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# Amrubicin monotherapy for elderly patients with relapsed extensive-disease small-cell lung cancer: A retrospective study

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## Abstract

**Background:** Previous studies have shown amrubicin (AMR) to be an effective second-line treatment option for small-cell lung cancer (SCLC). However, the efficacy of AMR in elderly patients with relapsed SCLC has not been sufficiently evaluated.

**Methods:** The medical records of elderly patients with relapsed SCLC who received AMR as second-line chemotherapy were retrospectively reviewed, and their treatment outcomes were evaluated.

**Results:** Thirty-one patients with a median age of 72 years (22 patients with sensitive relapse and 9 with refractory relapse) were analyzed. The median number of treatment cycles was four (range: 1–10), and the response rate was 29%. The median progression-free survival (PFS) and overall survival (OS) were 5.4 and 11.6 months, respectively. The OS of 22 patients who received third-line chemotherapy was 15.5 months. The PFS (6.2 vs. 3.2 months; $P = 0.002$) and OS (14.8 vs. 5.7 months; $P = 0.004$) were significantly longer in patients with sensitive relapse than those with refractory relapse. The frequency of grade 3 or higher neutropenia was high ($n = 18$, 58%), while febrile neutropenia was only observed in five patients (16%). Non-hematological toxic effects were relatively mild, and pneumonitis and treatment-related deaths were not observed.

**Conclusion:** AMR may be a feasible and effective regimen for elderly patients with relapsed SCLC.

## Introduction

Despite being one of the most chemo-sensitive solid tumor types, small-cell lung cancer (SCLC) has an extremely poor prognosis.[1] Most patients with SCLC experience relapse as a result of the emergence of drug-resistant tumor cells, even after remarkably successful induction therapy.[2–4] Approximately 50% of all SCLC patients in Japan are aged over 70 years,[5] and the Japan Lung Cancer Society recommends chemotherapy with carboplatin (CBDCA) plus etoposide (ETP) as the standard treatment modality for elderly patients with SCLC.[6]

Amrubicin hydrochloride is a fully synthetic 9-amino-anthracycline that is converted to its active metabolite amrubicinol in the liver. Amrubicin (AMR) inhibits DNA topoisomerase II and exerts a cytotoxic effect by stabilizing a topoisomerase-II-mediated cleavable complex. Its potency as a DNA intercalator is approximately one-tenth that of doxorubicin.[7,8] The catatonic activity of amrubicinol in vitro is 18–220-fold more potent than that of its parent compound.[9] The anti-tumor activity of amrubicin against several human tumor xenografts implanted in nude mice is more potent than that of the representative anthracycline

doxorubicin, with almost no cardiotoxicity.[10,11] One study showed AMR to be active against chemo-naïve SCLC[12] patients had a response rate of 79% and a median survival time of 11 months. These results support the evaluation of AMR monotherapy as a viable SCLC treatment. Previous clinical trials revealed that compared to topotecan, AMR significantly improved response and survival rates, particularly in patients with SCLC with refractory relapse.[13–16] Thus, AMR monotherapy has become the standard second-line chemotherapy for extensive-disease (ED)-SCLC in Japan. Regarding the dose of AMR monotherapy, Onoda *et al.* reported that 40 mg/m$^2$ showed significant activity and acceptable toxicity in previously treated SCLC patients.[16]

However, the efficacy of AMR in elderly patients with relapsed ED-SCLC has not been sufficiently evaluated. Therefore, this study evaluated the efficacy and safety of AMR in relapsed elderly patients with ED-SCLC.

## Methods

### Patient selection and data collection

The eligibility criteria for this retrospective study were as follows: histologically or cytologically proven SCLC; stage IV disease as defined by the Union for International Cancer Control Tumor Node Metastasis classification, 7th edition; age ≥ 70 years during the administration of AMR as second-line treatment at Kitasato University Hospital between March 2010 and December 2016; and measurable target lesions on imaging examination via chest radiography, computed tomography (CT) of the chest and abdomen, or other procedures such as magnetic resonance imaging (MRI) of the head, positron emission tomography (PET), or combined PET-CT imaging. The institutional ethics review board of the Kitasato University Hospital approved this study. Informed consent was not required because of the retrospective nature of the study.

