


ORIGINAL ARTICLE

Topotecan monotherapy for the treatment of relapsed small cell lung cancer in elderly patients: A retrospective analysis

Hisao Imai¹ , Yutaka Yamada², Hiroyuki Minemura³, Tomohide Sugiyama⁴, Mie Kotake¹, Kyoichi Kaira⁵, Kenya Kanazawa^{3,6}, Yoichi Nakamura⁴, Takashi Kasai⁴, Yoko Shibata³, Takayuki Kaburagi², Koichi Minato¹ & Gunma-Ibaragi-Fukushima-Tochigi (GIFT) Group

1 Division of Respiratory Medicine, Gunma Prefectural Cancer Center, Ohta, Japan

2 Division of Respiratory Medicine, Ibaraki Prefectural Central Hospital, Kasama, Japan

3 Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan

4 Division of Thoracic Oncology, Tochigi Cancer Center, Utsunomiya, Japan

5 Department of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Hidaka, Japan

6 Clinical Oncology Center, Fukushima Medical University Hospital, Fukushima, Japan

Keywords

Elderly; relapse; small cell lung cancer; topotecan.

Correspondence

Hisao Imai, Division of Respiratory Medicine, Gunma Prefectural Cancer Center, 617-1, Takahayashinishi, Ohta, Gunma 373-8550, Japan.

Tel: +81 276 38 0771

Fax: +81 276 38 0614

Email: m06701014@gunma-u.ac.jp

Received: 29 July 2018;

Accepted: 29 August 2018.

doi: 10.1111/1759-7714.12884

Thoracic Cancer 9 (2018) 1699–1706

Abstract

Background: Topotecan is one of the most active chemotherapeutic drugs for small cell lung cancer (SCLC). However, its efficacy in elderly patients with SCLC has not been validated. This study evaluated the feasibility and efficacy of topotecan monotherapy in elderly patients with relapsed SCLC.

Methods: Between January 2000 and March 2017, 43 patients aged ≥ 70 years received topotecan monotherapy for relapsed SCLC at four institutions. The clinical outcomes and adverse events of treatment were retrospectively analyzed.

Results: Twenty-nine patients (median age 75 years; range: 70–83 years) had sensitive-type relapse, while 14 (median age 78 years; range: 71–82 years) had refractory relapse. The median number of treatment cycles was two (range: 1–6). The response rate was 7.0% (10.3% and 0% in sensitive and refractory patients, respectively), while the disease control rate was 23.2% (20.6% and 42.8% in sensitive and refractory patients, respectively). Median progression-free survival was 1.9 months in sensitive patients and 1.4 months in refractory patients ($P = 0.87$). The median survival time from the start of topotecan therapy was 5.5 months in sensitive patients and 4.0 months in refractory patients ($P = 0.64$). Grade ≥ 3 hematological toxicities were as follows: leukopenia, 37.2%; neutropenia, 51.1%; anemia, 0%; thrombocytopenia, 32.5%; and febrile neutropenia, 9.3%. No treatment-related deaths occurred.

Conclusion: Although hematological toxicities (particularly neutropenia) were severe, topotecan showed favorable disease control in both sensitive and refractory patients. Topotecan may thus be a preferred treatment for elderly patients with relapsed SCLC.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers; it is an aggressive form of the disease with clinical and pathological features that are distinct from non-small cell lung cancer, and is characterized by rapid tumor development and metastasis.¹ In patients with

extensive-disease SCLC, chemotherapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival in such patients is rare.^{2,3} As patients with relapsed SCLC experience poor outcomes, it is imperative to investigate and develop more effective chemotherapeutic drugs.

