Journal of Rural Medicine

Original article

Evaluation of topotecan monotherapy for relapsed small-cell lung cancer after amrubicin monotherapy failure

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Abstract

Objective: The utility of topotecan monotherapy for relapsed small-cell lung cancer (SCLC) after failure of amrubicin monotherapy has not been evaluated. We aimed to investigate the efficacy and safety of topotecan monotherapy in patients with relapsed SCLC after amrubicin monotherapy.

Patients and Methods: We retrospectively analyzed data from 16 patients with relapsed SCLC who were treated with topotecan monotherapy after amrubicin monotherapy at our hospital.

Results: The response rate, progression-free survival, and overall survival were 0%, 32.5 days (95% confidence interval [CI] = 18–51), and 112 days (95% CI = 55–267), respectively. The most common adverse events (grade ≥3) were leukopenia (31.3%) and thrombocytopenia (31.3%), followed by anemia, anorexia, edema, and lung infections.

Conclusion: The efficacy of topotecan monotherapy for relapsed SCLC after amrubicin monotherapy is inconclusive. Therefore, further studies are warranted.

Key words: small-cell lung cancer, relapsed, topotecan, amrubicin

(J Rural Med 2021; 16(4): 250–255)

Introduction

Small-cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancers, is one of the most aggressive cancers[1]. As SCLC is associated with high chemosensitivity, systemic chemotherapy is the most important treatment modality for patients with SCLC[2]. However, most patients with SCLC experience disease progression during or after initial treatment, and refractory disease is common[3].

Topotecan monotherapy is the most common treatment for relapsed SCLC in the US and Europe[4]. In contrast, amrubicin is the most common treatment for relapsed SCLC in Japan. Topotecan is rarely used as a second-line treatment[4]. Topotecan monotherapy has been used in some heavily treated patients with relapsed SCLC as a late-line therapy, after amrubicin monotherapy, in Japan. The efficacy and safety of topotecan monotherapy after amrubicin treatment have not been investigated. In this study, we retrospectively assessed the use of topotecan monotherapy after amrubicin monotherapy in patients with relapsed SCLC at our hospital.

Received: March 24, 2021
Accepted: July 1, 2021
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Patients and Methods

Patients

In total, 16 patients with relapsed SCLC were treated with topotecan monotherapy after amrubicin monotherapy between January 2010 and September 2019 at Kainan Hospital. All patients had previously been treated with platinum-based doublet chemotherapy and had a performance status (PS) of 0–1 on the Eastern Cooperative Oncology Group scale. All SCLC cases were histologically or cytologically proven. All patients had adequate bone marrow and organ function before topotecan monotherapy.

The patients were intravenously administered topotecan (1 mg/m^2) for 5 consecutive days every 3–4 weeks until disease progression was confirmed radiographically, and unacceptable toxicity was noted, including patient withdrawal or death. The doses were decided at the discretion of the physician in charge, and subsequent doses of topotecan were modified based on hematological and non-hematological toxicities. Written informed consent for topotecan monotherapy was obtained from all patients before commencing topotecan treatment. This was a retrospective observational study. Informed consent for the study was obtained using the opt-out method on the hospital website. The study was approved by the ethics committee of Kainan Hospital Aichi Prefectural Welfare Federation of Agricultural Cooperatives (No. 20200217-04: approved on February 17, 2020). The data cut-off date was April 30, 2020.

Patient characteristics, patient response, and toxicity evaluations

Patient characteristics such as age, sex, PS, smoking status, and data on prior thoracic radiation and prior chemotherapy were retrospectively obtained from their medical records. The patients were evaluated using chest X-ray, computed tomography (CT) of the chest and abdomen, and CT or magnetic resonance imaging of the head to determine the stage, disease progression, or relapse of their disease before starting topotecan treatment. Limited disease (LD) was defined as follows: the cancer is only on the chest unilaterally, including the bilateral mediastinal and supraclavicular nodes, and can be treated with a single radiation field. Extensive disease (ED) is defined as a disease extending beyond the LD. Refractory relapse was defined as relapse during or less than 90 days after the completion of first-line chemotherapy. Sensitive relapse was defined as a relapse of more than 90 days after the completion of first-line chemotherapy. Adverse events and patient responses were retrospectively assessed using the Common Terminology Criteria for Adverse Events (version 5.0) and Response Evaluation Criteria for Solid Tumors (version 1.1).

