Original Article

Efficacy and safety of amrubicin therapy after chemoimmunotherapy in small cell lung cancer patients

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Background: Although the addition of immune checkpoint inhibitors (ICIs) to platinum-doublet chemotherapy has improved the efficacy of first-line therapy in extensive-disease small cell lung cancer (SCLC) patients, the best treatment option for patients with recurrent SCLC has not yet been determined. We conducted a retrospective study to evaluate the efficacy and safety of amrubicin (AMR) therapy after treatment with ICIs.

Methods: We retrospectively assessed patients with recurrent SCLC who received AMR after chemoimmunotherapy at the Niigata Lung Cancer Treatment Group from August 2019 to February 2021.

Results: This analysis included 30 patients. The median progression-free survival (PFS) and overall survival (OS) were 3.8 (95% CI: 2.7–4.2) and 10 (95% CI: 7.4–14.8) months, respectively. The median PFS and OS did not significantly differ between the sensitive and refractory groups [PFS; 3.1 (95% CI: 1.1–4.0) *vs.* 4.2 (95% CI: 2.3–4.8) months, P=0.1142, OS; 10.0 (95% CI: 5.2–14.8) *vs.* 10.4 (95% CI: 3.8–NE) months, P=0.5525]. The most common adverse event was grade ≥3 neutropenia, which occurred in 22 of 30 patients (73%), and 2 patients (7%) discontinued AMR due to adverse events.

Conclusions: AMR after chemoimmunotherapy shows good clinical efficacy and safety in patients with recurrent SCLC.

Keywords: Small cell lung cancer (SCLC); amrubicin; programmed cell death ligand-1 (PD-L1); immune checkpoint inhibitor (ICI)

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 10–15% of all lung cancers (1). SCLC is a highly malignant tumor with a rapid growth rate and early lymph node and distant metastasis, but it is characterized by high sensitivity to radiotherapy and chemotherapy. For decades, the standard first-line chemotherapy for extensive-disease SCLC (ED-SCLC) has been platinum-doublet therapies, such as cisplatin (CDDP)/carboplatin plus irinotecan and CDDP/carboplatin plus etoposide (ETP), as no new drugs

have been approved in the field of SCLC for approximately 20 years (2,3). Recent clinical trials have shown that the addition of the programmed cell death ligand-1 (PD-L1) inhibitors atezolizumab and durvalumab to platinum and ETP significantly prolonged the survival time of patients (4,5). Thus, the PD-L1 inhibitor plus platinum and ETP has become the standard first-line therapy for ED-SCLC.

Although SCLC is highly sensitive to first-line chemoimmunotherapy, most patients experience recurrence. The one-year progression-free rates after cisplatin plus irinotecan or cisplatin plus etoposide are only 8% and 12%, respectively (2). The addition of PD-L1 inhibitors to platinum plus ETP have led to some improvement in progression-free survival (PFS) and overall survival (OS); however, the one-year survival rates remain low, at only 10% to 13% (4,5). Because most patients with ED-SCLC require second-line therapy, a number of studies have been conducted to establish effective treatments for recurrent SCLC. Previous studies showed that nogitecan (6), CDDP plus ETP plus irinotecan (7), and amrubicin (AMR) (8) were effective treatment options for recurrent SCLC. Although patients with refractory SCLC respond poorly to chemotherapy, AMR has been shown to be effective, regardless of the mode of recurrence, and is a standard salvage treatment for recurrent SCLC (9,10). In a meta-analysis of second-line AMR, the progression-free survival (PFS) rates at 3, 6, and 9 months were 63% (95% CI: 57–69%), 28% (95% CI: 21–35%), and 10% (95% CI: 6–14%), respectively (11). However, all of the studies regarding second-line treatment for SCLC were performed before the approval of PD-L1 inhibitors, so standard second-line treatment options using PD-L1 inhibitor in combination with platinum and ETP still need to be established. In addition, the safety of AMR therapy after chemoimmunotherapy is not yet known. Moreover, in NSCLC, the efficacy of cytotoxic chemotherapy following immune checkpoint inhibitors (ICI) has increased (12). Thus, in this study, we retrospectively evaluated the therapeutic effects and safety of AMR therapy in SCLC patients who experience recurrence after chemoimmunotherapy. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-225/rc).