Advanced age is related to an increased risk of lung cancer. While the incremental increase in global life expectancy is linked to a corresponding rise in the incidence of lung cancer, the population at advanced age has witnessed a disproportionate increase in disease occurrence. A majority of lung cancers are diagnosed in patients > 65 years, which is the lower age limit for being designated as “elderly” in epidemiologic studies.⁴ Approximately 35% of patients with SCLC are ≥ 70 years old at diagnosis,⁵ thus tailoring management for patients of advanced age is becoming essential. The Japan Clinical Oncology Group recommends carboplatin plus etoposide as an effective and less toxic treatment for elderly patients with SCLC⁶ however, to date, there are no promising chemotherapeutic agents or treatments for elderly patients with relapsed SCLC. Furthermore, elderly patients sometimes tend to favor forgoing treatment; moreover, drug administration depends on individual factors, such as the extent of metastatic disease, performance status (PS) score, laboratory parameters, and quality of life.^{7–9} Hence, whether standard treatment in elderly patients is safe remains uncertain.¹⁰

SCLC can be divided into two categories: *refractory* and *sensitive*.^{11,12} Patients with sensitive disease are more likely to respond to second-line chemotherapy than those with refractory disease. In either case, the outcomes of second-line chemotherapy for patients with SCLC remain relatively poor.^{13,14}

Topotecan (known as nogitecan in Japan) is a specific topoisomerase I inhibitor and is the only drug approved for second-line chemotherapy for SCLC by the United States Food and Drug Administration. In a phase II trial by Ardizzoni *et al.*, topotecan was administered to patients with advanced SCLC as second-line therapy at a dose of 1.5 mg/m² for five consecutive days every three weeks.¹⁵ In that trial, the objective response rate (ORR) was 21.7%, with 7.6% of patients achieving a complete response (CR) and 14.1% a partial response (PR). The ORR was higher in patients with sensitive disease than in those with refractory disease (37.8% vs. 6.4%). In a randomized phase III trial, 211 patients with SCLC who experienced recurrence at least 60 days after the end of first-line chemotherapy were randomized to receive topotecan or combined chemotherapy with cyclophosphamide plus doxorubicin plus vincristine (CAV).¹⁶ Although topotecan did not improve outcomes compared to CAV (ORR 24.3% vs. 18.3%, $P = 0.28$; median time to progression 13.3 vs. 12.3 weeks, $P = 0.55$; and median overall survival [OS] 25 vs. 24.7 weeks, $P = 0.79$), the former was deemed the preferred treatment based on better symptom control. Thus, topotecan monotherapy is now regarded as the standard second-line chemotherapy for SCLC patients with sensitive disease.

The activity and toxicity of single-agent topotecan in elderly patients who have previously been treated for SCLC have not been fully assessed. Although a previous study of topotecan administered at a dose of 1.5 mg/m² (the Western standard dose) to elderly patients aged ≥ 65 years with relapsed SCLC was performed,¹⁷ no similar studies investigated the dose at 1.0 mg/m², which is the Japanese standard dose. Therefore, we retrospectively evaluated the effect and safety of topotecan monotherapy in previously treated elderly SCLC patients.

Methods

We performed retrospective analysis of the records of patients aged ≥ 70 years who were diagnosed with relapsed SCLC and treated with topotecan monotherapy between January 2000 and March 2017 at four Japanese institutions (Gunma Prefectural Cancer Center, Ibaraki Prefectural Central Hospital, Fukushima Medical University, and Tochigi Cancer Center). Histological diagnosis and SCLC staging were based on the World Health Organization classification and the tumor node metastasis (TNM) staging system, respectively.¹⁸ Eligibility criteria were: histologically or cytologically confirmed SCLC, unresectable stage III/IV disease before first-line treatment, and administration of a platinum-based combination first-line chemotherapy. Before receiving therapy, each patient underwent a physical examination, chest radiography, thoracic and abdominal computed tomography, bone scintigraphy or ¹⁸F-fluorodeoxyglucose positron emission tomography, and brain computed tomography or magnetic resonance imaging to determine the TNM stage. Patients who responded to initial chemotherapy and relapsed > 90 days after completing treatment were categorized as having sensitive relapse, while those who did not respond to initial chemotherapy or relapsed within 90 days were deemed to have refractory relapse. A clinical chart search for the participants, all of whom were topotecan-monotherapy naïve, was performed at each hospital. The institutional review boards at each facility approved the study protocol, and the requirement for written informed consent was waived because of the retrospective nature of the study. Topotecan was dissolved in 100 mL of normal saline and administered intravenously as a 30 minute infusion at a dose of 0.8–1.0 mg/m² on days one to five every three or four weeks. Granulocyte colony-stimulating factor was administered as a prophylactic agent against leukopenia or neutropenia at the physician's discretion but was not mandatory. Treatment continued until disease progression, the appearance of intolerable toxicity, or withdrawal of consent.