### Amrubicin regimen

Amrubicin dissolved in 20 mL normal saline was administered intravenously as a five-minute infusion once daily on days 1–3 every three weeks. The amrubicin dose was 40 mg/m$^2$/day. The treatment regimen was repeated for four to six cycles at the attending oncologists' discretion (i.e. after 4 cycles, the oncologist decided whether a fifth and sixth cycle was appropriate) and was continued until disease progression, unacceptable adverse events, or at the patient's request to discontinue.

### Response evaluation

Lesions were evaluated using plain chest radiography, CT of the chest and abdomen, PET or bone scintigraphy, and

CT or MRI of the cranium. To evaluate the tumors, CT imaging of the chest and abdomen was performed at least every two cycles. PET or bone scintigraphy and CT or MRI of the cranium was performed at six-month intervals or earlier if patients had significant tumor-associated symptoms. Tumor control was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. The best overall response and maximum tumor control were recorded as the tumor response.

### Toxicity assessment and treatment modification

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. At our institution, the criteria for dose reduction were grade 4 neutropenia lasting ≥ 4 days, febrile neutropenia, and grade 4 thrombocytopenia. If any of these events occurred, the AMR dose was reduced by 5 mg/m$^2$/day in subsequent cycles. Patients received supportive care as required. The treatment protocol specified that 50 μg/m$^2$/day or 2 μg/kg/day recombinant human granulocyte colony-stimulating factor (G-CSF) should be used in accordance with Japanese national health insurance coverage. The indications for G-CSF administration were as follows: (i) fever (in principle, body temperature > 37.5°C) with a neutrophil count of ≤ 1000/mm$^3$; (ii) a neutrophil count of 500/mm$^3$; and (iii) fever with a neutrophil count of ≤ 1000/mm$^3$ or a neutrophil count of 500/mm$^3$ during the previous course, followed by a neutrophil count of ≤ 1000/mm$^3$ after completing the same chemotherapy regimen. G-CSF as a prophylactic agent against leukopenia or neutropenia was administered at the physician's discretion.

### Statistical analyses

Progression-free survival (PFS) was defined as the interval between the start of AMR monotherapy and disease progression or death. Overall survival (OS) was defined as the interval between the start of AMR monotherapy and death or the last follow-up. Survival curves were plotted using the Kaplan–Meier method. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). $P$ values < 0.05 were considered significant.

## Results

### Patient characteristics

Thirty-one patients treated between March 2010 and December 2016 were included in this retrospective cohort study; all patients were subject to efficacy and safety analyses. The patients' demographic data are shown in Table 1. There were 26 men and 5 women, and the median

patient age was 73 years (range: 70–82). All patients had ED when they received AMR monotherapy. Of the 31 patients, 22 and 9 had sensitive and refractory relapses to prior chemotherapy, respectively. The regimens of prior chemotherapy were as follows: 22 patients received CBDCA/ETP; 6, cisplatin/ETP; and 3, CBDCA/irinotecan (CPT-11). The number of AMR treatment cycles per patient ranged from 1 to 10 (median 4 cycles).

## Response

Of the 31 patients, partial response, stable disease, and progressive disease were observed in 9, 15, and 5 patients, respectively. The tumor response was not evaluable in two patients because of early termination of the treatment protocol as a result of hospital transfer. The overall response rate was 29% (95% confidence interval [CI] 13.0–45.0%) (Table 2).

## Survival

The median follow-up time was 10.7 months. The median PFS and OS for all patients was 5.4 (95% CI 3.7–7.1) and 11.6 (95% CI 8.6–14.6) months, respectively (Fig 1). The median PFS according to the type of relapse to prior regimen was significantly longer in the patients with sensitive relapse than those with refractory relapse (6.2 vs.

**Table 1** Patient characteristics and prior chemotherapy regimen

| Patient characteristics | N = 31 |
|---|---|
| Gender | |
| Male/Female | 26/5 |
| Age (years) | |
| Median (range) | 73 (70–82) |
| Smoking history | |
| Current/former | 30/1 |
| ECOG PS score | |
| 0–1/2 | 24/7 |
| Type of relapse to prior regimen | |
| Sensitive/refractory | 22/9 |
| Median (range) | 138 (106–145) |
| Stage | |
| Limited/extensive | 0/31 |
| Brain metastasis | |
| Yes/No | 4/27 |
| Number of chemotherapy cycles | |
| Median (range) | 4 (1–10) |
| Prior regimen | |
| CBDCA/ETP | 22 |
| CDDP/ETP | 6 |
| CBDCA/CPT-11 | 3 |

CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; ECOG PS, Eastern Cooperative Oncology Group performance status; ETP, etoposide.