Methods

Study design and patients

We retrospectively analyzed consecutive SCLC patients who received AMR monotherapy as second-line chemotherapy after receiving first-line therapy with a combination of a PD-L1 inhibitor, platinum and ETP at participating institutions of the Niigata Lung Cancer Treatment Group from August 22, 2019, to February 28, 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000044632) and was approved by the Institutional Review Board of Niigata University (registration number: 2020-0488), Niigata Prefectural Shibata Hospital (registration number: 237), Nagaoka Red Cross Hospital (registration number: 210717), Nagaoka Chuo General Hospital (registration number: 519), Niigata City General Hospital (registration number: 21-021), Nishiniigata Chuo Hospital (registration number: 2107), Saiseikai Niigata Hospital (registration number: E21-03) and Niigata Cancer Center Hospital (registration number: 2021-105). Individual consent for this retrospective analysis was waived. We collected data using the case report forms from the participating institutions. The data cleaning was carried out by the clinical trial office of the Niigata Lung Cancer Treatment Group ant authors.

Study assessment

All patient data were collected retrospectively. PFS was defined as the interval between the start of AMR monotherapy and disease progression or death. OS was defined as the interval between the start of AMR monotherapy and death. Tumor response and disease progression were determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In this study, “sensitive relapse” was defined as relapse at an interval of 60 days or more after the last dose of ETP, and "refractory relapse" was defined as no response to first-line chemoimmunotherapy or relapse within 60 days after the last dose of ETP. The safety of AMR was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Table 1 Baseline characteristics

Characteristics	N=30
Median age, y [range]	71 [46–87]
Sex, n [%]	
Male	23 [77]
Female	7 [23]
ECOG performance status, n [%]	
0	4 [13]
1	19 [63]
2	6 [20]
4	1 [3]
Smoking history, n [%]	
Current or former	28 [93]
Never	2 [7]
Disease stage, n [%]	
Extensive-disease	25 [83]
Relapse after chemoradiotherapy	4 [13]
Relapse after radiotherapy	1 [3]
1st line therapy, n [%]	
Atezolizumab + CBDCA + ETP	30 [100]
Response to 1st line therapy, n [%]	
PR	24 [80]
SD	3 [10]
PD	3 [10]
Using G-CSF in 1st line, n [%]	5 [17]
Type of relapse, n [%]	
Sensitive relapse	15 [50]
Refractory relapse	15 [50]

ECOG, Eastern Cooperative Oncology Group; CBDCA, carboplatin; ETP, etoposide; PR, partial response; SD, stable disease; PD, progressive disease; G-CSF, granulocyte colony stimulating factor.

Statistical analyses

Survival curves were plotted using the Kaplan-Meier method, and significant differences were tested with the log-rank test. All the reported P values are 2-sided, and P<0.05 was considered significant. Statistical analysis was performed using JMP Pro 16 statistical software (SAS Institute, Cary, NC, USA).

Table 2 Response to amrubicin

Response	Number of pts [%]
PR	14 [47]
SD	8 [27]
PD	6 [20]
NE	2 [7]
ORR [95% CI], %	47 [30–64]
DCR [95% CI], %	73 [56–86]
AMR cycle, median [range]	4 [1–11]

Pts, patients; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate; AMR, amrubicin.

Results

Characteristics of the study population

From August 2019 to February 2021, 30 patients were enrolled in this study. The median follow-up time from the start of AMR was 8 months (95% CI: 7.1–10.4). *Table 1* shows the baseline characteristics. The median age was 71 years (range, 46–87). The performance status (PS) was 0 for 4 patients (13%), 1 for 19 patients (63%), 2 for 6 patients (20%), and 4 for one patient (3%). Twenty-eight patients (93%) were current or former smokers, and 2 patients were never smokers. Twenty-five patients (83%) were diagnosed with ED-SCLC, 4 patients (13%) received chemoimmunotherapy due to recurrence after chemoradiotherapy, and one patient (3%) received chemoimmunotherapy due to recurrence after radiotherapy. All patients received atezolizumab, carboplatin (CBDCA) and ETP as first-line treatment. There were 15 patients (50%) with sensitive relapse and 15 patients (50%) with refractory relapse.