The best overall response and maximum tumor shrinkage were recorded. Radiographic tumor responses were defined according to the Response Evaluation Criteria in

Solid Tumors, version 1.1: CR, the disappearance of all target lesions; PR, a decrease in the sum of the target lesion diameters by at least 30% compared to baseline; progressive disease (PD), an increase of at least 20% in the sum of the target lesion diameters compared to the smallest sum during the study; and stable disease (SD), insufficient shrinkage or expansion to qualify as PR or PD.¹⁹ Progression-free survival (PFS) was calculated from the start of treatment with topotecan monotherapy until PD or death from any cause; OS represented the interval between the first day of treatment with topotecan monotherapy and death, or was otherwise censored on the date of the last follow-up. Survival curves were calculated using the Kaplan–Meier method. Adverse events that were associated with topotecan monotherapy were graded according to the Common Terminology Criteria for Adverse Events version 4.0. After failure of topotecan monotherapy, patients were permitted to undergo any subsequent treatment(s), including the continuation of topotecan. Univariate and multivariate analyses were performed using a stepwise Cox proportional hazards model to identify independent prognostic factors. A *P* value < 0.05 was considered indicative of statistical significance. All statistical analyses were performed using JMP version 11.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between January 2000 and March 2017, 43 consecutive patients were treated with topotecan monotherapy at four institutions. Twenty-nine patients had sensitive disease and 14 had refractory disease; all were assessed for response, survival, and safety. The patients' baseline characteristics are shown in Table 1. The patients were predominantly men (39, 90.6%), and the median age of the entire population was 76 years (range: 70–83). A majority of patients (30, 69.7%) had received ≥ 2 lines of chemotherapy prior to being administered topotecan monotherapy, while the remainder had received one prior line of treatment. All patients had been pretreated using a platinum-combination regimen containing a topoisomerase inhibitor: topoisomerase I inhibitor (irinotecan, *n* = 1); topoisomerase II inhibitor (etoposide, *n* = 37); and both topoisomerase I and II inhibitors (*n* = 5).

Response and treatment delivery

Table 2 shows the chemotherapeutic agent delivery doses and responses. None of the patients in either group achieved a CR. Dose reduction was more frequent in

Table 1 Baseline patient characteristics (*n* = 43)

Characteristics	Sensitive group	Refractory group
Number of patients	29	14
Gender		
Male	25	14
Female	4	0
Age (years) at the time of TOP treatment		
Median	75	78
Range	70–83	71–82
70–74 years	13	5
75–79 years	12	4
≥ 80 years	4	5
ECOG-PS at the time of TOP treatment		
0/1/2/3	3/18/8/0	5/6/2/1
Disease extent at diagnosis		
LD	14	2
ED	15	12
Prior therapy		
Chemotherapy alone	24	14
Chemotherapy and thoracic radiation	5	0
Chemotherapy and surgery	0	0
Line of treatment		
Second	7	6
Third	19	7
Fourth	3	1
Previous chemotherapy†		
Platinum	31	16
Etoposide	27	14
Irinotecan	5	1
Amrubicin	21	8
Others	1	0
Prior treatment with topoisomerase inhibitor-based regimen		
Topoisomerase-I	1	0
Topoisomerase-II	24	13
Both	4	1

†Total number of patients. ECOG-PS, Eastern Cooperative Oncology Group performance status (score); ED, extensive disease; LD, limited disease; TOP, topotecan.

patients initially receiving 1.0 mg/m²/day than those who started at 0.8 mg/m²/day.

