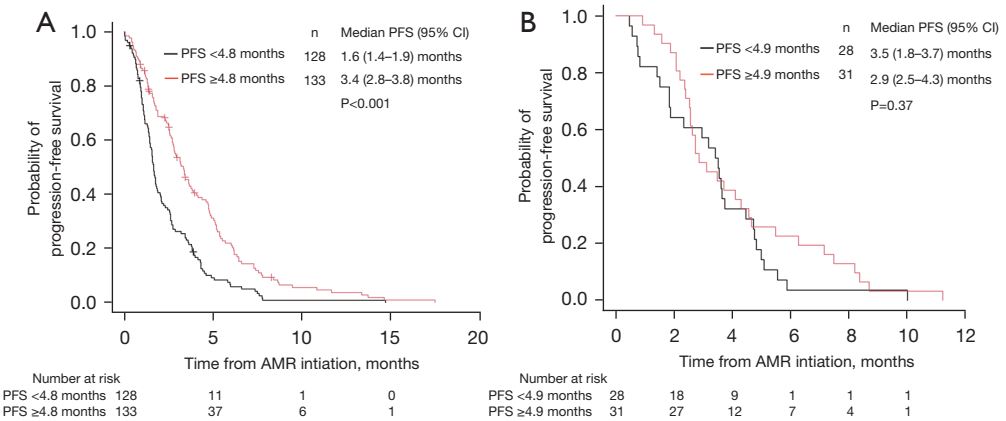

Figure 4 Kaplan-Meier curve for PFS following AMR monotherapy, classified by the response to first-line treatment in (A) the platinum plus etoposide group and (B) the platinum plus irinotecan group. (A) The median PFS following AMR was significantly longer in patients who showed a better response to platinum plus etoposide therapy (PFS ≥4.8 months group) than in others (PFS <4.8 months group) (3.4 *vs.* 1.6 months, P<0.001). (B) There was no significant correlation in the median PFS following AMR between patients who showed a good response to platinum plus irinotecan therapy and those who showed a poor response (2.9 *vs.* 3.5 months, P=0.37). PFS, progression-free survival; CI, confidence interval; AMR, amrubicin.

A

Subgroup	No. of patients	Hazard ratio	HR [95% CI]
Age ≥75 years	87/261		1.05 [0.79–1.39]
Female	61/261		0.95 [0.70–1.30]
Poor ECOG PS at 1st line initiation	39/259		1.05 [0.72–1.53]
Poor ECOG PS at AMR initiation	42/254		1.79 [1.25–2.57]
PFS following first line treatment >4.8 months	133/261		0.57 [0.44–0.75]
Combined use of atezolizumab	23/261		0.81 [0.41–1.61]

B

Subgroup	No. of patients	Hazard ratio	HR [95% CI]
Age ≥75 years	4/59		2.59 [0.86–7.77]
Female	19/59		1.06 [0.59–1.91]
Poor ECOG PS at 1st line initiation	3/59		1.60 [0.48–5.29]
Poor ECOG PS at AMR initiation	6/59		0.89 [0.33–2.43]
PFS following first line treatment >4.9 months	31/59		0.71 [0.39–1.31]

Figure 5 Subgroup analysis of PFS of AMR in (A) the platinum plus etoposide group and (B) the platinum plus irinotecan group. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; AMR, amrubicin.

platinum-based chemotherapy until immunochemotherapy was approved for clinical use (3,4). A previous clinical phase 3 trial showed that chemotherapy with cisplatin plus irinotecan resulted in a significantly longer OS than that with cisplatin plus etoposide (12.8 *vs.* 9.4 months) (18); however, other phase 3 trials failed to confirm this observation (19,20). Thus, based on several clinical trials for untreated patients with ES-SCLC, two cytotoxic combined regimens have existed as double standard therapies for first-line treatment in patients with ES-SCLC for decades. In this study, we focused on the aspects of the drug mechanism of action related to the clinical outcomes of amrubicin monotherapy in the second-line setting for ES-SCLC. Previous preclinical studies have reported that treatment