Treatment delivery and response to AMR therapy

Ten patients (33%) were treated with AMR at a dose of 40 mg/m^2 on days 1–3 every 3 weeks, 12 patients (40%) received 35 mg/m^2, and 8 patients (27%) received 30 mg/m^2. Overall, the dosage was reduced in 5 patients (17%). The median number of treatment cycles was 4 (range, 1–11) (*Table 2*). Twenty-five patients (83%) discontinued AMR due to disease progression, 2 patients (7%) stopped AMR due to adverse events (AEs), 2 patients (7%) discontinued AMR at patients' request and one patient (3%) continued AMR treatment at the time of data cut-off. Partial response (PR)

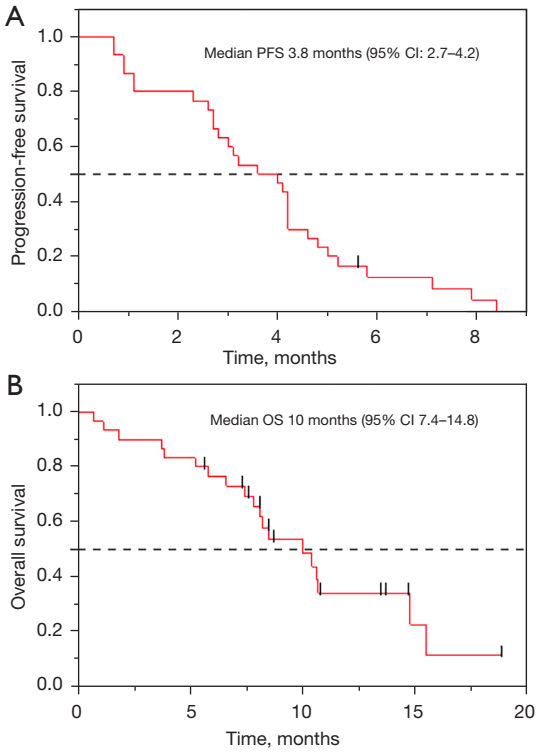

Figure 1 Progression-free survival (A) and overall survival (B) curves of patients treated with amrubicin. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

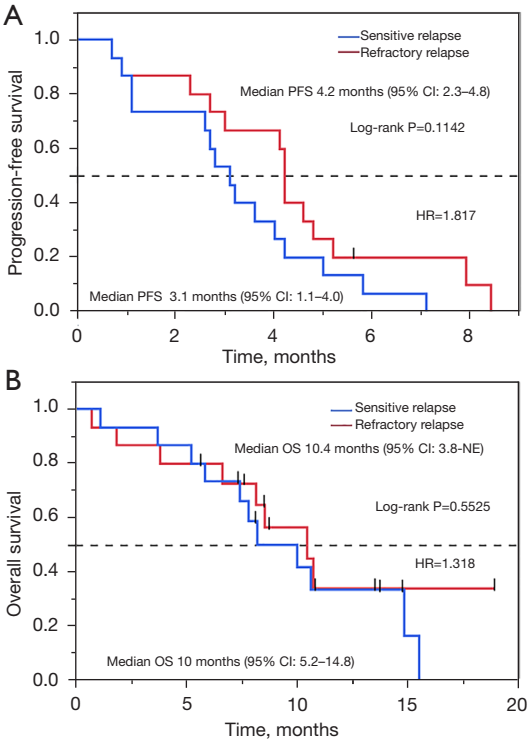

Figure 2 Progression-free survival (A) and overall survival (B) of patients treated with amrubicin according to the mode of relapse. PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not evaluable; HR, hazard ratio.

was achieved in 14 patients (47%), stable disease (SD) in 8 (27%), and progressive disease (PD) in 6 (20%). The overall response rate (ORR) was 47% (95% CI: 30–64%), and the disease-control rate (DCR) was 73% (95% CI: 56–86%).

