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# The efficacy of amrubicin third-line chemotherapy in patients with relapsed extensive-disease small-cell lung cancer: A retrospective and historical study in a single institute

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**Keywords**
Amrubicin; febrile neutropenia; relapsed extensive-disease small-cell lung cancer; salvage chemotherapy.

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## Abstract

**Background:** The efficacy of amrubicin for relapsed small-cell lung cancer (SCLC) has been reported in previous studies. Few reports, however, describe the efficacy and survival benefit of third-line amrubicin chemotherapy in patients with extensive disease (ED)-SCLC.

**Methods:** We retrospectively analyzed the clinical records of ED-SCLC patients treated with amrubicin salvage chemotherapy as a third-line chemotherapy between January 2005 and July 2016 (salvage amrubicin group). The efficacy and toxicities of amrubicin were evaluated. Overall survival (OS) in the amrubicin salvage group was compared with OS among ED-SCLC patients treated with at least second-line chemotherapy between May 2000 and July 2016 and without subsequent amrubicin salvage chemotherapy.

**Results:** A total of 18 patients with a median age of 70 years were analyzed in the amrubicin salvage group. The median number of treatment cycles of amrubicin was four. The response rate was 27.8% (95% confidence interval (CI), 7.1%–48.5%), and the disease control rate (DCR) was 66.7% (95% CI, 44.9%–88.4%). Median progression-free survival was 2.9 months (95% CI, 1.0–4.9 months), and median OS after an initial chemotherapy was 18.1 months (95% CI, 10.2–26.0 months). OS in the amrubicin salvage group was significantly longer than in the no-amrubicin group ($n$ = 19; 12.6 months, 95% CI, 11.5–13.8 months, $P$ = 0.005). The frequency of neutropenia greater than grade 3 was 72.2%, with febrile neutropenia developing in 38.9% of patients in the amrubicin salvage group.

**Conclusions:** Despite a high frequency of febrile neutropenia, amrubicin salvage chemotherapy may improve OS in patients with relapsed ED-SCLC.

## Introduction

Small-cell lung cancer (SCLC) is a very chemosensitive solid tumor which accounts for approximately 15% of all lung cancer cases.[1,2] Two-thirds of SCLC is classified as extensive disease (ED). Several meta-analyses have found that first-line etoposide or irinotecan combined with platinum (cisplatin or carboplatin) chemotherapy improves overall survival (OS) in most cases of ED-SCLC.[3–8] However, most patients experience relapse as a result of intrathoracic tumor growth and extrapulmonary distant spread. The prognosis for OS after relapse in SCLC is approximately three months without chemotherapy after second-line treatment, and treatment options are limited.[9]

Amrubicin hydrochloride is a third-generation anthracycline and potent topoisomerase II inhibitor. In clinical trials, amrubicin is associated with an equivalent median survival time to topotecan for sensitive SCLC and with

  

improved OS compared to topotecan for refractory SCLC (6.2 months vs. 5.7 months, respectively; $P = 0.047$).[10] In addition, in a systematic review and meta-analysis of 803 patients who received second-line amrubicin, amrubicin was associated with better OS for refractory-relapsed cases compared with topotecan.[11] Based on these clinical studies, the 2014 Japanese lung cancer guidelines recommended amrubicin as an optional agent for second-line chemotherapy for ED-SCLC in Japan.

Little information is available, however, regarding efficacy and survival benefits of third-line amrubicin chemotherapy in patients with ED-SCLC compared with what is known about second-line amrubicin. Rechallenge with a first-line platinum-based treatment has been performed in clinical practice for patients with sensitive ED-SCLC.[12] Thus, certain patients with ED-SCLC have been challenged with third-line chemotherapies including amrubicin in clinical practice. We conducted a retrospective and historical study in patients with third-line amrubicin for ED-SCLC in our hospital (designated here as the amrubicin salvage group), focusing on efficacy and toxicity, and compared OS in this group with that among patients treated with two or more regimens without amrubicin.

