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ORIGINAL RESEARCH

Impact of Amrubicin Monotherapy as Second-Line Chemotherapy on Outcomes in Elderly Patients with Relapsed Extensive-Disease Small-Cell Lung Cancer

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Satoshi Igawa[1]
Taihei Ono[1]
Masashi Kasajima[1]
Hideaki Manabe[1]
Tomoya Fukui[1]
Hisashi Mitsufuji[2]
Masanori Yokoba[3]
Masaru Kubota[3]
Masato Katagiri[3]
Jiichiro Sasaki[4]
Katsuhiko Naoki[1]

[1]Department of Respiratory Medicine, Kitasato University School of Medicine, Sagamihara-City, Kanagawa 252-0374, Japan; [2]Kitasato University School of Nursing, Sagamihara-City, Kanagawa 252-0329, Japan; [3]School of Allied Health Sciences, Kitasato University, Sagamihara-City, Kanagawa 252-0373, Japan; [4]Research and Development Center for New Medical Frontiers, Kitasato University School of Medicine, Sagamihara-City, Kanagawa 252-0374, Japan

Purpose: Amrubicin (AMR) is an anticancer drug for patients with relapsed small-cell lung cancer (SCLC). However, the efficacy of AMR in elderly patients with relapsed SCLC after chemotherapy by carboplatin plus etoposide (CE) has not been sufficiently evaluated.

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

Results: Forty-one patients with a median age of 76 years were analyzed. The overall response rate was 26.8%. Median progression-free survival (PFS) and overall survival (OS) were 3.5 and 8.1 months, respectively. While the median PFS of 4.7 and 2.8 months in the sensitive relapse and the refractory relapse group differed significantly (P=0.043), respectively, the median OS of 10.7 and 6.8 months in the respective relapse groups did not indicate a statistically significant difference (P=0.24). The median PFS in a group with a modified Glasgow prognostic score (mGPS) of 0 and a group with a mGPS 1 or 2 were 4.5 and 1.6 months (P=0.052), respectively, and the median OS in the respective mGPS groups were 10.7 and 4.4 months (P=0.034). Multivariate analysis identified good performance status, limited disease, and mGPS 0 as favorable independent predictors of PFS and OS of AMR monotherapy. Grade 3 or higher neutropenia was observed in 23 patients (56%), and febrile neutropenia was observed in nine patients (22%). Non-hematological toxic effects were relatively mild, and pneumonitis and treatment-related deaths were not observed.

Conclusion: AMR is an effective and feasible regimen for elderly patients with relapsed SCLC after CE therapy.

Keywords: small-cell lung cancer, amrubicin, elderly, second-line chemotherapy, modified Glasgow prognostic score

Introduction

Although small-cell lung cancer (SCLC) is one of the most chemo-sensitive solid tumor types, its prognosis is extremely poor.[1] Most patients with SCLC experience relapse owing to the emergence of drug-resistant tumor cells even after successful induction therapy.[2–4] Approximately 50% of all SCLC patients in Japan are 70 years of age and older.[5] Until 2019, chemotherapy with carboplatin plus etoposide (CE) was the standard treatment modality for elderly patients with SCLC, as recommended by the Japan Lung Cancer Society.[6] Recently, a Phase III randomized

Correspondence: Satoshi Igawa
Department of Respiratory Medicine, Kitasato University School of Medicine, 1-15-1, Kitasato, Minami-Ku, Sagamihara-City, Kanagawa 252-0374, Japan
Tel +81 42 778 8506
Fax +81 42 778 6412
Email igawa@kitasato-u.ac.jp

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trial (IMpower-133) demonstrated that adding an immune checkpoint inhibitor (atezolizumab) to CE improved both progression-free survival (PFS) and overall survival (OS).[7]

The synthetic prodrug amrubicin (AMR) hydrochloride is a 9-amino-anthracycline derivative that is metabolized in the liver to its active form, amrubicinol. It blocks DNA topoisomerase II, which generates a cytotoxic effect by stabilizing a cleavable DNA-topoisomerase II complex. Amrubicinol has an approximately 10-fold lower DNA-intercalating potency than the representative anthracycline drug doxorubicin.[8,9] The in vitro cell-growth inhibitory activity of amrubicinol is 18- to 220-fold higher than that of its prodrug.[10] AMR has almost no cardiotoxicity, and its antitumor activity against several human tumor xenografts implanted in nude mice is more potent than that of doxorubicin.[11,12] In a previous study using AMR against chemo-naïve SCLC,[13] the patients had a response rate of 79% and a median survival time of 11.0 months. These results indicated that the treatment of SCLC with AMR monotherapy is very beneficial. Previous clinical trials revealed that compared with topotecan, AMR significantly improved the response and survival rates, particularly in patients with SCLC with refractory relapse.[14–17] Thus, AMR monotherapy has become the standard second-line chemotherapy for extensive-disease (ED)-SCLC in Japan.