Kaplan-Meier PFS and OS curves in the total population are shown in *Figure 1*. The median PFS was 3.8 months (95% CI: 2.7–4.2), and the median OS was 10 months (95% CI: 7.4–14.8). PFS did not significantly differ between the sensitive and refractory groups [3.1 months (95% CI: 1.1–4.0) in the sensitive relapse group *vs.* 4.2 months (95% CI: 2.3–4.8) in the refractory relapse group, HR =1.817, P=0.1142] (*Figure 2A*). Similarly, there was no significant difference in OS between the sensitive and refractory groups (10 months (95% CI: 5.2–14.8) in the sensitive relapse group *vs.* 10.4 months (95% CI: 3.8–NE) in the refractory relapse group, HR =1.318, P=0.5525) (*Figure 2B*).

Table 3 shows the tumor response to AMR therapy in the sensitive and refractory groups. There were no significant differences in ORR (40% *vs.* 53%, P=0.4635) or DCR (73% *vs.* 73%, P=1).

Safety

The most common AEs were hematological toxicities, including grade 3 or 4 neutropenia in 22 patients (73%), anemia in 4 patients (13%) and thrombocytopenia in 7 patients (23%) (*Table 4*). Febrile neutropenia (FN) was observed in 3 patients (10%). Nonhematological toxicities were generally mild, and drug-induced interstitial lung disease (ILD) occurred in only one case (3%). AMR was discontinued due to ILD (1, 3%) and malaise (1, 3%). Polyethylene glycol conjugated granulocyte colony-stimulating factor (PEG-G-CSF) was used in 13 patients, of which 2 patients (15%) developed FN after the use of PEG-G-CSF.

Subsequent systemic cancer treatment regimens

Of the 30 patients, one was still on AMR therapy at the data cut-off. The subsequent treatments after AMR therapy are shown in *Table 5*. Of the 29 patients, 21 (72%) received subsequent treatment, and the most common subsequent

Table 3 Responses to chemoimmunotherapy and AMR

Response to prior therapy	Total	Response to AMR					
		PR	SD	PD	NE	ORR, %	DCR, %
Overall	30	14	8	6	2	47	73
Type of relapse							
Sensitive	15	6	5	4	0	40	73
Refractory	15	8	3	2	2	53	73
Response to chemoimmunotherapy							
PR	24	11	5	6	1	46	67
SD	3	1	1	0	1	33	67
PD	3	1	2	0	0	33	100

AMR, amrubicin; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate.

Table 4 Adverse events

Adverse event	All grade	≥ Grade3
Hematologic, n [%]		
Neutropenia	25 [83]	22 [73]
Anemia	18 [60]	4 [13]
Thrombocytopenia	16 [53]	7 [23]
Nonhematologic, n [%]		
Febrile neutropenia	3 [10]	3 [10]
Interstitial lung disease	1 [3]	0
Nausea/vomiting	4 [13]	0
Mucositis oral	2 [7]	0
Anorexia	7 [23]	1 [3]
Constipation	11 [37]	0
Diarrhea	1 [3]	0
Alopecia	3 [10]	0
Malaise	4 [13]	1 [3]
Liver dysfunction	6 [20]	0

therapy was irinotecan in 10 cases (34%). Other treatments were as follows: nogitecan in 4 patients (14%), CBDCA plus nab-paclitaxel in 4 (14%), CBDCA plus ETP in 2 (7%), and CDDP plus irinotecan in one patient (3%).

Table 5 Subsequent treatment

Treatment	Number of pts [%]
Irinotecan	10 [34]
Nogitecan	4 [14]
CBDCA + nab-PTX	4 [14]
CBDCA + ETP	2 [7]
CDDP + Irinotecan	1 [3]
No treatment	8 [28]

pts, patients; nab-PTX, nab-paclitaxel; ETP, Etoposide; CBDCA, carboplatin; CDDP, cisplatin.

Discussion

This study investigated the effectiveness and safety of AMR therapy after the combination of a PD-L1 inhibitor, platinum and ETP in SCLC. AMR therapy showed favorable therapeutic efficacy even after chemoimmunotherapy associated with acceptable toxicities. These data indicated that AMR therapy is a useful treatment option for SCLC patients with recurrence after chemoimmunotherapy.