**Table 2** Clinical response to amrubicin monotherapy

| Response | N = 42 |
|---|---|
| Complete response | 0 |
| Partial response | 9 |
| Stable disease | 15 |
| Progressive disease | 5 |
| Not evaluable | 2 |
| Response rate (%) | 29.0 |
| 95% CI | 13.0–45.0 |

CI, confidence interval.

3.2 months, respectively; $P = 0.002$) (Fig 2a). Similarly, the median OS was also significantly different between the two groups (14.8 in the sensitive group vs. 5.7 months in the refractory group; $P = 0.004$) (Fig 2b). A total of 22 patients (71%) received third-line chemotherapy. Specifically, 6, 6, 5, 4, and 1 patient received carboplatin and etoposide (CE) retreatment, AMR retreatment, CPT-11 monotherapy, topotecan monotherapy, and CBDCA/CPT-11, respectively. The 22 patients achieved a median OS of 15.5 months (95% CI 9.1–21.9).

## Toxicity assessment and dose modification

The patients' toxicity profiles are summarized in Table 3. The most common adverse events were hematological toxicities, such as neutropenia and leukopenia. Grade 3 or higher neutropenia and leukopenia occurred in 18 (58%) and 13 (42%) patients, respectively. Febrile neutropenia occurred in five patients (16%). A total of 118 cycles were administered. Dose reduction to 35 mg/m$^2$/day was required in nine patients (29%) as grade 4 neutropenia lasted ≥ 4 days in four patients in whom febrile neutropenia did not occurred, and febrile neutropenia in other five patients, respectively. One patient required a subsequent dose reduction to 30 mg/m$^2$/day because of grade 4 neutropenia lasting ≥ 4 days. Non-hematological toxic effects were relatively mild, and pneumonitis and treatment-related deaths were not observed.

## Discussion

This retrospective study assessed the efficacy of AMR for the treatment of refractory SCLC in elderly patients previously treated with platinum-based chemotherapy. Notably, AMR yielded a clinical response rate of 29%, a median PFS of 5.4 months, and a median OS of 11.6 months in the second-line setting for elderly patients with ED-SCLC.

The majority of SCLC patients commonly experience relapse after first-line chemotherapy, thus subsequent chemotherapy should be considered.[17] The efficacy of second-line chemotherapy usually depends on tumor
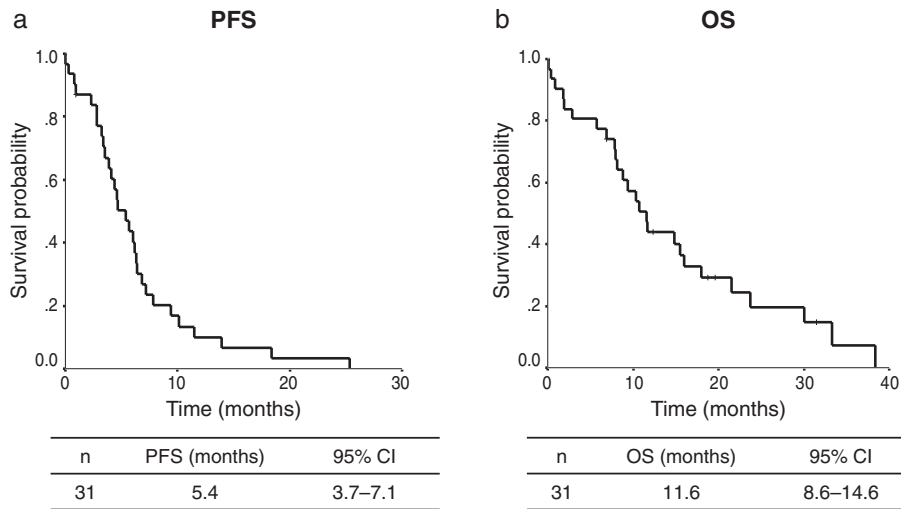
a
## PFS



| n | PFS (months) | 95% CI |
|---|---|---|
| 31 | 5.4 | 3.7–7.1 |

b
## OS



| n | OS (months) | 95% CI |
|---|---|---|
| 31 | 11.6 | 8.6–14.6 |

**Figure 1** Kaplan–Meier plots of (**a**) progression-free survival (PFS) and (**b**) overall survival (OS) of all patients. CI, confidence interval.