However, the efficacy of AMR in elderly patients with relapsed ED-SCLC after CE therapy has not been sufficiently evaluated. Therefore, in this study, we focused on evaluating the efficacy and safety of AMR in relapsed elderly patients with ED-SCLC.

Patients and Methods

Patient Selection and Data Collection

The WHO classification for lung cancer was revised as the 4th edition in 2015.[18] SCLC, large cell neuroendocrine carcinoma and carcinoid tumors were classified as neuroendocrine tumors in the revised classification. Among the subtypes of neuroendocrine tumors, we focused elderly patients with SCLC in this study. The eligibility criteria for this retrospective study were as follows: histologically or cytologically proven SCLC; age ≥70 years during the administration of AMR as second-line treatment of CE therapy at Kitasato University Hospital between March 2010 and December 2019; 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 clinical stage at the initial diagnosis of SCLC was determined using the World Health Organization classification, version 8. Patients with clinical stage IIIC, IVA, and IVB of the TNM classification were included to have ED-SCLC. In this study, we evaluated a representative marker of systemic inflammatory responses, such as the modified Glasgow prognostic score (mGPS).[18] Briefly, patients with albumin (Alb) ≥3.5 g/dL and C-reactive protein (CRP) ≤1 mg/dL were defined as mGPS 0, patients with Alb ≥3.5 g/dL and CRP > 1 mg/dL or Alb < 3.5 g/dL and CRP ≤1 mg/dL were defined as mGPS 1, and patients with Alb <3.5 g/dL and CRP >1 mg/dL were defined as mGPS 2.[19]

Amrubicin Regimen

AMR dissolved in 20 mL normal saline was administered intravenously as a 5-minute infusion once daily on days 1 to 3 every 3 weeks. The AMR dose was 40 mg/m^2/day. The treatment regimen was repeated at the attending oncologist's discretion (after four 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.

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 2 cycles. PET or bone scintigraphy and CT or MRI of the cranium were performed at 6-month intervals or earlier if patients had significant tumor-associated symptoms. Tumor control was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines (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 the national health insurance coverage of Japan. The indications for G-CSF administration were as follows: (a) fever (in principle, body temperature above 37.5 °C) with a neutrophil count of ≤1000/mm^3; (b) a neutrophil count of 500/mm^3; and (c) 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 is a prophylactic agent against leukopenia or neutropenia that was administered at the physician's discretion.

Statistical Analyses

All data were analyzed with a cut-off date of March 1, 2020. PFS was measured from the start of AMR monotherapy to treatment failure (death, documentation of disease progression) or date of censoring at the last follow-up examination. OS was defined as the interval between the start of AMR monotherapy and death from any cause or date of censoring at the last follow-up. The survival curves were plotted using the Kaplan–Meier method, and differences based on relevant parameters, including performance status (PS), type of relapse to prior chemotherapy, and mGPS, were analyzed by the Log rank test. Variables, including gender, PS, stage, brain metastasis status, type of relapse to prior chemotherapy, and mGPS, were used for fitting Cox's proportional hazard models to predict the hazard rates for PFS and OS of AMR monotherapy. The differences in the response rates according to the type of relapse were compared using Fisher's exact test. P value <0.05 was used as the criterion for statistical significance. All statistical analyses were performed using the SPSS software program, version 23 (SPSS Inc., Chicago, Illinois) for Windows.

Results

Patient Characteristics

Forty-one patients who were treated between March 2010 and December 2019 were identified in this retrospective cohort study; all patients were included in the efficacy and safety analyses. The patients' demographic data are shown in Table 1. There were 35 men and six women, and the median patient age was 76 (range, 70–85) years. Among the 41 patients, 11 SCLC patients had LD, and 30 SCLC patients had ED at the initial diagnosis of SCLC.

Table 1 Patient Characteristics

Patient Characteristics	N=41
Sex Male/female	35/6
Age (years) Median (range)	76 (70–85)
Smoking history Current smoker/ever smoker	40/1
ECOG PS 0–1/2	34/7
Type of relapse to prior regimen Sensitive/refractory	19/22
Stage Limited/extensive	11/30
Brain metastasis Yes/no	6/35
Modified Glasgow Prognostic Score 0 (CRP≤1 mg/dl and Alb≥3.5 g/dl) 1 or 2 (CRP>1 mg/dl or Alb<3.5 g/d)	 24 17
Number of cycles Median (range)	4 (1–10)
Dose of amrubicin (mg/m^2) 30/35/40	1/8/32

Abbreviations: Alb, albumin; CRP, C-reactive protein.

When the AMR monotherapy was administered, 19 had a sensitive relapse and 22 a refractory relapse to an earlier CE therapy. The number of AMR treatment cycles per patient ranged from 1 to 10 (median, four cycles). According to mGPS, 24 patients had mGPS 0, and 17 patients had mGPS 1 or 2.