## Methods

This retrospective study was approved by the institutional review board of Shinshu University School of Medicine (approval number: 4354) and conducted in accordance with the principles of the Declaration of Helsinki. We retrospectively investigated consecutive patients with ED-SCLC diagnosed and treated at Shinshu University Hospital between May 2000 and July 2016. A total of 91 ED-SCLC patients were diagnosed and treated in our hospital. The patients were grouped based on history before ($n = 24$) and after ($n = 67$) amrubicin approval for clinical practice in our hospital at 2005. Among these patients, eight before 2004 and 37 after 2005 were treated with at least two or more chemotherapy regimens, respectively (Fig. 1). Third-line amrubicin was used as salvage chemotherapy in 18 of 37 patients after the approval for clinical practice in 2005. Patients treated with second-line amrubicin ($n = 4$), patients lost to follow-up ($n = 2$) and patients treated with fourth- and fifth-line amrubicin ($n = 2$) were excluded from the analysis. The other 11 patients were treated with salvage chemotherapy without amrubicin, or with best supportive care. Thus, including eight patients treated with at least two or more chemotherapies from May 2000 to December 2004, a total of 19 patients were used as control groups (without amrubicine salvage therapy). We examined the serial chemotherapy regimen and selected patients treated with more than two chemotherapy regimens. OS among the selected patients was evaluated, as were the clinical characteristics, response to third-line amrubicin, and toxicities. For the identified and selected patients, we performed an electronic clinical record search. Patient privacy was protected when using individual patient information.

Histological diagnosis and SCLC stage were based on the World Health Organization classification, version 7. Performance status (PS) was estimated according to the Eastern Cooperative Oncology Group classification, and the response to amrubicin therapy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST),

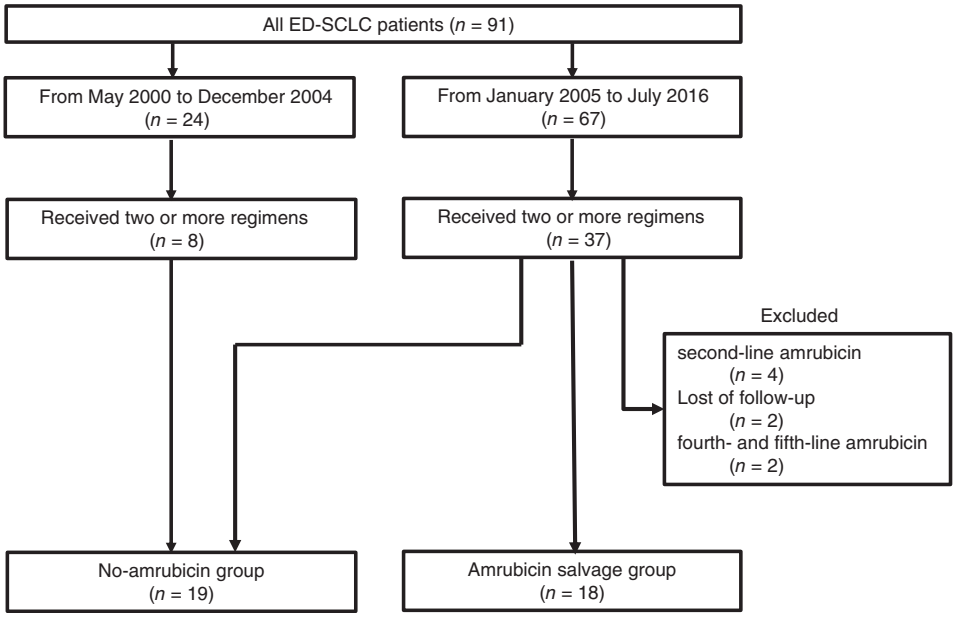


**Figure 1** Flow chart of patients in the study. ED-SCLC, extensive-disease small-cell lung cancer.

 

version 1.1. The disease control rate (DCR) was defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). The objective response rate (CR + PR) and DCR(CR + PR + SD) were calculated. Toxicities associated with amrubicin therapy were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Amrubicin was administrated intravenously once daily on days 1–3 every four weeks, and treatment was continued until disease progression or intolerable toxicity. Attending physicians determined the initial dose setting, reduction, and discontinuation of amrubicin. Progression-free survival (PFS) and OS were defined respectively as the time from initiation of amrubicin to the documentation of PD and the interval from the initial date of first-line chemotherapy to the date of death or the last follow-up visit. OS was compared between patients treated or not with third-line amrubicin salvage chemotherapy.

### Statistical analysis

Efficacy (objective response rate, DCR) and safety were evaluated in all patients treated with amrubicin. Kaplan-Meier plots were used for PFS and OS analyses, and medians and 95% confidence intervals (CIs) were determined. OS differences with and without amrubicin salvage chemotherapy were compared using the log-rank test. The cutoff date for follow-up in the present study was 31 July 2018. Statistical analyses were performed using SPSS statistics, version 19 (IBM). Comparisons were analyzed using Fisher's exact test, with $P < 0.05$ indicating statistical significance.

