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ORIGINAL ARTICLE

Lower optimal dose of amrubicin for relapsed small-cell lung cancer: a retrospective study

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Abstract

Background Amrubicin (AMR) is one of the most active agents for small-cell lung cancer (SCLC). However, hematologic toxicity and infection at a commonly used dose (40 mg/m^2) is problematic; the optimal dose remains undetermined.

Patients and methods To evaluate the optimal dose of AMR in terms of efficacy and safety, we reviewed consecutive data on patients with relapsed SCLC who received AMR at doses of 40, 35, and 30 mg/m^2 (on days 1–3) at Nippon Medical School Hospital between October 2010 and November 2021.

Results We reviewed the data of 86 patients (20, 45, 27 who received AMR doses of 40, 35, 30 mg/m^2, respectively) according to our study criteria. For patients ≥75 years, the proportion who received second-line treatment tended to be higher in the 30–35 mg/m^2 group. Objective response rates were 37/46/35%, median progression-free survival (PFS) were 3.0/4.7/3.2 months, and median overall survival (OS) were 7.8/16.3/8.0 months, respectively. Grade 4 neutropenia occurred in 58/39/31% of patients, which was higher for the 40 mg/m^2 group. The incidence of febrile neutropenia did not differ between groups. Multivariate analysis identified the AMR dose was not associated with longer PFS and OS.

Conclusion Treatment with AMR between 30 and 35 mg/m^2 showed relatively mild hematologic toxicity compared with AMR at 40 mg/m^2, without any significant difference in efficacy. Lower dose of AMR for relapsed SCLC could be a promising treatment option.

Keywords Amrubicin · Small-cell lung cancer · Relapsed · Febrile neutropenia · Optimal dose

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 13–15% of all types of lung cancers [1]. While immune checkpoint inhibitors combined with chemotherapy have modestly improved the overall survival (OS) of patients with extensive-stage SCLC, the prognosis of SCLC remains poor. This is because almost all patients with extensive-stage SCLC, and more than half of patients with limited-stage disease, relapse after first-line chemotherapy, with or without thoracic radiotherapy. The median OS of patients with relapsed SCLC is generally 2–4 months without continuous chemotherapy [2] and treatment options are limited.

Amrubicin (AMR) is a topoisomerase II inhibitor. It is a completely synthetic anthracycline anti-tumor agent developed and approved only in Japan [3]. A randomized phase III trial comparing single-agent AMR at 40–45 mg/m^2 on days 1 to 3 and carboplatin plus etoposide in chemotherapy-naive elderly (≥70 years) patients with extensive SCLC was terminated early because of high treatment-related mortality in the AMR arm [4]. It was concluded that AMR at 40–45 mg/m^2 was too toxic and intolerable in elderly patients with extensive SCLC. However, of 62 patients enrolled, the median OS, time to progression, and objective response rate (ORR) were 10.9 months, 4.7 months, and 74.2% in the amrubicin arm and 11.3 months, 4.4 months, and 60% in the carboplatin plus etoposide arm, respectively. This suggests similar activity of AMR to carboplatin plus etoposide as first-line treatment for SCLC. In a phase III trial comparing 40 mg/m^2 AMR on days 1 to 3 and topotecan as second-line treatment for SCLC [5], the ORR (31.1% vs. 16.9%, $P < 0.001$) and median progression-free survival (PFS)

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(4.1 months vs. 3.5 months, $P=0.018$) were significantly in favor of AMR. However, treatment with AMR failed to improve OS over topotecan (median OS: 7.5 months vs. 7.8 months, $P=0.170$). This might be due partly to more febrile neutropenia (FN) (10% vs. 3%, $P=0.03$) and grade 3 or greater infection (16% vs. 10%) in the AMR arm. Thus, the dose of AMR employed in the phase III study might have been higher than optimal.

The dose of AMR recommended in the package insert is 45 mg/m^2 on days 1 to 3 every 3 weeks. However, in clinical practice we often use AMR at a reduced dose, such as 40, 35, 30 mg/m^2, based on data from several clinical trials. To evaluate the optimal dose of AMR for SCLC in terms of efficacy and safety, we conducted a retrospective analysis of patients with relapsed SCLC who received AMR.

Material and methods

Patient selection

We reviewed the consecutive data of patients with relapsed SCLC who received AMR at doses of 45, 40, 35, and 30 mg/m^2 (on days 1 to 3) at the Nippon Medical School Hospital from October 2010 to November 2021. We carried out a retrospective review of the medical records of these patients after obtaining approval of the protocol from the institutional review board of the Nippon Medical School Hospital.