Response

A partial response was observed in 11 out of 41 patients, indicating an overall response rate of 26.8% (95% confidence interval [CI]: 12.7–40.9%, Table 2). The tumor response was not evaluable in two patients owing to early termination of the treatment protocol triggered by their hospital transfer. Among eight patients receiving 35mg^2 of AMR, partial response was observed in two patients indicating 25% of response rate. SD was observed in one patient receiving 30mg^2 of AMR. The response rate was 31.6% (95% CI: 11.7–51.5%) in patients with sensitive relapse and 22.7% (95% CI: 4.8–40.7%) in patients with refractory relapse, indicating no statistically significant differences (P=0.52).

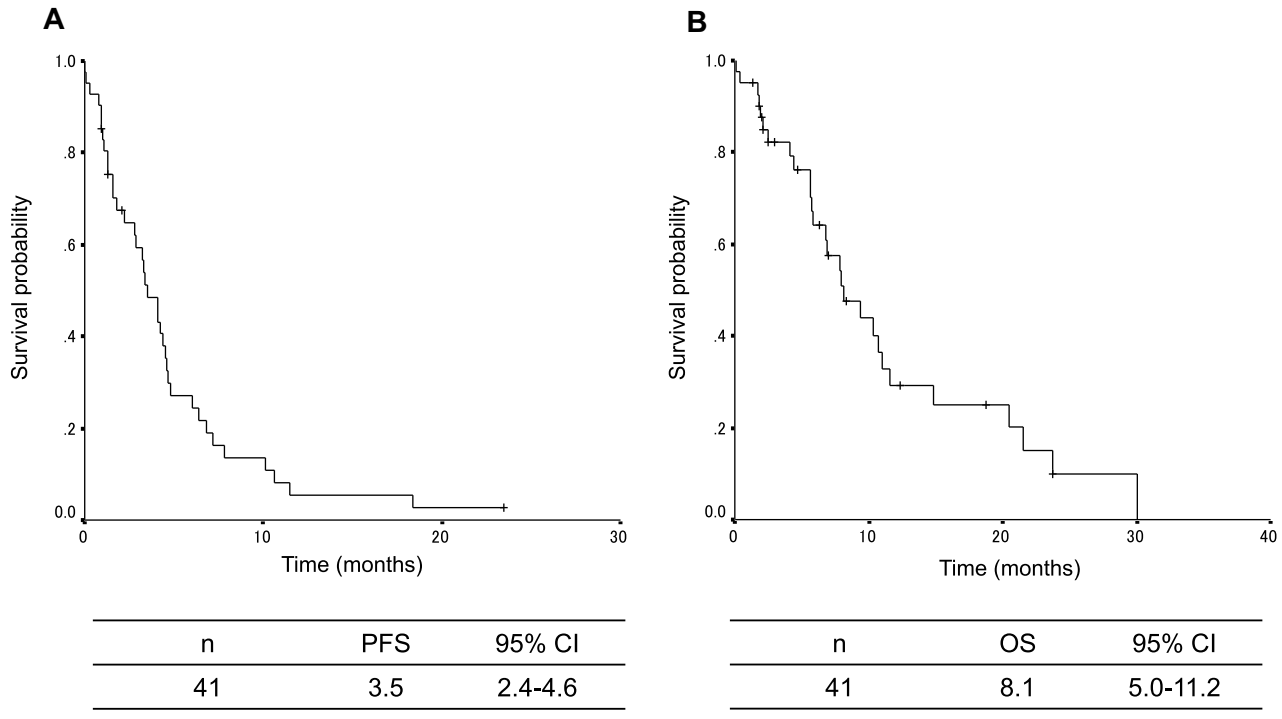
Table 2 Response to Amrubicin Monotherapy

	Total (n=41)	Sensitive Relapse (n=19)	Refractory Relapse (n=22)	*P* value *
Complete response	0	0	0	
Partial response	11	6	5	
Stable disease	15	9	6	
Progressive disease	13	4	9	
Not evaluable	2	1	1	
Response rate	26.8%	31.6%	22.7%	0.52
(95% confidence interval)	(12.7–40.9)	(11.7–51.5)	(4.8–40.7)	

Note: * Chi-squared test.
Abbreviation: CI, confidence interval.