In previous clinical studies, AMR has shown good antitumor activity in patients with relapsed SCLC, and AMR is the most commonly used treatment for recurrent SCLC in Japan (9,10,13,14). Our study showed that the ORR was 47%, the median PFS was 3.8 months and the

median OS was 10 months, similar to previous studies (ORR 31–53%, median PFS 3.5–4.4 months and median OS 7.5–11.2 months). A number of Japanese clinical trials have shown the effectiveness of AMR in patients with refractory relapse (10,14,15). Although AMR and topotecan showed similar efficacy against recurrent SCLC in a global phase III study, subgroup analysis revealed that AMR significantly improved OS in patients with refractory relapse compared with topotecan (15). The current study also demonstrated similar efficacy in both patients with refractory and sensitive relapse (*Table 3* and *Figure 2*). Overall, the data on the antitumor therapeutic effects of AMR therapy in this study are comparable those from studies conducted before the advent of chemoimmunotherapy.

It is well known that AMR causes severe hematological toxicities (9,10,13,15). Although nonhematological toxicities due to AMR are generally mild, AMR can sometimes cause lethal ILD (16,17). Because ICIs can be detected more than 20 weeks after the last administration, there is a possibility that PD-L1 inhibitors exist in patients at the start of AMR and increase AEs (18). This study showed that the rates of grade 3 or more hematological toxicities (neutropenia 83%, anemia 13%, thrombocytopenia 23% and FN 10%) were similar to the results from previous studies (neutropenia 41–94%, anemia 15–26%, thrombocytopenia 5–27% and FN 5–27%) (9,10,13,15). In our study, PEG-G-CSF was used in 13 patients, of which 2 patients (15%) developed FN after the use of PEG-G-CSF. Yoh *et al.* reported that AMR-induced ILD was observed in 7 out of 100 patients, and 3 patients died from ILD (17). Because pre-existing pulmonary fibrosis was significantly associated with the development of ILD, they concluded that AMR should be avoided in patients with pulmonary fibrosis. In our study, none of the patients had pre-existing pulmonary fibrosis, and one patient (3%) developed grade 2 ILD after AMR therapy. Patients with pulmonary fibrosis are often not treated with ICIs, which seemed to be one of the reasons for the low incidence of ILD in this study.

The limitations of this study are that it is a retrospective observational study and that the number of cases is relatively small. The prospective studies will be required to further evaluate the effect of AMR or other cytotoxic agents after chemoimmunotherapy for the patients with SCLC in the future. Second, AMR is available in limited countries. Third, patients who were eligible for this study had been treated with chemoimmunotherapy as first-line treatment and might have a good condition. Patients at risk of developing ILD are not given ICI as primary therapy, which may be related to the lower risk of developing ILD in this study. However, since the purpose of this study was to investigate the therapeutic efficacy and safety of AMR therapy after chemoimmunotherapy, such bias was not considered a problem. Fourth, the standard initial dose of AMR is 40 mg/m^2, but in this study only 10 out of 30 patients (33%) received AMR at a dose of 40 mg/m^2, which may have affected the safety considerations.

To the best of our knowledge, this study is the first to evaluate AMR therapy after chemoimmunotherapy, and we believe that the results of this study will be helpful for future clinical practice.

Conclusions

In this study, AMR therapy after PD-L1 inhibitor combined with platinum and ETP was found to have a certain therapeutic effect and did not increase the number of AEs. AMR therapy seems to be a promising salvage treatment option for SCLC patients who experience recurrence after chemoimmunotherapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-225/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-225/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-225/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-225/coif). Kohei Kushiro has received personal fees from Kyowa Kirin. SW has received personal fees from Eli Lilly, Novartis Pharma, Chugai Pharma, Boehringer Ingelheim, Ono Pharmaceutical, Taiho Pharmaceutical, Pfizer,

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000044632) and was approved by the Institutional Review Board of Niigata University (registration number: 2020-0488), Niigata Prefectural Shibata Hospital (registration number: 237), Nagaoka Red Cross Hospital (registration number: 210717), Nagaoka Chuo General Hospital (registration number: 519), Niigata City General Hospital (registration number: 21-021), Nishiniigata Chuo Hospital (registration number: 2107), Saiseikai Niigata Hospital (registration number: E21-03) and Niigata Cancer Center Hospital (registration number: 2021-105). Individual consent for this retrospective analysis was waived.

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