We defined recurrence within 90 days after platinum-containing chemotherapy as a refractory relapse and recurrence of 90 days or more as a sensitive relapse. Patients with relapsed SCLC who received AMR were considered eligible and included in the analyses of our study. Patients diagnosed as having large cell neuroendocrine carcinoma (LCNEC) were excluded, because LCNEC was treated not only as SCLC but also as non-small cell lung cancer (NSCLC) and the aim of this study was to investigate the efficacy and safety of lower dose AMR for SCLC.

Data collection

Baseline patient characteristics at the start of AMR were collected from medical records. Data collected included: age, Eastern Cooperative Oncology Group performance status (PS), sex, treatment line, clinical stage at initial visit (limited or extensive), type of relapse (sensitive or refractory), history of therapy with immune checkpoint inhibitors (ICI), and the site and number of metastases. Data regarding AMR treatment were also collected, including the number of courses administered, dose reduction, use of granulocyte-colony stimulating factor (G-CSF), best overall response, and adverse events (AEs; neutropenia, FN, anemia, thrombocytopenia, pneumonitis, and other non-hematological AEs). Post-treatments after AMR were also investigated.

Treatment

Amrubicin (45, 40, 35, or 30 mg/m^2) was administered intravenously on days 1 to 3 with an interval of 3 weeks or more. The treatment regimen and dose for each individual patient with relapsed SCLC was selected after discussion at the plenary conference of our department, and included medical oncologists.

All patients in our study were periodically followed up at our outpatient department from the start of AMR treatment for relapsed SCLC. We conducted systemic surveillance at the follow-up examinations by performing computed tomography (CT) at least once in 3–4 months, according to the consensus at our single facility. Magnetic resonance imaging (MRI) and positron emission tomography-CT were also performed if they were required.

Efficacy and toxicity evaluation

The objective tumor response to treatment was determined according to Response Evaluation Criteria for Solid Tumors, version 1.1 [6]. The disease control rate (DCR) was defined as the percentage of patients who achieved a complete response, partial response or stable disease. The PFS was calculated from the day of the start of AMR treatment for relapsed SCLC to the day of detection of re-recurrence or the day of death from any cause. The OS was calculated as the time from the start of AMR treatment for relapsed SCLC to the last date of confirmation of survival or the date of death from any cause. The data cut-off date was February 28, 2022.

Toxicity data was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

The PFS and OS were calculated using a Kaplan–Meier method. To investigate the association of any patient characteristics at the start of AMR treatment for relapsed SCLC with survival (PFS and OS) in the 40 mg/m^2 and 35 mg/m^2, a Cox proportional hazard model was used. The variables examined were age (<75 vs. ≥ 75 years), PS (0–1 vs. 2–3), type of relapse (sensitive vs. refractory), treatment line (second vs. third or more), number of metastatic sites (0–1 vs. 2 or more) and dose of AMR (40 mg/m^2 vs. 35 mg/m^2). All statistical analyses were performed using IBM® SPSS®, version 27.0.

Results

Patient characteristics

From October 2010 to November 2021, 95 patients were treated with AMR at our hospital. Of these patients, we identified 87 (92%) as having SCLC while the remaining eight had LCNEC. Of 87 patients with SCLC, a patient who had received first-line treatment, including AMR as a clinical trial, was excluded from our study. In the end, the data of 86 patients with relapsed SCLC who had been treated with AMR were analyzed in our study. Of the 86 patients, 19 had received AMR at a dose of 40 mg/m^2, 41 received 35 mg/m^2, and 26 received 30 mg/m^2. There was no patient treated with the AMR at 45 mg/m^2. Baseline characteristics were as follows (Table 1): Overall patient population: median age (range), 70 (47–87) years; male/female ratio, 68/18; PS 0/1/2/3, 17/60/8/1; treatment line second/third/fourth, 73/11/2; limited/extensive stage at initial diagnosis, 34/52; sensitive/refractory relapse, 36/50; and brain/liver/bone metastasis, 29/19/19. Prior ICI was administered before AMR in seven patients. Forty-two patients had two or more metastatic sites. The 30 mg/m^2 group had a higher proportion of elderly patients (≥ 75 years) who had two or more metastatic sites than the 40–35 mg/m^2 group. Patients in the 40 mg/m^2 group had a lower proportion of patients who underwent second-line treatment and sensitive relapse than those in the 35–30 mg/m^2 group. Prior ICI before AMR had been performed in none of the patients of the 40 mg/m^2 group.