Survival

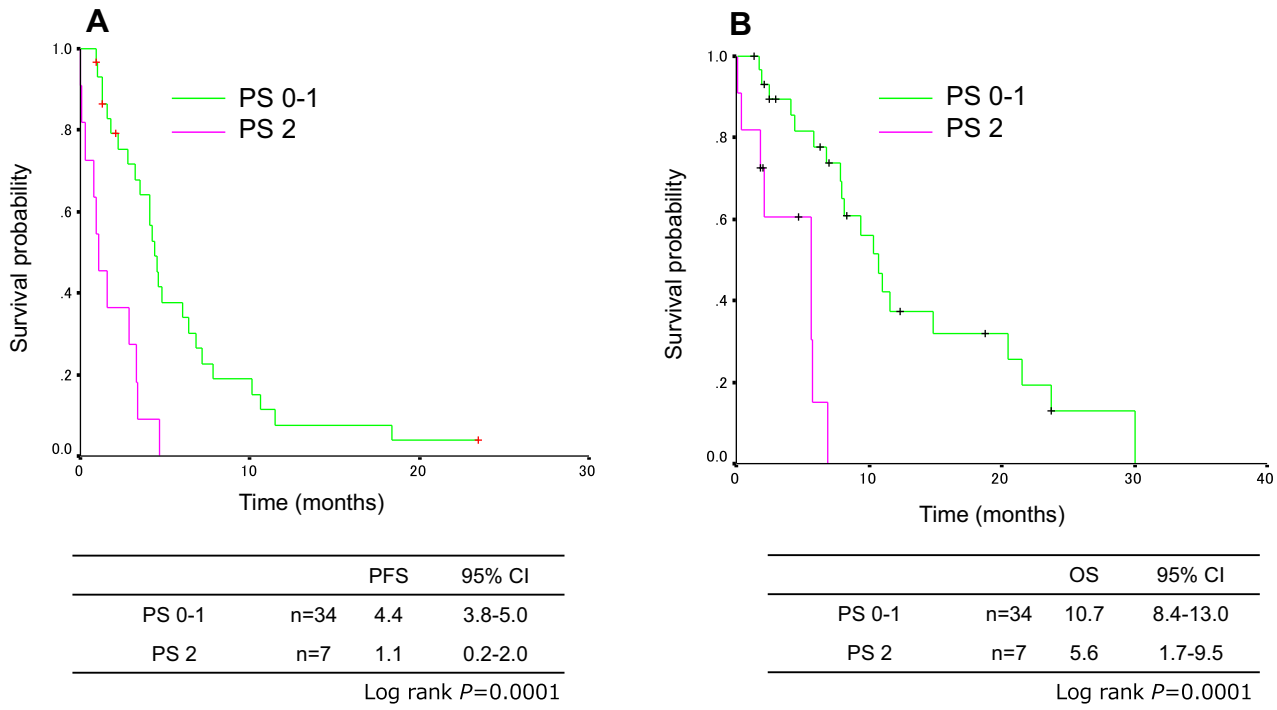
The median PFS and OS for all patients were 3.5 (95% CI: 2.4–4.6) and 8.1 (95% CI: 5.0–11.2) months, respectively (Figure 1). The median follow-up time was 8.2 months. The median PFS according to the type of relapse to the prior regimen was significantly higher in patients with sensitive relapse than in those with refractory relapse (4.7 [95% CI: 2.3–7.1] months vs 2.8 [95% CI: 0.5–5.1] months, *P*=0.043, Figure 2A). However, the median OS did not significantly differ between the two groups (10.7 [95% CI: 8.3–13.1] months in the sensitive group vs 6.8 [95% CI: 4.2–9.4] months in the refractory group, *P*=0.24, Figure 2B). Patients with a PS of 0–1 had a significantly higher median PFS than those with a PS of 2 (4.4 [95% CI: 3.8–5.0] months vs 1.1 [95% CI: 0.2–2.0] months, *P*=0.0001, Figure 3A). Similarly, the median OS did significantly differ between these two patient groups (10.7 [95% CI: 8.4–13.0] months in the sensitive group vs 5.6 [95% CI: 1.7–9.5] months in the refractory group, *P*=0.0001, Figure 3B). Moreover, the median PFS according to the mGPS tended to be higher in patients with an mGPS of 0 than in those with an mGPS of 1 or 2 (4.5 [95% CI: 3.7–5.3] months vs 1.6 [95% CI: 0.9–2.3] months, *P*=0.052, Figure 4A). Moreover, the median OS did significantly varied between these two groups (10.7 [95% CI: 8.1–13.3]