Statistical analysis

Progression-free survival (PFS) and overall survival (OS) rates were analyzed using the Kaplan–Meier method. PFS was measured from the start of topotecan monotherapy to the date of progressive disease, death, or the last follow-up. OS was defined as the time between treatment initiation and death, or the last follow-up. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria)[5].

Results

The clinical characteristics of all patients are shown in Tables 1 and 2. The median age of the patients was 68.5 years (range, 52–76 years), and our sample included 12 men and 4 women. None of the patients had a poor PS (3 or 4). All patients had previously been treated with platinum-based chemotherapy as a first-line chemotherapy. Nine patients (56.3%) had been treated with three or more lines of chemotherapy before receiving topotecan monotherapy. Twelve patients had been treated with irinotecan before topotecan. Three patients exhibited LD and 13 exhibited ED at the time of diagnosis. Four patients were classified as having a sensitive relapse and the remaining 12 as refractory relapses.

The chemotherapy delivery and treatment outcomes of topotecan monotherapy are shown in Tables 2 and 3. The median number of topotecan monotherapy cycles was 1 (range, 1–2 cycles). The topotecan dose was decreased in almost half of the patients (0.5–0.79 mg/m^2). Partial response (PR) was not detected in any patient. Three patients had stable disease (SD), and two of the three patients showed refractory relapse. The response rate (RR) and disease control rate (DCR) were 0% and 18.8%, respectively. The median PFS and OS were 32.5 days (95% confidence interval [CI] = 18–51 days) and 112 days (95% CI = 55–267 days), respectively (Figure 1a and 1b).

The toxicities of topotecan are summarized in Table 4. The major adverse events (grade ≥3) were leukopenia (31.3%), neutropenia (37.5%), thrombocytopenia (31.3%), anemia (12.5%), anorexia (6.3%), edema (6.3%), and lung infection (6.3%). No grade 4 adverse hematological or non-hematological events were observed. Topotecan monotherapy did not result in any deaths. Other hematological and non-hematological toxicities were mild and easily managed.

Discussion

We presented the results of the efficacy and safety of topotecan monotherapy in patients with relapsed SCLC after amrubicin monotherapy. The RR, DCR, PFS, and OS in our study were 0%, 28.8%, 32.5 days (95% CI = 18–51), and 112 days (95% CI = 55–267), respectively. Two of the three patients with SD experienced a refractory relapse. Severe leukopenia/neutropenia and thrombocytopenia were observed in some patients, but all resolved with treatment. This is the first report to examine topotecan monotherapy after amrubicin monotherapy in relapsed SCLC.

DiBonaventura *et al.*[4] reported that topotecan is the most common second-line treatment for ED-SCLC in the US and Europe. In contrast, amrubicin is the most common second-line treatment for ED-SCLC in Japan. For patients with refractory relapse in Japan, topotecan and amrubicin have been used in 4.9% and 51.7% of patients, respectively.

Table 1 Characteristics of patients with relapsed small cell lung cancer included in this study

		Number of patients
Age	Median (range)	68.5 (52–76) years
Sex	Male	12
	Female	4
ECOS PS	0	5
	1	11
Smoking status	Never	1
	Ever	15
Disease extent at diagnosis	LD	3
	ED	13
Type of first-line chemotherapy	CBDCA + VP-16	9
	CDDP + VP-16	1
	CDDP + CPT-11	5
	CBDCA + CPT-11	1
Sensitivity to first-line chemotherapy	Sensitive relapse	4
	Refractory relapse	12
Number of prior regimens	2	7
	3	4
	4	3
	5	1
	6	1
Prior topoisomerase inhibitor	AMR	16
	CPT-11	12
Previous thoracic radiation therapy	Yes	5
	No	11

ECOG: Eastern Cooperative Oncology Group; PS: performance status; LD: limited disease; ED: extensive disease; CBDCA: carboplatin; VP-16: etoposide; CDDP: cisplatin; CPT-11: irinotecan; AMR: amrubicin.