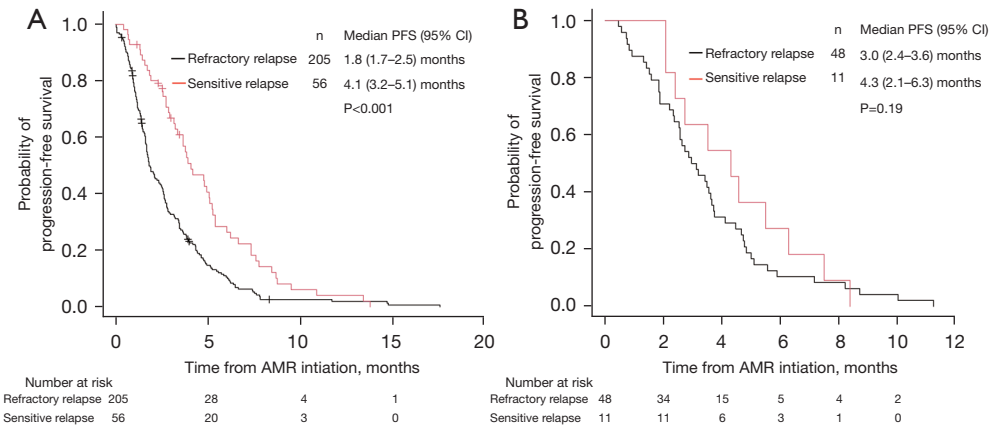

Figure 6 Kaplan-Meier curve for PFS following AMR monotherapy, classified based on whether sensitive or refractory relapse in (A) the platinum plus etoposide group and (B) the platinum plus irinotecan group. (A) The median PFS following AMR was significantly longer in patients classified as sensitive relapse compared to refractory relapse in the platinum plus etoposide group (4.1 *vs.* 1.8 months, P<0.001). (B) There was no significant correlation in the median PFS following AMR between patients classified as sensitive relapse and refractory relapse in the platinum plus irinotecan group (4.3 *vs.* 3.0 months, P=0.19). PFS, progression-free survival; CI, confidence interval; AMR, amrubicin.

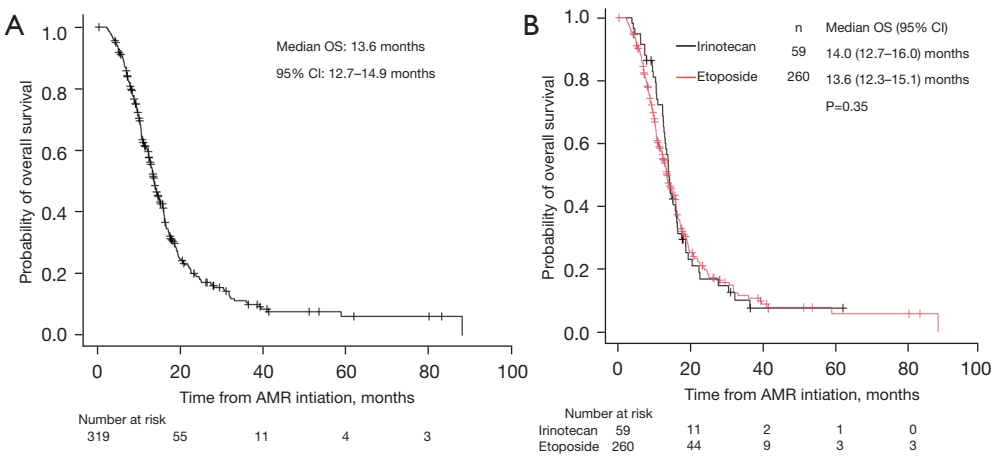

Figure 7 Kaplan-Meier curve for OS following AMR monotherapy in all patients. (A) The median OS in all patients was 13.6 months. (B) There was no significant difference between the median OS of the platinum plus irinotecan group and that of the platinum plus etoposide group (14.0 *vs.* 13.6 months, P=0.35). OS, overall survival; CI, confidence interval; AMR, amrubicin.

with topoisomerase I inhibitors led to the downregulation of topoisomerase I activity and reciprocal enhancement of topoisomerase II activity using tumor cell lines, thereby resulting in high sensitivity to topoisomerase II inhibitors (21-23). Indeed, our current observations in 320 patients with ES-SCLC showed that, compared with etoposide (topoisomerase II inhibitor) treatment, first-line treatment with irinotecan (topoisomerase I inhibitor) was associated with prolonged PFS following amrubicin (topoisomerase II inhibitor) treatment. Murakami *et al.* reported that in 82 patients with chemotherapy-refractory SCLC, the efficacy of amrubicin was poorer in patients who were previously treated with etoposide, which is consistent with the results of our study (24). Interestingly, the PFS following amrubicin monotherapy was positively associated with the PFS following etoposide-containing chemotherapy in the first-line setting. Given that responders to the etoposide-containing regimen had better outcomes with amrubicin in the second-line setting, PFS might be a promising clinical factor in selecting responders to second-line amrubicin,

although both are topoisomerase II inhibitors.