n	PFS	95% CI
41	3.5	2.4-4.6

n	OS	95% CI
41	8.1	5.0-11.2

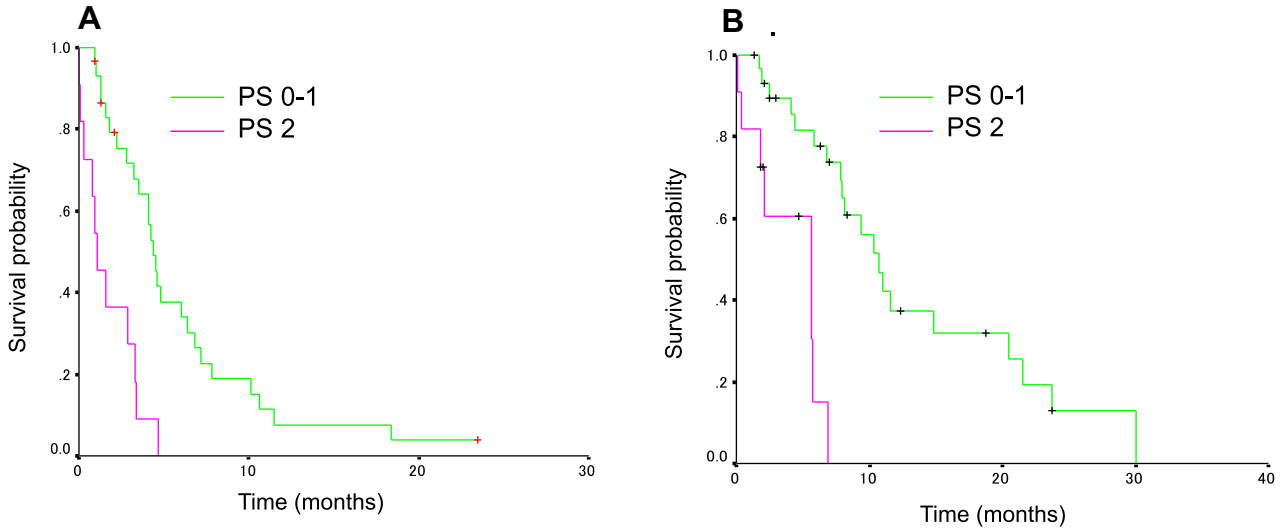
Figure 1 Kaplan–Meier plots of survival. (**A**) Progression-free survival (PFS) and (**B**) overall survival (OS) of all patients. CI, confidence interval.



		PFS	95% CI
PS 0-1	n=34	4.4	3.8-5.0
PS 2	n=7	1.1	0.2-2.0
Log rank *P*=0.0001			

		OS	95% CI
PS 0-1	n=34	10.7	8.4-13.0
PS 2	n=7	5.6	1.7-9.5
Log rank *P*=0.0001			

Figure 2 Kaplan–Meier plots of survival according to the type of relapse. (**A**) PFS and (**B**) OS.