**Table 1** Patient characteristics

| Category | Number (%) | Number (%) |
|---|---|---|
| Treatment content | With amrubicin | Without amrubicin |
| Total number of patients | 18 | 19 |
| Gender (Male/Female) | 14 (77.8)/4 (22.2) | 17 (89.5)/2 (10.5) |
| Median age (range), years | 69 (56-81) | 68 (48-84) |
| ECOG performance status | | |
| | (first-line/third-line) | (first-line) |
| 0 | 5 (27.8)/2 (11.1) | 3 (15.8) |
| 1 | 10 (55.6)/12 (66.7) | 13 (68.4) |
| 2 | 2 (11.1)/4 (22.2) | 2 (10.5) |
| 3 | 1 (5.5)/0 (0.0) | 1 (5.3) |
| Smoking history | | |
| current + former | 16 (88.9) | 17 (89.5) |
| never | 2 (11.1) | 2 (10.5) |
| Metastasis | | |
| Brain Yes/No | 2 (11.1)/16 (88.9) | 3 (15.8)/16 (84.2) |
| Liver Yes/No | 6 (33.3)/12 (66.7) | 4 (21.1)/15 (78.9) |
| Bone Yes/No | 4 (22.2)/14 (77.8) | 6 (31.6)/13(68.4) |
| Pleural Yes/No | 5 (27.8)/13 (72.2) | 7 (36.8)/12 (63.2) |
| Prior regimen (first/second) | | |
| Platinum+CPT-11/ platinum+VP-16 | 12 (66.7) | 8 (42.1) |
| Platinum+VP-16/platinum +CPT-11 | 3 (16.7) | 2 (10.5) |
| Platinum+VP-16/ platinum+VP-16 | 3 (16.7) | 6 (31.6) |
| Platinum+VP-16/CPT-11 | — | 1 (5.3) |
| Platinum+NGT/platinum+ NGT+CAV | — | 1 (5.3) |
| Clinical trial/platinum+ CPT-11 | — | 1 (5.3) |

CPT-11, irinotecan; VP-16, etoposide; NGT, topotecan; CAV, cyclophosphamide + doxorubicin + vincristine

## Results

### Patient characteristics

The clinical characteristics of patients are listed in Table 1. In the amrubicin salvage chemotherapy group, 14 patients were men and four were women, with a median age of 70 years (range: 57–81 years). At the time of amrubicin therapy, two patients (11.1%) had a PS of 0; 12 patients (66.7%) had a PS of 1; and four patients (22.2%) had a PS of 2. Sixteen (88.9%) were current- or former-smokers, and two (11.1%) were never-smokers. Two patients (11.1%) had brain metastases, six (33.3%) liver metastases, four (22.2%) bone metastases, and five (27.8%) pleural metastases. All patients received two platinum-based chemotherapy rounds before amrubicin monotherapy. A platinum + irinotecan as first-line treatment was administered to 12 patients (66.7%), and six (33.3%) received a platinum + etoposide regimen. Platinum + etoposide as second-line treatment was administered to 15 patients (83.3%), and three (16.7%) received a platinum + irinotecan regimen.

A total of 19 patients who were treated without amrubicin also were enrolled as control (Table 1). Treatment in this group included 11 patients (57.9%) of only best supportive care after second-line chemotherapy, eight were treated with third-line, four with over third-line chemotherapy and four received radiotherapy. PS after second-line treatment in this group was 10 patients (52.6%) for PS of 1, and nine patients (47.4%) for PS of 2.