Table 1 Patient characteristics

	Total (n = 86)		40 mg/m^2 (n = 19)		35 mg/m^2 (n = 41)		30 mg/m^2 (n = 26)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age (years)								
Median (range)	70	(47–87)	68	(47–87)	69	(47–80)	72.5	(52–84)
≥ 75 years	18	(21)	3	(16)	7	(17)	8	(31)
Performance status								
0	17	(20)	6	(31)	9	(22)	2	(8)
1	60	(70)	11	(58)	28	(68)	21	(81)
2	8	(9)	2	(11)	3	(7)	3	(12)
3	1	(1)	0	(0)	1	(2)	0	(0)
Sex								
Male	68	(79)	17	(89)	31	(76)	20	(77)
Female	18	(21)	2	(11)	10	(24)	6	(23)
Treatment line								
2nd	73	(85)	11	(58)	38	(93)	24	(92)
3rd	11	(13)	6	(32)	3	(7)	2	(8)
4th	2	(2)	2	(11)	0	(0)	0	(0)
Initial diagnosis								
Limited stage	34	(40)	6	(32)	17	(41)	11	(42)
Extended stage	52	(60)	13	(68)	24	(59)	15	(58)
Type of relapse*								
Sensitive	36	(42)	6	(32)	19	(46)	11	(42)
Refractory	50	(58)	13	(68)	22	(54)	15	(58)
Pre-treatment of ICI								
Chemotherapy without ICI	79	(92)	19	(100)	38	(93)	22	(85)
Chemotherapy with ICI	7	(8)	0	(0)	3	(7)	4	(15)
Metastasis								
Brain	29	(34)	5	(26)	14	(34)	10	(38)
Liver	19	(22)	5	(26)	8	(20)	6	(23)
Bone	19	(22)	2	(11)	11	(27)	6	(23)
2 or more metastatic sites	42	(49)	8	(42)	19	(46)	15	(58)

*Sensitive relapse: within 90 days after platinum-containing chemotherapy

AMR, amrubicin; ICI, immune checkpoint inhibitor

Treatment and efficacy

The details of treatment delivery and efficacy of AMR are shown in Table 2 and Fig. 1. In the 40, 35 and 30 mg/m^2 AMR groups, the median number of courses (range) were 2 (1–9), 4 (1–12) and 2.5 (1–12); dose reductions after the second cycle were 16%, 17%, and 15%; and uses of G-CSF (primary and secondary prophylaxis) were 11% and 0%, 7% and 2%, 4% and 8%, respectively.

In the 40 mg/m^2 AMR group, the ORR was 37% (CR 0% and PR 37%), and the DCR was 63% (SD 26%). In the 35 mg/m^2 AMR group, the ORR was 46% (CR 0% and PR 46%), and the DCR was 75% (SD 29%). In the 30 mg/m^2 AMR group, the ORR was 35% (CR 0% and PR 35%) and the DCR was 70% (SD 35%). The reasons for AMR discontinuation in each group were mainly due to early PD.

The median PFS (95% confidence interval [CI]) in the 40, 35, and 30 mg/m^2 AMR groups were 3.2 (1.7–4.7), 4.7 (2.8–6.5), and 3.4 (2.4–4.4) months, respectively (Fig. 1A). The median OS rates from the start of AMR therapy (95% CI) in the 40, 35, and 30 mg/m^2 groups were 7.8 (4.6–10.9), 16.1 (9.4–22.8), and 8.0 (5.3–10.7) months, respectively (Fig. 1B).

Toxicities

The AEs are summarized in Table 3. Grade 4 neutropenia occurred in 58/39/31% of patients and grade 3–4 FN in 11/17/19% of patients in 40, 35, and 30 mg/m^2 AMR groups, respectively. Grade 3–4 thrombocytopenia occurred in 26% of patients in the 40 mg/m^2 AMR group, which was higher than in the 35 and 30 mg/m^2 AMR groups. Grade 4 hyponatremia occurred in 5% of patients in the 35 mg/m^2 AMR group. No grade 3–4 pneumonitis and treatment-related deaths occurred in any groups.