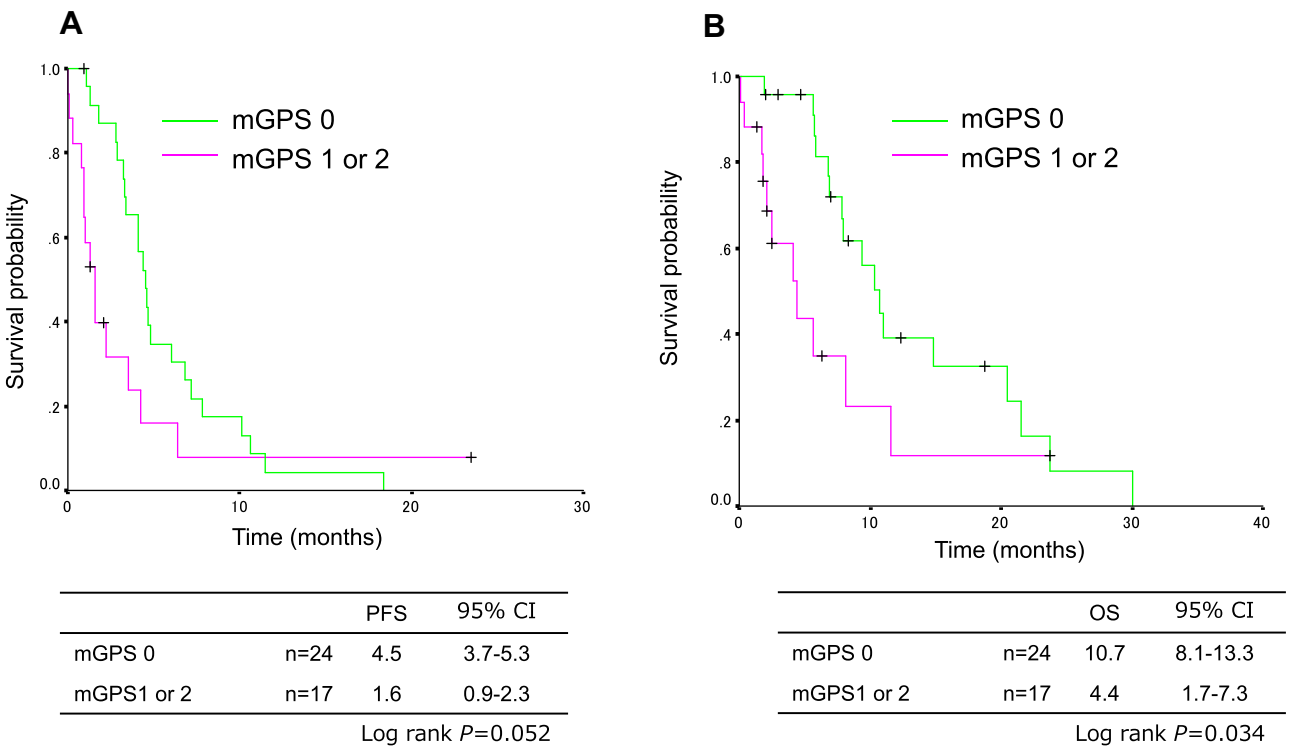


		PFS	95% CI
PS 0-1	n=34	4.4	3.8-5.0
PS 2	n=7	1.1	0.2-2.0
Log rank *P*=0.0001			

		OS	95% CI
PS 0-1	n=34	10.7	8.4-13.0
PS 2	n=7	5.6	1.7-9.5
Log rank *P*=0.0001			

Figure 3 Kaplan–Meier plots of survival according to performance status (PS). (**A**) PFS and (**B**) OS.

months in patients with mPFS 0 vs 4.4 [95% CI: 1.7–7.3] months in patients with mPFS 1 or 2, *P*=0.034, Figure 4B). Multivariate analysis identified good PS, limited disease (LD), and mGPS 0 as favorable independent predictors of PFS and OS in AMR monotherapy for elderly patients with relapsed SCLC (Tables 3 and 4).



		PFS	95% CI
mGPS 0	n=24	4.5	3.7-5.3
mGPS1 or 2	n=17	1.6	0.9-2.3
		Log rank *P*=0.052	

		OS	95% CI
mGPS 0	n=24	10.7	8.1-13.3
mGPS1 or 2	n=17	4.4	1.7-7.3
		Log rank *P*=0.034	

Figure 4 Kaplan–Meier plots of survival according to the modified Glasgow prognostic score (mGPS). (**A**) PFS and (**B**) OS.

Toxicity Assessment and Dose Modification

The patients' toxicity profiles are summarized in Table 5. The most common adverse events were hematological toxicities, such as neutropenia and leukopenia. Grade 3 or higher neutropenia and leukopenia occurred in 19 (46%) and 23 (56%) of the patients, respectively. Grade 3 or higher thrombocytopenia occurred in 11 (27%). Febrile neutropenia occurred in 9 patients (22%). A total of 152 cycles were administered. Among patients receiving 40 mg/m^2/day as a starting dose of AMR, a dose reduction to 35 mg/m^2/day was required in 10 patients (31%) since such as febrile neutropenia, grade 4 neutropenia lasted ≥4 days and grade 4 thrombocytopenia, but none of these patients required a subsequent dose reduction among them. Among patients receiving 35 mg/m^2/day of AMR, a dose reduction to 30 mg/m^2/day was required in one patient (13%) since grade 4 neutropenia lasted ≥4 days, but the patient did not require a subsequent dose reduction. A dose reduction was not required in one patient receiving an AMR starting dose of 30 mg/m^2/day. Non-hematological toxic effects were relatively mild, and pneumonitis and treatment-related deaths did not occur.

Discussion

This retrospective study assessed the efficacy of AMR for the treatment of relapsed SCLC in elderly patients who had been previously treated with CE. Remarkably, our analysis revealed that AMR monotherapy was associated with a clinical response rate of 26.8%, a median PFS of 3.5 months, and a median OS of 8.1 months in the second line setting for elderly patients with ED-SCLC. In refractory cases, we observed a response rate of 22.7%, a PFS of 2.8 months, and an OS of 6.8 months. Considering that ED-SCLC patients typically have an OS of approximately about six weeks by a best supportive care,[20] it is a critical piece of information that the findings of our study support the significance of AMR for refractory relapsed cases in elderly patients.

Among Euro-American cases with relapsed SCLC, topotecan has been the most widely used chemotherapy regimen for relapsed or refractory SCLC.[21,22] However, it is known that TOP is not so effective for refractory cases based on a finding that an objective response rate by topotecan for the cases was only 5%.[23] Horita reported a valuable systematic review and meta-analysis to evaluate clinical benefit and adverse events of AMR for patients with relapsed SCLC.[24] The study revealed that AMR

Table 3 Univariate and Multivariate Analyses for Progression-Free Survival

PFS	Univariate Analysis		Multivariate Analysis	
Variable	**Hazard Ratio (95% CI)**	***P* value**	**Hazard Ratio (95% CI)**	***P* value**
Sex Female Male	 1 (Ref.) 1.52 (0.62–3.72)	 0.36	 Excluded	
Performance status 0–1 2	 1 (Ref.) 4.01 (0.84–3.30)	 0.001	 1 (Ref.) 5.12 (2.10–12.5)	 0.0003
Stage Limited disease Extensive disease	 1 (Ref.) 4.33 (1.61–11.7)	 0.004	 1 (Ref.) 4.67 (1.70–12.8)	 0.003
Type of relapse to prior chemotherapy Sensitive relapse Refractory relapse	 1 (Ref.) 1.90 (0.96–3.75)	 0.064	 Excluded	
Brain metastasis Negative Positive	 1 (Ref.) 1.05 (0.40–2.77)	 0.91	 Excluded	
Modified Glasgow Prognostic Score 0 1–2	 1 (Ref.) 1.84 (0.92–3.72)	 0.086	 1 (Ref.) 2.20 (1.06–4.56)	 0.033

Abbreviations: CI; confidence interval; PFS, progression-free survival.