Of these, 17 were men and two were women, with a median age of 68 years (range: 48–84 years). At the first-line therapy, three patients (15.8%) had a PS of 0; 13 (68.4%) had a PS of 1; two (10.5%) had a PS of 2; and one (5.3%) had a PS of 3. Seventeen patients (89.5%) were current- or former-smokers, and two (10.5%) were never-smokers. Three patients (15.8%) had brain metastases, four (21.1%) liver metastases, six (31.6%) bone metastases, and seven (31.9%) pleural metastases. Platinum + irinotecan as

  

**Table 2** Efficacy and dose of amrubicin

| Category | Number (%) |
|---|---|
| Best overall response | |
| Complete response | 0 (0.0) |
| Partial response | 5 (27.8) |
| Stable disease | 7 (38.9) |
| Progressive disease | 6 (33.3) |
| Overall response rate (%) (95% CI) | 27.8 (7.1–48.5) |
| Disease control rate (%) (95% CI) | 66.7 (44.9–88.4) |
| Cycles of chemotherapy | |
| Median (range) | 4 (1-10) |
| Starting dose (mg/m$^2$ daily days 1–3) | |
| 40 | 11 (61.1) |
| 35 | 3 (16.7) |
| 30 | 4 (22.2) |

first-line treatment was administered to eight patients (42.1%), nine (47.4%) received a platinum + etoposide regimen, and two (10.5%) received other regimens. Platinum + etoposide as second-line treatment was administered to 14 patients (73.7%), three (15.8%) received a platinum + irinotecan regimen, and two (10.5%) received other regimens. There were no significant differences in clinical factors between those treated with and without amrubicin in PS ($P$ = 0.629), sex ($P$ = 0.348), age ($P$ = 0.575), smoking history ($P$ = 0.956), or metastatic lesions (brain, liver, bone, and pleural: $P$ = 0.688, 0.415, 0.535, and 0.569, respectively).

## Efficacy and treatment delivery

The response rate and dose of amrubicin are summarized in Table 2. Analysis of the response rate was performed in all patients. There was no patient with CR, five patients had PR, seven patients had SD, and six patients had PD. The objective response rate was 27.8% (95% CI, 7.1%–48.5%), and the DCR was 66.7% (95% CI, 44.9%–88.4%). The median number of cycles of treatment was four (range: 1–10). The starting dose of amrubicin was 40 mg/m$^2$ daily in 11 patients (61.1%), 35 mg/m$^2$ daily in three patients (16.7%), and 30 mg/m$^2$ daily in four patients (22.2%). Five patients (27.8%) received subsequent-line chemotherapy. The regimens were carboplatin + irinotecan in one patient, carboplatin + paclitaxel in one, and rechallenge of amrubicin in three.

## Survival

PFS and OS are shown in Figs 2 and 3, respectively. The median PFS after amrubicin salvage chemotherapy was 2.9 months (95% CI, 1.0–4.9 months). The time from the start of amrubicin monotherapy until time of death was 5.2 months (95% CI, 3.2–7.3 months). OS was 18.1 months (95% CI, 10.2–26.0 months) in patients having amrubicin salvage chemotherapy. The two-year survival rate was 27.8%.

The OS for the 19 patients treated without amrubicin was 12.6 months (95% CI, 11.5–13.8 months). The OS for the group treated with amrubicin was significantly longer than for the group without amrubicin treatment (18.1 months vs. 12.6 months; $P$ = 0.005).

## Toxicity

Toxicities were evaluated in all patients, as summarized in Table 3. The most common grade 3–4 adverse event associated amrubicin was neutropenia ($n$ = 13; 72.2%), followed by leukopenia ($n$ = 12; 66.7%), thrombocytopenia ($n$ = 2; 11.1%), anemia ($n$ = 2; 11.1%), and pulmonary toxicity ($n$ = 1; 5.5%). Febrile neutropenia was observed in seven patients (38.9%), all of whom had a starting dose of 40 mg/m$^2$ daily. Among patients with PS 2, febrile neutropenia and pulmonary toxicity were observed in one patient, respectively. All nonhematologic events excluding