Table 2 Detailed characteristics and response of 16 patients to topotecan therapy in this study

Case No.	Age	Sex	Disease extent at diagnosis	Type of first-line chemotherapy	Sensitivity to first-line chemotherapy	Number of prior regimens	Response to topotecan therapy	Time to progression (days)	Survival (days)
1	59	Male	ED	CBDCA+VP-16	Sensitive	3	PD	29	267
2	74	Male	LD	CBDCA+VP-16	Refractory	3	PD	47	100
3	63	Female	ED	CDDP+CPT-11	Refractory	2	PD	95	222
4	63	Male	LD	CDDP+VP-16	Sensitive	3	PD	18	61
5	71	Female	ED	CBDCA+VP-16	Refractory	3	PD	29	176
6	72	Male	ED	CDDP+CPT-11	Refractory	2	PD	16	36
7	69	Female	ED	CBDCA+VP-16	Refractory	2	PD	60	429
8	76	Male	ED	CBDCA+VP-16	Refractory	2	PD	36	109
9	52	Male	ED	CBDCA+VP-16	Refractory	4	PD	51	1008
10	52	Male	ED	CDDP+CPT-11	Refractory	2	PD	16	48
11	73	Male	ED	CBDCA+VP-16	Refractory	2	PD	29	101
12	59	Male	ED	CBDCA+CPT-11	Refractory	6	SD	50	149
13	56	Male	ED	CDDP+CPT-11	Refractory	5	PD	23	55
14	76	Male	ED	CDDP+CPT-11	Sensitive	4	PD	6	8
15	69	Male	LD	CBDCA+VP-16	Refractory	2	SD	56	115
16	68	Female	ED	CBDCA+VP-16	Sensitive	4	SD	54	270

LD: limited disease; ED: extensive disease; CBDCA: carboplatin; VP-16: etoposide; CDDP: cisplatin; CPT-11: irinotecan; SD: stable disease; PD: progressive disease.

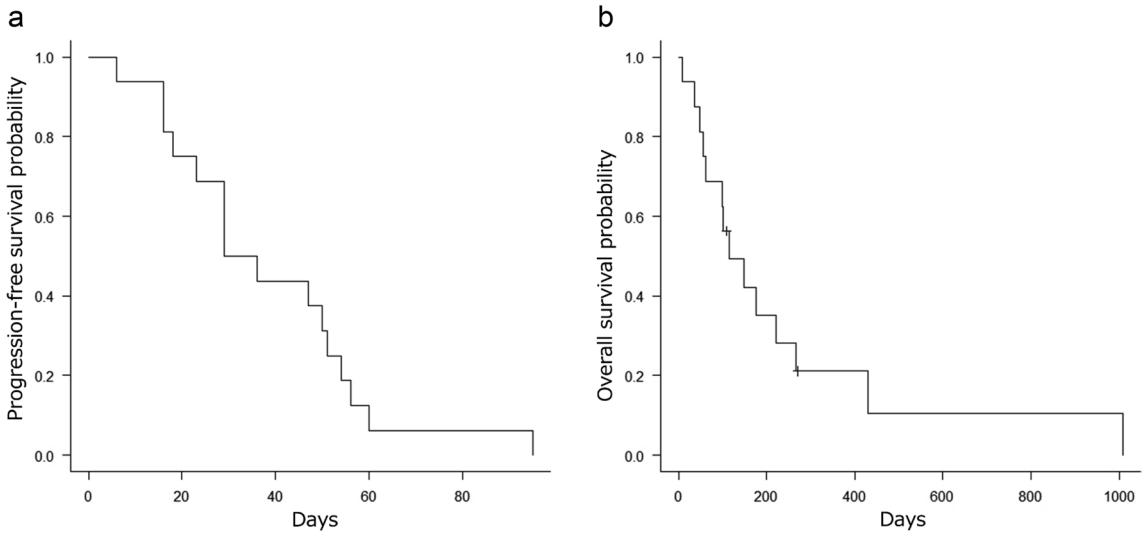

Figure 1 Kaplan–Meier survival curves of progression-free (a) and overall (b) survival of the 16 patients treated with topotecan monotherapy. The median progression-free survival (PFS) time was 32.5 days (95% confidence interval [CI] = 18–51), and the median overall survival (OS) time was 112 days (95% CI = 55–267).

Table 3 Chemotherapy delivery and treatment outcomes of topotecan monotherapy

		Number of patients
Number of topotecan cycles	1	11
	2	5
Topotecan dose	0.5–0.79 mg/m^2	8
	0.8–1.0 mg/m^2	8
Subsequent chemotherapy	PTX	3
	AMR	2
	CPT-11	2
	Nab-PTX	1
	DTX	1
	CBDCA + VP-16	1
	CBDCA + VP-16 + Atezo	1
	None	9
Type of response	CR	0
	PR	0
	SD	3
	PD	13
RR and DCR		% (95% CI)
	RR (CR + PR)	0 (0–17.1)
	DCR (CR + PR + SD)	18.8 (4–45.6)
After topotecan therapy		days (range)
	PFS	32.5 (6–95)
	OS	112 (8–1,008)

PTX: paclitaxel; AMR: amrubicin; CPT-11: irinotecan; Nab-PTX: nanoparticle albumin-bound paclitaxel; DTX: docetaxel; CBDCA: carboplatin; VP-16: etoposide; Atezo: atezolizumab; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RR: response rate; DCR: disease control rate; CI: confidence interval; PFS: progression free survival; OS: overall survival.