Table 4 Univariate and Multivariate Analyses for Overall Survival

OS	Univariate Analysis		Multivariate Analysis	
Variable	**Hazard Ratio (95% CI)**	***P* value**	**Hazard Ratio (95% CI)**	***P* value**
Sex Female Male	 1 (Ref.) 1.43 (0.49–4.12)	 0.52	 Excluded	
Performance status 0–1 2	 1 (Ref.) 6.64 (2.28–19.3)	 0.001	1 (Ref.) 6.47 (2.06–20.3)	 0.001
Stage Limited disease Extensive disease	 1 (Ref.) 2.65 (1.06–6.62)	 0.037	 1 (Ref.) 2.79 (1.07–7.28)	 0.036
Type of relapse to prior chemotherapy Sensitive relapse Refractory relapse	 1 (Ref.) 1.60 (0.73–3.51)	 0.25	 Excluded	
Brain metastasis Negative Positive	 1 (Ref.) 0.52 (0.12–2.22)	 0.38	 Excluded	
Modified Glasgow Prognostic Score 0 1–2	 1 (Ref.) 2.28 (1.04–4.99)	 0.04	1 (Ref.) 2.49 (1.11–7.28)	 0.027

Abbreviations: CI, confidence interval; OS, overall survival.

Table 5 Toxicities During AMR Chemotherapy

Toxicity	N=41, Grade		
	≤ 2	3, 4	≥3, %
Neutropenia	8	7, 16	23 (56)
Leukopenia	13	10, 9	19 (46)
Thrombocytopenia	13	5, 6	11 (27)
Anemia	30	5,0	5 (12)
Febrile neutropenia		9	9 (22)
Fatigue	5	0	0 (0)
Nausea	6	0	0 (0)
Constipation	3	3	3 (2)
Anorexia	13	0	0 (0)
Diarrhea	3	0	0 (0)
Total bilirubin	6	0	0 (0)
AST/ALT	7	0	0 (0)
Creatinine	2	0	0 (0)
Hyperkalemia	5	0	0 (0)
Mucositis	1	0	0 (0)
Dysgeusia	1	0	0 (0)

Abbreviations: AMR, amrubicin; ALT, alanine transaminase; AST, aspartate transaminase.

provides a better objective response for both types of relapse, a similar OS for sensitive-relapsed cases, better OS for refractory-relapsed cases, and a similar AE profile except for a higher risk febrile neutropenia compared to topotecan, and thus concluded that AMR is much more beneficial for Japanese patients with relapsed SCLC.[24] We showed a list of clinical studies regarding AMR for relapsed SCLC patients including our present study in Table 6, indicating that the response rate of our study is comparable to those of the previous studies performed for mainly non-elderly patients.

Notably, Imai et al showed that AMR was effective and safe for elderly patients with relapsed ED-SCLC, reporting 3.4 months of PFS and 6.1 months of OS.[26] In their study, the PFS and OS among the refractory cases were 2.7 and 5.5 months, respectively. Thus, the findings of our study in refractory cases are consistent with the observations of the previous study, indicating that AMR is a beneficial treatment option for elderly patients with either refractory or sensitive relapsed SCLC.

Data from earlier publications[27,28] and a phase III study[29] did not identify significant differences in the objective response rate and OS between the CE and AMR. Moreover, we previously reported that chemo-naïve elderly patients with ED-SCLC who received CE achieved a significantly longer PFS than those receiving AMR,[30] consequently indicating that CE is the appropriate standard therapy for this population as well. The treatment landscape of SCLC is rapidly evolving. The published results of the first-line randomized trial comparing CE with CE plus atezolizumab (IMpower-133) indicated a longer PFS and OS among patients receiving atezolizumab, including elderly patients.[7,31] The results of Impower-133 have changed the standard of care for elderly ED-SCLC patients and, thus, it should be mentioned that CE containing regimen is still the preferred regimen in chemotherapy for ED-SCLC patients.