Post-treatment

Post-treatments after AMR are shown in Table 4. The best supportive care only was given to 58%, 41%, and 77% of

Table 2 Treatment delivery and efficacy of AMR

	40 mg/m^2 (n = 19)		35 mg/m^2 (n = 41)		30 mg/m^2 (n = 26)	
	n	(%)	n	(%)	n	(%)
Number of courses						
Median (range)	2	(1–9)	4	(1–12)	2.5	(1–12)
Dose reduction after 2nd cycle	3	(16)	7	(17)	4	(15)
Use of G-CSF						
Primary prophylaxis	2	(11)	3	(7)	1	(4)
Secondary prophylaxis	0	(0)	1	(2)	2	(8)
Best overall response, n (%)						
CR	0	(0)	0	(0)	0	(0)
PR	7	(37)	19	(46)	9	(35)
SD	5	(26)	12	(29)	9	(35)
PD	6	(32)	8	(20)	6	(23)
NE	1	(5)	2	(5)	2	(8)
ORR (%)						
All		37		46		35
Sensitive relapse		17		53		45
Refractory relapse		46		41		27
DCR (%)						
All		63		75		70
Sensitive relapse		50		84		82
Refractory relapse		69		68		60
Reason for AMR discontinuation						
PD	15	(79)	30	(73)	20	(77)
AEs	2	(11)	3	(7)	3	(12)
Physician's choice other than AEs	2	(11)	8	(20)	3	(12)

AMR, amrubicin; CR, complete response; DCR, disease control rate; G-CSF, granulocyte colony-stimulating factor; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

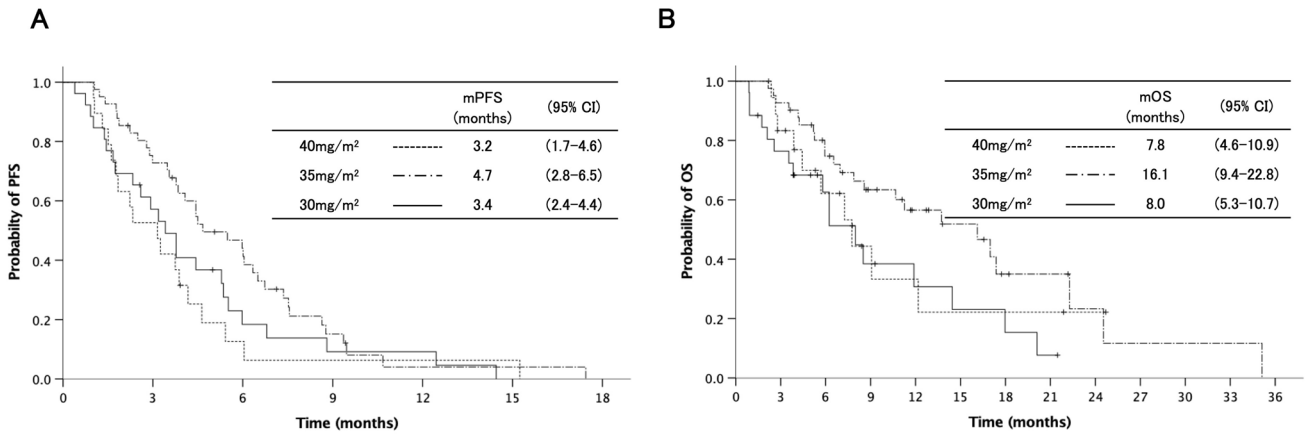

Fig. 1 Kaplan–Meier survival curves of relapsed patients according to AMR dose. **A** PFS comparing 30 vs. 35 vs. 40 mg/m2 AMR groups. **B** OS comparing 30 vs. 35 vs. 40 mg/m2 AMR groups. Abbreviations: AMR, amrubicin; CI, confidential interval; mOS, median overall survival; mPFS, median progression-free survival

Table 3 Toxicities of AMR treatment

Adverse events	40 mg/m^2 (n = 19)			35 mg/m^2 (n = 41)			30 mg/m^2 (n = 26)		
	Grade 3	Grade 4	Grade 3–4	Grade 3	Grade 4	Grade 3–4	Grade 3	Grade 4	Grade 3–4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutropenia	2 (11)	11 (58)	13 (68)	7 (17)	16 (39)	23 (56)	7 (27)	8 (31)	15 (58)
Febrile neutropenia	1 (5)	1 (5)	2 (11)	7 (17)	0 (0)	7 (17)	5 (19)	0 (0)	5 (19)
Anemia	3 (16)	0 (0)	3 (16)	5 (12)	0 (0)	5 (12)	5 (19)	0 (0)	5 (19)
Thrombocytopenia	3 (16)	2 (11)	5 (26)	3 (7)	3 (7)	6 (15)	4 (15)	0 (0)	4 (15)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other non-hematological toxicities	1 (5)	0 (0)	1 (5)	1 (2)	2 (5)	3 (7)	0 (0)	0 (0)	0 (0)
Increased creatinine	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Hyponatremia	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)