Recent clinical trials have demonstrated that immunochemotherapy has better patient outcomes than chemotherapy when used as first-line treatment for ES-SCLC (12,13). However, there is limited evidence to validate the sequence of first-line treatment and second-line amrubicin monotherapy for patients with ES-SCLC. Current observations showed that not only the sequential use of topoisomerase I followed by topoisomerase II inhibitors but also the sensitivity-based selection of topoisomerase I and II inhibitors could be predicted to improve the PFS following amrubicin therapy irrespective of its combination with immune checkpoint inhibitors. In contrast, chemotherapy of platinum plus irinotecan treatment could be a better option for ineligible patients for immune checkpoint inhibitors, such as autoimmune diseases with a high risk of severe immune-related adverse events. Further prospective investigations are needed to confirm our observations regarding the relationship between immunochemotherapy and second-line treatment.

There are some limitations to our study. First, this was a retrospective study, and the first-line treatments differed depending on the institution, although we also used propensity score analysis. Second, while the results of phase 3 trials on cisplatin plus irinotecan regimens varied by country, all patients in this cohort were Japanese. However, our findings in real-world settings regarding the selection of topoisomerase inhibitors for ES-SCLC treatment are notable and could help improve ES-SCLC prognosis. Further investigations are required to address these issues.

Conclusions

The observations in this study suggest that patients previously treated with the topoisomerase I inhibitor irinotecan-containing regimen might have promising outcomes with amrubicin monotherapy by switching the target for topoisomerase inhibition. Further prospective studies are required to clarify the best sequence strategy for the first- and second-line treatments for ES-SCLC. Our results showed that different types of topoisomerase inhibitors could affect the PFS following second-line amrubicin monotherapy in patients with ES-SCLC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committees of the Kyoto Prefectural University of Medicine (No. ERB-C-1927-3) and all hospitals involved. However, the requirement for informed consent was waived because this was a retrospective study, and the official website was used as an opt-out method, which was approved by the Ethics Committee of each hospital.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
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 2006;24:4539-44.
3. Dómine M, Moran T, Isla D, et al. SEOM clinical guidelines for the treatment of small-cell lung cancer (SCLC) (2019). Clin Transl Oncol 2020;22:245-55.
4. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer 2015;121:664-72.
5. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016;34:3740-8.
6. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
8. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
9. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
10. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
11. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC). J Thorac Oncol 2018;13:1393-9.
12. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
13. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51-65.
14. Horita N, Yamamoto M, Sato T, et al. Amrubicin for relapsed small-cell lung cancer: a systematic review and meta-analysis of 803 patients. Sci Rep 2016;6:18999.
15. Chhatriwala H, Jafri N, Salgia R. A review of topoisomerase inhibition in lung cancer. Cancer Biol Ther 2006;5:1600-7.
16. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol 2014;32:4012-9.
17. Kurata T, Okamoto I, Tamura K, et al. Amrubicin for non-small-cell lung cancer and small-cell lung cancer. Invest New Drugs 2007;25:499-504.
18. 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 2002;346:85-91.
19. Kim DW, Kim HG, Kim JH, et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin versus Etoposide Plus Cisplatin in Chemotherapy-Naïve Korean Patients with Extensive-Disease Small Cell Lung Cancer. Cancer Res Treat 2019;51:119-27.
20. Zatloukal P, Cardenal F, Szczesna A, et al. A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. Ann Oncol 2010;21:1810-6.
21. Sugimoto Y, Tsukahara S, Oh-hara T, et al. Elevated expression of DNA topoisomerase II in camptothecin-resistant human tumor cell lines. Cancer Res 1990;50:7962-5.
22. Gupta RS, Gupta R, Eng B, et al. Camptothecin-resistant mutants of Chinese hamster ovary cells containing a resistant form of topoisomerase I. Cancer Res 1988;48:6404-10.
23. Tan KB, Mattern MR, Eng WK, et al. Nonproductive rearrangement of DNA topoisomerase I and II genes: correlation with resistance to topoisomerase inhibitors. J

Natl Cancer Inst 1989;81:1732-5.
24. Murakami H, Yamamoto N, Shibata T, et al. A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901). Lung Cancer 2014;84:67-72.