Turning now to second line therapy by PD-1 inhibitor, the CheckMate-032 trial reported that the ORR and PFS of single agent nivolumab were 11% and 1.4 months in previously treated SCLC patients.[32] Moreover, there was a recent press release that the phase III randomized trial (CheckMate-331) comparing nivolumab with standard of care (topotecan or amrubicin) in second-line therapy of ED-SCLC did not meet the primary endpoint of OS.[33] As a result, the FDA approved nivolumab monotherapy for third-line SCLC.[34] Considering

Table 6 Clinical Studies Regarding Amrubicin Monotherapy for Relapsed SCLC Patients

	Study Type	n	Dose (mg/m^2)	Age (Median)	Refractory Relapse (%)	Response Rate (%)
Murakami[14]	Phase II	82	40	66	100	32.9
Kaira[15]	Phase II	29	35	67	66	44.8
Inoue[16]	Phase II	29	40	64	41	37.9
Onoda[17]	Phase II	60	40	67	27	51.7
Pawel[25]	Phase III	424	40	62	47	31.1
Igawa[45]	Retrospective	27	35, 40	67	27	29.6
Present study	Retrospective	41	30, 35, 40	76	54	26.8

the few available regimens as second-line chemotherapy for ED-SCLC patients whereas CE plus atezolizumab regimen was established as a new first line standard of care, it is certain that AMR represents an essential treatment option for elderly patients with relapsed ED-SCLC. We would like to emphasize that our study generated critical results demonstrating the efficacy and safety profile of AMR for the elderly patient population in the second-line setting.

We demonstrated that the pretreatment mGPS in patients with ED-SCLC was an independent predictor of PFS and OS, as well as PS and stage. The mGPS for lung cancer, which is based on serum Alb and CRP, was first described in 2003.[35] It is a useful marker reflecting the state of inflammation and nutrition that has been identified as a prognostic factor in meta-analyses for non-SCLC (NSCLC).[36,37] Although the mGPS has a clear cut-off value,[19] few studies have considered the prognostic value of the mGPS for SCLC in contrast to the large number of studies in NSCLC and various other cancers.[38–40] Furthermore, the prognosis of cancer patients is correlated to the nutritional status, and one-third of patient deaths are caused by malnutrition rather than cancer, and Alb is a convenient marker indicating the nutritional status.[41] A previous study of pretreatment prognostic factors for survival in SCLC showed that Alb is significantly correlated with survival.[42] Moreover, another study reported that mGPS was useful as a prognostic factor for OS in ED-SCLC patients, including the non-elderly population.[43] To our knowledge, this is the first study describing the mGPS as a predictor of PFS and OS of AMR monotherapy for elderly SCLC patients relapsed to prior CE therapy.

Considering a recommending dose of AMR for elderly cases, previous Japanese studies indicated that 35 mg/m^2 dose could be selected to relapsed SCLC patients,[15,44,45] besides, a 25% of response rate was observed in patients receiving 35mg^2 of AMR in our study. Thus, it is sure that both of 35 mg/m^2 and 40 mg/m^2 of AMR is recommended for relapsed elderly SCLC patients.

We previously reported a retrospective observational study[46] and a non-randomized Phase II study,[47] indicating that 40 mg/m^2 of AMR could be considered as an appropriate treatment option for chemotherapy-naive elderly or poor-risk patients with ED-SCLC. Thus, we choose 40 mg/m^2 of AMR as a starting dose for elderly patients with relapsed SCLC in the clinical practice. Meanwhile, although an AMR dose of 45 mg/m^2 was reportedly effective, it produced intolerable toxicities and even treatment-related deaths in other studies.[48,49] Furthermore, a randomized phase III study previously reported by Sekine et al indicated that higher incidences of febrile neutropenia and interstitial lung disease of grade 3 or worse occurred with 45 mg/m^2 AMR; the authors concluded that AMR at 45 mg/m^2 is intolerable in chemo-naïve elderly Japanese patients with ED-SCLC.[27] These findings demonstrate that the appropriate AMR dose is critical for avoiding fatal adverse events, such as severe neutropenia or febrile neutropenia.

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

Conclusion

In our study, AMR was an effective and beneficial regimen for elderly patients with relapsed SCLC after CE therapy. We would like to emphasize that our new findings provide guidance on AMR monotherapy for pursuing a new direction in clinical research on the treatment of elderly patients with relapsed SCLC. We are currently conducting a prospective observational study evaluating the clinical outcomes of AMR monotherapy in SCLC patients relapsed to prior CE plus atezolizumab therapy.

Abbreviations

Alb, albumin; AMR, amrubicin; CE, carboplatin plus etoposide; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; ED, extensive-disease; G-CSF, granulocyte colony-stimulating factor; LD, limited disease; mGPS, modified Glasgow prognostic score; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; SCLC, small-cell lung cancer.

Ethics Approval and Informed Consent

The ethical review board committee of Kitasato University and its affiliated hospitals approved the present study, which received ethical approval for the use of an opt-out method.

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Disclosure

The authors report no conflicts of interest in this work.

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