a



| Type of relapse to prior regimen | | PFS | 95% CI |
|---|---|---|---|
| —— Sensitive relapse | n=22 | 6.2 | 4.9–7.5 |
| - - - Refractory relapse | n=9 | 3.2 | 2.0–4.4 |
| | | | Log Rank P=0.002 |

b



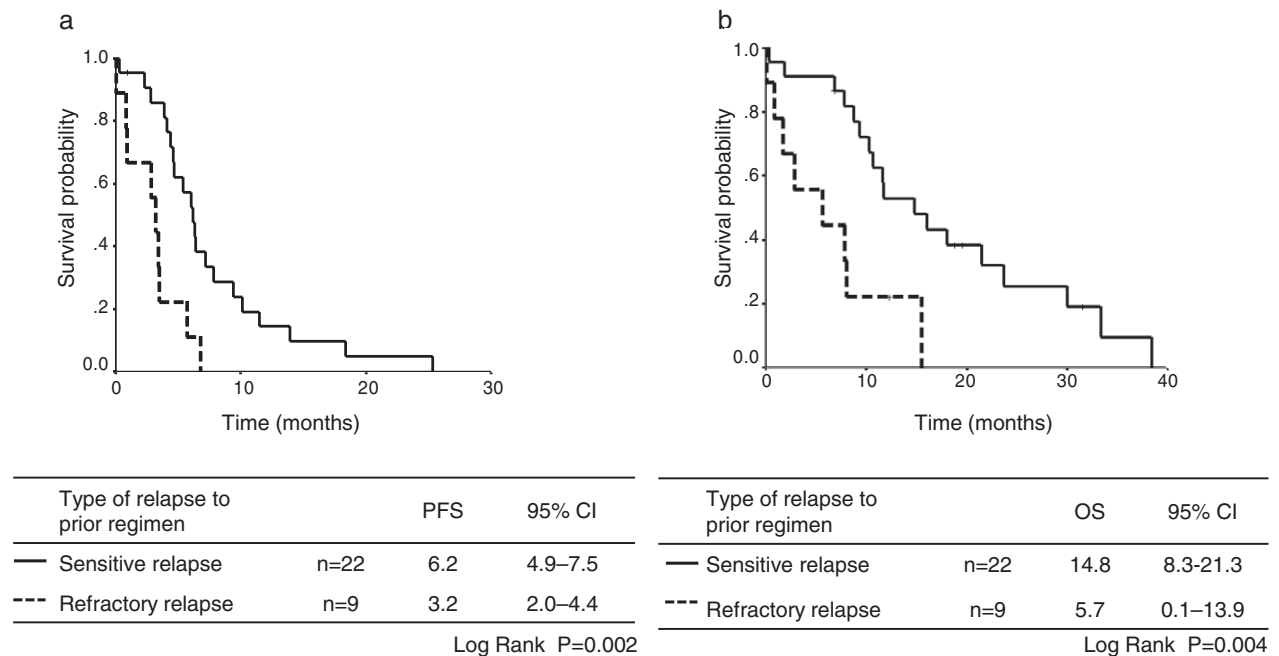| Type of relapse to prior regimen | | OS | 95% CI |
|---|---|---|---|
| —— Sensitive relapse | n=22 | 14.8 | 8.3-21.3 |
| - - - Refractory relapse | n=9 | 5.7 | 0.1–13.9 |
| | | | Log Rank P=0.004 |

**Figure 2** (**a**) Progression-free survival (PFS) and (**b**) overall survival (OS) according to type of relapse to prior chemotherapy. CI, confidence interval.

responsiveness to prior chemotherapy, that is, whether the tumor is sensitive or refractory. In a Japanese randomized phase II study that compared AMR with topotecan,[15] the median PFS and OS in the AMR arm were 2.6 and 5.3 months, respectively, in the refractory cases. Additionally, in a randomized phase III study comparing AMR with topotecan, the median PFS and median OS in the AMR arm were 2.8 and 6.2 months, respectively, in the refractory cases.[18] Two single-arm phase II studies of 40 mg/m$^2$ AMR for refractory relapsed SCLC patients reported median PFS of 2.6 and 3.5 months.[13,16] In the present study, the OS and PFS of the patients with refractory

relapse were significantly shorter than those of patients with sensitive relapse, and the results were consistent with those of previous studies.[13,15,16,18] Thus, it is reasonable to conclude that AMR is a plausible treatment option in both refractory and sensitive relapsed SCLC in the elderly.