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Supplementary

Table S1 AEs of AMR treatment

Items	Platinum plus irinotecan (n=50), n (%)	Platinum plus etoposide, (n=241), n (%)	P value
Grade ≥3 AEs (occurring in ≥5% of patients)			
Hematologic			
Anemia	0 (0.0)	15 (6.2)	0.08
Febrile neutropenia	3 (6.0)	16 (6.6)	1
Neutropenia	39 (78)	140 (57.9)	0.01
Nonhematologic			
Pneumonitis	2 (4.0)	17 (7.0)	0.75
Discontinuation due to AEs	6 (10.5)	32 (13.0)	0.82
Treatment-related deaths	0 (0.0)	6 (2.5)	0.59

AE, adverse event; AMR, amrubicin.

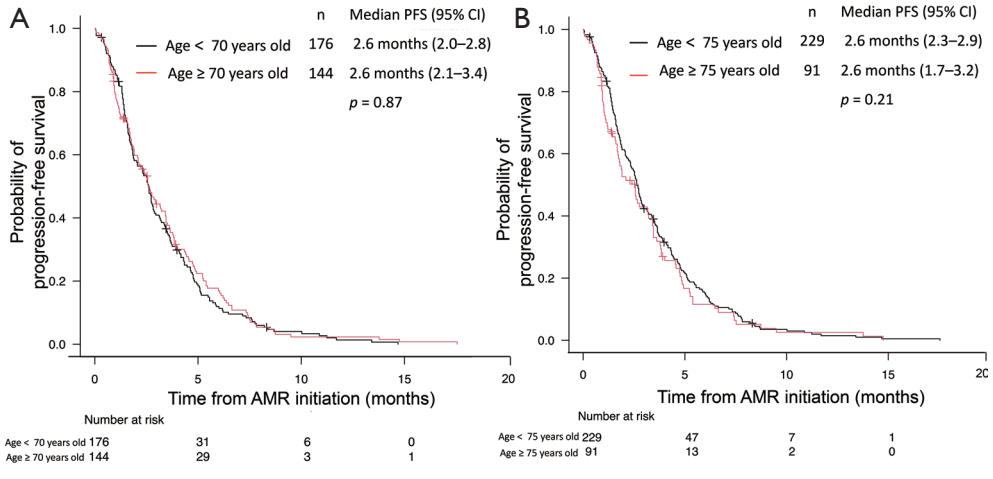

Figure S1 Kaplan-Meier curve for PFS following AMR monotherapy in elderly patients and young patients divided at (A) 70 years old and (B) 75 years old. There was no significant difference in PFS following AMR. PFS, progression-free survival; AMR, amrubicin.

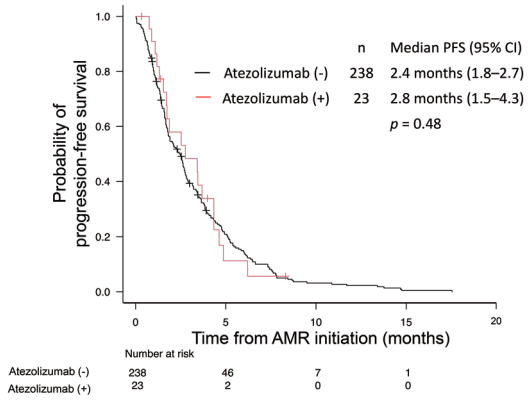

Figure S2 Kaplan-Meier curve for PFS following AMR monotherapy in patients treated with or without atezolizumab. There was no significant correlation in the median PFS between patients treated with and without atezolizumab (84 *vs.* 72 days, P=0.48). PFS, progression-free survival; AMR, amrubicin; CI, confidence interval.

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