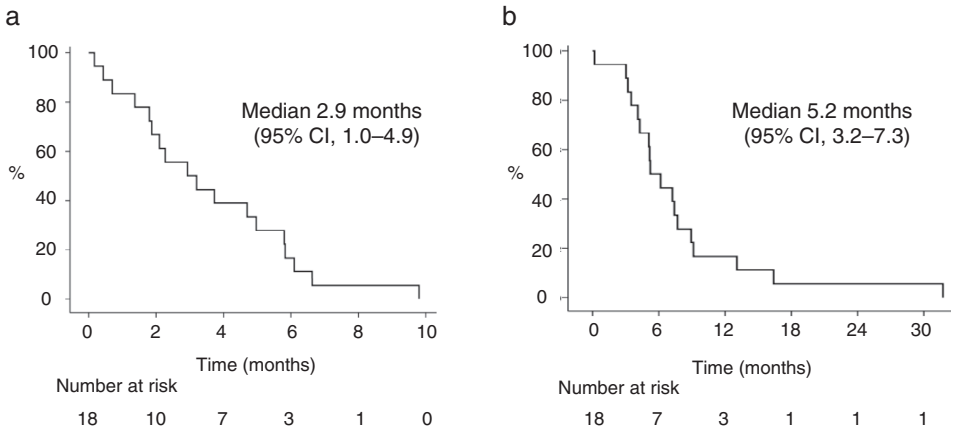


**Figure 2** Kaplan-Meier analyses of outcomes following treatment with amrubicin. Kaplan-Meier analyses of progression-free survival (**a**) and the time from the start of amrubicin monotherapy until time of death (**b**).

 

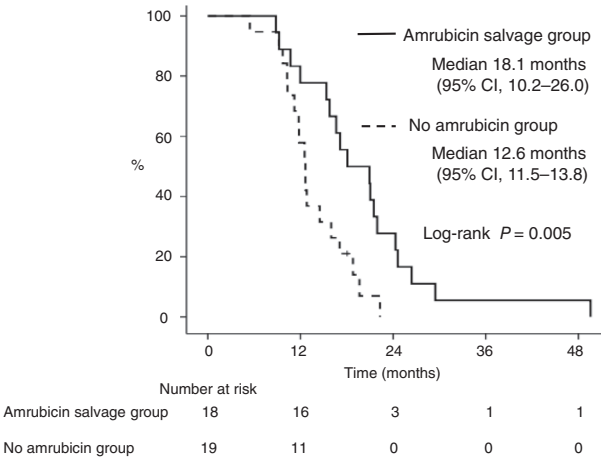


**Figure 3** Kaplan-Meier curves of overall survival (OS) by treatment with amrubicin between January 2005 and July 2016 or without amrubicin between May 2000 and July 2016. The median OS periods of the group treated with amrubicin was significantly longer without amrubicin (18.1 months vs. 12.6 months; $P = 0.005$).

pulmonary toxicity were mild. There were no treatment-related deaths.

## Discussion

Here, we summarize the efficacy and toxicities of third-line amrubicin salvage therapy in patients with relapsed ED-SCLC and show a survival benefit of the salvage amrubicin based on the historical analysis in our institute. The efficacy of third-line treatment for SCLC has been previously reported in several studies. In an international analysis at five large cancer centers, the response rate and the time from third-line chemotherapy until the time of death were 18% and 4.7 months, respectively.[13] In the retrospective analysis of a US-based community oncology electronic medical record, 334 patients were enrolled. The response rate and the time from third-line chemotherapy until time of death were 21.3% and 4.4 months, respectively.[14] With regard to the treatment of amrubicin as third-line chemotherapy, there have been two retrospective clinical studies in Japan. Although the sample sizes were small in both studies, the response rates were 14%[15] and 44.0%,[16] respectively. In the present study, the response rate (27.8%) and time from amrubicin monotherapy until time of death (5.2 months) were comparable to these studies.

With regard to toxicity, higher incidences of febrile neutropenia were observed with amrubicin, but there were no treatment-related deaths. The frequencies of grade 3 or 4 hematologic toxicities in the present study, such as anemia and thrombocytopenia, were comparable to previous studies.[17,18] In a retrospective study of advanced non-SCLC patients receiving amrubicin as a third- or more-line chemotherapy, grade 3 or 4 hematologic toxicities included neutropenia (61.1%), leukopenia (58.3%), thrombocytopenia (22.2%), and anemia (11.1%).[19] In our study, rates of grade 3 or 4 neutropenia, leukopenia, thrombocytopenia, and anemia were 72.2%, 66.7%, 11.1%, and 11.1%, respectively. These results suggested that the frequency of grade 3 or higher hematologic toxicities in our study were equivalent to the previous study. However, the frequency of febrile neutropenia was high (seven patients, 38.9%) compared with previous studies.[13,14] In our study, the frequency of febrile neutropenia was higher for the starting dose of 40 mg/m$^2$ daily in 11 patients compared to that of ≤35 mg/m$^2$ daily in seven patients (63.6% vs. 0.0%; $P = 0.002$). Routine prophylactic use of granulocyte colony-stimulating factor (G-CSF) has been reported to reduce febrile neutropenia in SCLC patients treated with amrubicin.[20,21] In the present study, none of the patients received prophylactic G-CSF. Thus, we should consider a reduced starting dose and/or prophylactic use of G-CSF as third-line chemotherapy for SCLC.