In our previous retrospective cohort study, elderly patients with SCLC who received CE achieved a significantly longer PFS than those receiving AMR in the first-line treatment,[19] accordingly indicating that CE is an effective standard chemotherapeutic for chemo-naïve elderly patients with ED-SCLC. Given the few available regimens for second-line chemotherapy for ED-SCLC

**Table 3** Toxicities during AMR chemotherapy

| Toxicity | N = 31 Grade | | |
|---|---|---|---|
| | ≤ 2 | 3, 4 | ≥ 3 (%) |
| Neutropenia | 8 | 9, 9 | 58 |
| Leukopenia | 10 | 8, 5 | 42 |
| Thrombocytopenia | 16 | 4, 3 | 23 |
| Anemia | 18 | 2, 0 | 6 |
| Febrile neutropenia | | 5, 0 | 16 |
| Fatigue | 7 | 0, 0 | 0 |
| Nausea | 3 | 1, 0 | 3 |
| Constipation | 5 | 0, 0 | 0 |
| Anorexia | 2 | 2, 0 | 6 |
| Diarrhea | 3 | 0, 0 | 0 |
| Infection | 4 | 0, 0 | 0 |
| Elevated AST/ALT | 7 | 0, 0 | 0 |
| Elevated total bilirubin | 6 | 0, 0 | 0 |
| Elevated creatinine | 3 | 0, 0 | 0 |
| Vasculitis | 3 | 0 (0) | 0 |
| Dysgeusia | 1 | 0 | 0 |

ALT, alanine transaminase; AST, aspartate transaminase.

patients, it is reasonable to conclude that AMR is inevitably essential for elderly patients with relapsed ED-SCLC. In this regard, we would like to emphasize that the present study provides meaningful results showing the efficacy and safety profile of AMR for the elderly population in the second-line setting.

Previous studies found that an AMR dose of 40 mg/m$^2$ showed adequate activity and acceptable toxicity in previously treated SCLC patients.[13–16,20,21] Meanwhile, an AMR dose of 45 mg/m$^2$, while effective, produced intolerable toxicities and even treatment-related deaths in other studies.[22,23] Sekine *et al.* conducted a valuable randomized phase III study that showed that higher incidences of febrile neutropenia and interstitial lung disease of grade 3 or worse occurred with 45 mg/m$^2$ AMR; they concluded that AMR at 45 mg/m$^2$ is toxic and intolerable in chemo-naïve elderly Japanese patients with ED-SCLC.[24] These findings show that the AMR dose is critical for avoiding fatal adverse events, such as severe neutropenia or febrile neutropenia. Therefore, we selected 40 mg/m$^2$ AMR as a starting dose for elderly patients with relapsed SCLC. In addition, data from previous literature and a phase III study[24] showed no significant differences in OS and objective response rate between CE and AMR, indicating that CE is more suitable as a first-line chemotherapy.[19,25,26]

Imai *et al.* showed that AMR was effective and safe for elderly patients with relapsed ED-SCLC, reporting PFS of 3.4 months and OS of 6.1.[27] In their study, the PFS and OS in the refractory cases were 2.7 and 5.5 months, respectively. Our findings are consistent with these results. Furthermore, Imai *et al.* reported that post-progression survival has a greater effect on OS after first-line

chemotherapy in elderly patients with lung cancer, including those with ED-SCLC, suggesting that subsequent treatments in elderly ED-SCLC patients affect OS.[28,29] AMR is accordingly essential to achieve long-term post-progression survival after failure of first-line chemotherapy. Moreover, patients in our study who received third-line chemotherapy after AMR failure achieved OS of 15.5 months, indicating the importance of successive chemotherapy in prolonging post-progression survival.

This study has several limitations. First, the results cannot be considered definitive because of the retrospective single-center design and relatively small sample size. Second, although the individuals included in this study were elderly, data regarding their quality of life were not evaluated.

In conclusion, AMR may be an effective and feasible regimen for elderly patients with relapsed SCLC. Our findings represent a basis for a new direction for clinical research for the treatment of elderly patients with relapsed SCLC. Accordingly, the results in the current study should be validated in prospective studies.

## Acknowledgments

## Disclosure

No authors report any conflict of interest.

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