Table 4 Toxicity of chemotherapy

	All grade	Grade 3
Hematological toxicity		
Leukopenia	15	5
Neutropenia	15	6
Anemia	15	5
Thrombocytopenia	14	2
Non-hematological toxicity		
Anorexia	2	1
Nausea	2	0
Constipation	1	0
Diarrhea	1	0
Fatigue	3	0
Malaise	3	0
Peripheral sensory neuropathy	2	0
Dry skin and eczema	1	0
Edema	1	0
Insomnia	2	0
Lung infection	1	1
Dyspnea	1	0
Elevated AST/ALT	4	0
Hyponatremia	2	0
Hyperkalemia	1	0
Febrile neutropenia	1	1

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

Some previous studies suggested that amrubicin would be a good choice to treat relapsed SCLC, especially for refractory-relapsed cases and the Asian population[6–9]. Furthermore, in ED-SCLC, the percentage of patients who can progress to second-line treatment is low (19.8%) and even lower after third-line treatment (6.8%)[4]. Therefore, topotecan is infrequently used in Japan. When topotecan is used, it is usually used as a late-line treatment after amrubicin monotherapy for relapsed SCLC.

The results of our study indicated that the efficacy of topotecan monotherapy after amrubicin was lower than that reported previously for topotecan monotherapy for relapsed SCLC as a second-line therapy[7–10]. To date, the therapeutic sequences of amrubicin and topotecan for relapsed SCLC have not been clinically studied. Topotecan is a topoisomerase 1 inhibitor, while amrubicin is a topoisomerase 2 inhibitor. Hence, topotecan may be expected to have a therapeutic effect in patients with SCLC after amrubicin monotherapy. However, in this study, we could not demonstrate the efficacy of topotecan monotherapy, although three patients had SD, and two of the three patients showed refractory relapse. The reasons for our study outcomes may be explained by the high number of refractory relapse cases (75%) and heavily treated cases in our study. Inoue *et al.*[9] reported that the response rate in topotecan was better in patients with sensitive relapse SCLC (21%) than in those with refractory relapse SCLC (0%). In addition, irinotecan, a topoisomerase 1 inhibitor similar to topotecan, was used in 75% of the patients before topotecan monotherapy, which may be an important consideration in our study results. Park *et al.*[11] showed that the objective response rate of topotecan monotherapy was 12% in patients with irinotecan-refractory SCLC. However, Ogawara *et al.*[12] showed that topotecan treatment was equally effective for patients who had received prior treatment with irinotecan. Additional studies are warranted to reveal the influence of prior use of topoisomerase inhibitors on late-line topotecan monotherapy.

According to the National Comprehensive Cancer Network (NCCN) guidelines (Version 1.2021), several anticancer drugs, such as lurbinectedin[13], nivolumab[14, 15], pembrolizumab[16], paclitaxel[17, 18], docetaxel[19], irinotecan[20], and gemcitabine[21, 22], are recommended for relapsed SCLC. Several recent Japanese studies have also reported the efficacy of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in heavily treated patients with relapsed SCLC[23, 24]. To date, there have been no established treatment options for patients with heavily treated SCLCs. In Japan, irinotecan and amrubicin are usually used as early line chemotherapy for patients with SCLC. A clinical study of post-amrubicin and irinotecan therapy for relapsed SCLC would be of interest.

The limitations of our study were the small sample size, retrospective nature, and single-facility and single-arm design. Larger prospective trials are warranted to further investigate the clinical outcomes of topotecan monotherapy after amrubicin monotherapy for relapsed SCLC. Since topotecan is used infrequently for patients with relapsed SCLC in Japan and the percentage of SCLC patients who can receive third- or late-line treatment is very low, it may be difficult to plan a large-scale prospective study.

Conclusion

In conclusion, topotecan monotherapy after amrubicin monotherapy showed acceptable toxicities but poor efficacy in patients with relapsed SCLC. Further investigations are required to validate our findings. Finally, the information presented here may provide a new direction for clinical research on the best treatment option for patients with SCLC after amrubicin monotherapy.

Conflict of interest: The authors have no conflicts of interest to declare.

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