**Table 3** Toxicity of amrubicin

| Adverse event | Any grade (%) | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|---|
| Neutropenia | 15 (83.3) | 0 (0.0) | 2 (11.1) | 4 (22.2) | 9 (50.0) |
| Febrile neutropenia | 7 (38.9) | | | 7 (38.9) | |
| Leukopenia | 15 (83.3) | 3 (16.7) | 0 (0.0) | 8 (44.4) | 4 (22.2) |
| Anemia | 16 (88.9) | 4 (22.2) | 10 (55.6) | 2 (11.1) | 0 (0.0) |
| Thrombocytopenia | 14 (77.8) | 10 (55.6) | 2 (11.1) | 2 (11.1) | 0 (0.0) |
| Fatigue | 4 (22.2) | 1 (5.5) | 3 (16.7) | 0 (0.0) | 0 (0.0) |
| Nausea | 4 (22.2) | 4 (22.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Constipation | 5 (27.8) | 5 (27.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diarrhea | 2 (11.1) | 2 (11.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Elevated AST/ALT | 1 (5.5) | 0 (0.0) | 1 (5.5) | 0 (0.0) | 0 (0.0) |
| Elevated total bilirubin | 2 (11.1) | 1 (5.5) | 1 (5.5) | 0 (0.0) | 0 (0.0) |
| Infection | 2 (11.1) | 0 (0.0) | 2 (11.1) | 0 (0.0) | 0 (0.0) |
| Pulmonary toxicity | 1 (5.5) | 0 (0.0) | 0 (0.0) | 1 (5.5) | 0 (0.0) |

  

Amrubicin salvage chemotherapy had a survival benefit for patients with ED-SCLC compared with no amrubicin salvage chemotherapy in our analysis. In the present study, clinical factors did not differ between patients with and without amrubicin salvage chemotherapy. The number of chemotherapies as subsequent-line therapy was also similar between the two groups. Furthermore, it was suggested that amrubicin could be effective for refractory-relapsed cases.[22] In the present study, 17 patients were refractory-relapsed types of the 18 in the amrubicin salvage group. Thus, amrubicin salvage chemotherapy could contribute to prolonged survival in patients with ED-SCLC. In addition, OS in 67 patients after clinical approval of amrubicin (15.4 months; 95% CI, 10.9–19.8 months) was significantly prolonged compared to that for 24 patients (10.3 months; 95% CI, 8.5–12.1 months) before introduction of amrubicin in our institute ($P$ = 0.013; data not shown). However, toxicities in patients with PS 2 were severe and none responded to amrubicin salvage therapy. Thus, it is important to select patients with favorable PS (0–1) when considering amrubicin as the third-line treatment for ED-SCLC. Our historical analysis suggested that amrubicin therapy for appropriate ED-SCLC patients could contribute to a prolonged survival; however, further clinical trials are required to support this data.

In a randomized phase II trial for patients with sensitive relapsed SCLC, PFS, and OS did not differ significantly between the second-line amrubicin and platinum rechallenge group. However, patients treated with an amrubicin and platinum compound regimen showed longer survival than those treated with only an amrubicin or platinum compound regimen (17.6 months vs. 10.7 months, respectively; $P$ = 0.0055).[23] These survival data, including our present results, suggest that addition of amrubicin in serial chemotherapies after second-line could prolong OS in patients with ED-SCLC.

The current study has limitations. First, the present study involved a retrospective analysis, and the number of included cases was small. Thus, we could not perform analyses according to sensitive and refractory types of SCLC. Second, because attending physicians decided on an induction for amrubicin as second- or more-line therapy, selection bias for patients might be present. Third, control group included patients who did not receive third-line chemotherapy or radiotherapy because of poor PS. Fourth, we had no data on clinical parameters underlying the decision for, or against, amrubicin indication. Thus, further evaluation of amrubicin in large-scale studies is necessary in these populations.

In conclusion, third-line amrubicin chemotherapy for relapsed ED-SCLC could be an effective regimen and considered as salvage chemotherapy, even in third-line chemotherapy. Although the frequency of febrile neutropenia was high, reduction of the starting dose and prophylactic use of G-CSF may reduce the frequency of febrile neutropenia.

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## Disclosure

No authors report any conflict of interest.

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