AMR, amrubicin

Table 4 Post-treatment after AMR

	40 mg/m^2 (n = 19)		35 mg/m^2 (n = 41)		30 mg/m^2 (n = 26)	
	n	(%)	n	(%)	n	(%)
Chemotherapy						
Without ICI	6	(32)	16	(39)	5	(19)
With ICI	2	(11)	5	(12)	0	(0)
Best supportive care only	11	(58)	17	(41)	20	(77)
No recurrence	0	(0)	2	(5)	1	(4)
Unknown	0	(0)	1	(2)	0	(0)

AMR, amrubicin; ICI, immune checkpoint inhibitor

patients in 40, 35, and 30 mg/m^2 AMR groups, respectively. Chemotherapy with ICI was given to 11%, 12%, and 0% of patients in 40, 35 and 30 mg/m^2 AMR groups, respectively.

Evaluation of prognostic factors

Based on the results of multivariate analysis carried out using a Cox proportional hazards model, with adjustments for the factors previously described and dose of AMR, three or more treatment lines were identified as being significantly associated with shorter PFS and OS. Refractory relapse was significantly associated with shorter PFS, but not associated with shorter OS. The presence of two or more metastatic sites was identified as being significantly associated with shorter OS, but was not associated with shorter PFS. In patients who had received 35 mg/m^2 of AMR, the adjusted HRs for PFS and OS comparing 40 mg/m^2 AMR were as follows: PFS, 0.76 (95% CI 0.40–1.46); OS, 1.15 (95% CI 0.50–2.61; shown in Table 5).

Discussion

To the best of our knowledge, this study is the most detailed and largest consecutive data analysis regarding the optimal dose of AMR for patients with relapsed SCLC. Treatment with AMR at 30–35 mg/m^2 was found to be active with relatively less hematologic toxicity than AMR at 40 mg/m^2.

In a phase II study of 35 mg/m^2 AMR on days 1 to 3, a total of 66 patients with previously treated lung cancer (37 NSCLC and 29 SCLC)[7] reported that ORR, PFS, and OS were 44.8%, 4.0 months, and 12.0 months, respectively, in 29 patients with SCLC; this is similar to our study results. A retrospective analysis of 18 elderly (≥ 70 years) patients with refractory relapsed SCLC revealed that two patients received 25 mg/m^2, and eight patients 30 mg/m^2 and 35 mg/m^2, respectively, with a total response of 33% [8]. The authors concluded that the recommended dose was 30 mg/m^2 in elderly patients. Another retrospective analysis of AMR revealed that ORR and median OS for 25 patients who received 35 mg/m^2 AMR were 56.0% and 5.5 months, with similar AEs to those reported in a previous phase II study with AMR at a dose of 40 mg/m^2 [9]. Considering prior reported results and our data showing good efficacy and feasibility, we consider lower dose of AMR for relapsed SCLC could be a promising treatment option.

The ORR and DCR in patients with sensitive relapse were low in the 40 mg/m^2 group. The small number of patients might be the most likely possibility, because patients with sensitive relapse were only 6 in the 40 mg/m^2 group. Although we considered a possibility of the difference in the disease activity, the rate of brain, liver, and bone metastasis

Table 5 Analysis using a Cox proportional hazards model of the factors influencing PFS and OS from start of amrubicin in the 40 and 35 mg/m^2 groups

Factors	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age						
< 75	1			1		
≥ 75	1.09	0.47–2.54	0.85	2.31	0.81–6.57	0.12
PS						
0–1	1			1		
2–3	2.99	1.01–8.84	**0.048**	2.58	0.76–8.78	0.13
Type of relapse						
Sensitive	1			1		
Refractory	3.53	1.68–7.40	**< 0.001**	2.16	0.86–5.46	0.10
Treatment line						
2nd	1			1		
3rd or more	3.41	1.45–8.04	**0.005**	4.55	1.60–13.0	**0.005**
Number of metastatic sites						
0–1	1			1		
2 or more	0.83	0.45–1.55	0.56	3.39	1.37–8.38	**0.008**
Dose of AMR						
40 mg/m^2	1			1		
35 mg/m^2	0.76	0.40–1.46	0.42	1.15	0.50–2.61	0.75

For all tests for significance, a *P* value < .05 was considered statistically significant (in bold)

AMR, amrubicin; CI, confidential interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status

and 2 or more metastatic sites were similar in the three groups. There was another possibility that the higher proportion of 3rd or more treatment line in the 40 mg/m^2 group (43%) had some effects on the results.

Being elderly, and having a poor PS, high creatinine level, high lactate dehydrogenase level, and two or more metastatic lesions are considered poor prognostic factors for patients with extensive SCLC [10, 11]. Using a Cox proportional hazards model, we assessed the factors influencing PFS and OS from start of AMR therapy by comparing 40 and 35 mg/m^2 groups. PS, type of relapse and treatment line affected PFS while treatment line and number of metastatic sites affected OS. However, the dose of AMR was not associated with both PFS and OS. These results also indicated a low dose of AMR would not be a significant negative factor for efficacy.

Adverse events associated with dose of AMR have not been clearly reported in previous articles. The most important toxicities are FN and pneumonitis due to treatment of AMR in patients with relapsed SCLC. No occurrence occurred of pneumonitis in our study. The incidence of FN was similar in 40, 35, and 30 mg/m^2 AMR groups, which might be due to the more frequent use of G-CSF in the 40 mg/m^2 group, and that more elderly and frail patients were treated with a lower dose. The incidences of grade 3–4 neutropenia and thrombocytopenia were also higher in the 40 compared to 35 and 30 mg/m^2 AMR groups. Adverse events other than grade 3–4 neutropenia and thrombocytopenia in the groups with lower dose of AMR were not fewer. The reason would be probably due to more vulnerable patients being treated with lower dose. It could be difficult to show the reasons for recommendation of lower dose of AMR in terms of AEs from our retrospective analysis. However, considering good efficacy in addition to similar non-hematological toxicities and relatively mild hematological toxicities, lower dose of AMR for relapsed SCLC could be a treatment option according to the patient condition.

Our study had several limitations. First, differences existed in baseline patient characteristics and treatment details (e.g. age, PS, type of relapse, metastatic sites, pre-treatment, number of courses, and use of G-CSF) among patients of the 40, 35 and 30 mg/m^2 AMR groups because of the retrospective nature of the study. However, consecutive data in a single institution were reviewed without the exclusion of unfavorable data. We considered our results to be highly objective and close to general clinical practice. Second, the selection of AMR dose was affected by patients' characteristics. It may be that age and treatment line affected the dose of AMR selected since 40 mg/m^2 AMR tended to be chosen for younger patients and for third or fourth line therapy. In comparison, 30 mg/m^2 AMR tended to be selected for patients 75 years or over. Although the dose of AMR selected may have had some effect on the results of the analysis, patients who received 30–35 mg/m^2 AMR experienced a better treatment course, in terms of feasibility and safety, in our study. Third, it is possible that ICI treatment may have had an effect on treatment outcomes. The effect of using ICI before AMR is unknown. Platinum-doublet chemotherapy with ICI has become a standard first-line regimen in SCLC [12, 13]. As described in Tables 1 and 4, pre- and post-treatments related to ICI differed for each group. No pre-treatment with ICI occurred for the 40 mg/m^2 AMR group and no post-treatment with ICI in the 30 mg/m^2 AMR group.

Conclusion

Amrubicin at 30–35 mg/m^2 showed similar efficacy and a relatively mild hematologic toxicity compared with AMR at 40 mg/m^2. According to our retrospective study, lower dose of AMR for relapsed SCLC could be a promising treatment option.

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Declarations

Conflict of interest Dr. Kubota received research fund from Nihon Kayaku, AstraZeneca and payment or honoraria for lectures and presentations from Chugai Pharmaceutical. Dr. Seike received payment or honoraria for lectures and presentations from AstraZeneca, Chugai Pharmaceutical, Taiho Pharmaceutical, MSD, Ono Pharmaceutical, Bristol–Myers Squibb, Eli Lilly Japan, Takeda Pharmaceutical, Nihon Kayaku, Nippon Boehringer Ingelheim, Pfizer, Kyowa–Hakko Kirin, and Novartis. No other disclosures were reported.

Ethics statement The protocol of this study was approved by the Institutional Review Board of Nippon Medical School Hospital (B-2022-538).

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