Survival

The median PFS for all patients following the first topotecan administration was 1.8 months (Fig 1a), while the median OS was 5.0 months (Fig 1b). Patient survival between the groups was similar: the median PFS was 1.9 and 1.4 months (*P* = 0.87), while the median OS was 5.5 and 4.0 months (*P* = 0.64) in the sensitive and refractory groups, respectively (Fig 2). Univariate and multivariate analyses showed that the extent of disease at diagnosis (limited vs. extensive) and the PS score (0–1 vs. 2–3) at the time of topotecan treatment were independent prognostic factors for PFS; however, univariate and multivariate

Table 2 Treatment delivered and tumor response

Characteristic	Sensitive group	Refractory group	Total
Response			
CR	0	0	0
PR	3	0	3
SD	3	6	9
PD	21	7	28
NE	2	1	3
Response rate (%)	10.3	0	7
Disease control rate (%)	20.6	42.8	23.2
No. of treatment cycles			
Median	2	2	—
Range	1–6	1–4	—
Starting dose (mg/m ² /day)			
0.8	5	6	11
1	24	8	32
Dose reduction			
Starting dose 0.8 mg/m ² /day			
Yes/no	1/4	0/6	1/10
Starting dose 1.0 mg/m ² /day			
Yes/no	3/21	4/4	7/25

CR, complete response; NE, not evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

analyses showed that none of the factors were prognostic for OS (Table 3).

Toxicity

The drug-related adverse events in all 43 patients are shown in Table 4. The most frequent drug-related adverse

event was myelosuppression. Grade 3 or 4 neutropenia was observed in 51.1% of the patients, while grade 3 or 4 leukopenia occurred in 37.2%. Febrile neutropenia was observed in four patients (9.3%). Grade 3 or 4 anemia did not occur, while grade 3 or 4 thrombocytopenia was reported in 14 patients (32.5%). Four patients received prophylactic administration of granulocyte-colony stimulating factor during treatment with topotecan monotherapy. The incidences of non-hematologic toxicities were low; the most frequent grade 3 or 4 non-hematologic toxicities included anorexia (6.9%), nausea/vomiting (2.3%), and pneumonitis (2.3%). No treatment-related deaths occurred. An analysis of myelosuppression according to administration dose revealed that hematologic toxicities in patients administered 0.8 mg/m²/day were identical to those administered 1.0 mg/m²/day (Table 4).

Discussion

This retrospective study assessed the efficacy and safety of topotecan monotherapy in elderly patients with relapsed SCLC who had previously been treated with a platinum-based regimen. This treatment demonstrated no new safety concerns in this patient group and was tolerable.

The incidence rate of SCLC is expected to rise with the growing geriatric population.^{20,21} While patients of advanced age with good PS and normal organ functions are generally prescribed chemotherapeutic regimens that are comparable to those administered to younger

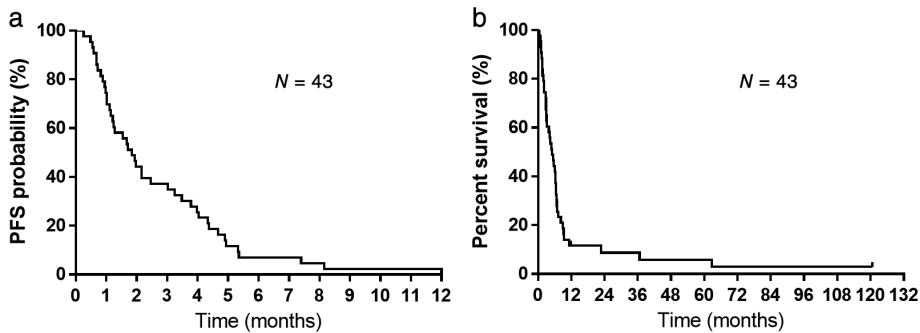


Figure 1 Kaplan–Meier survival estimates for the entire study population (n = 43): (a) progression-free survival (PFS, median 1.8 months); and (b) overall survival (median 5.0 months).

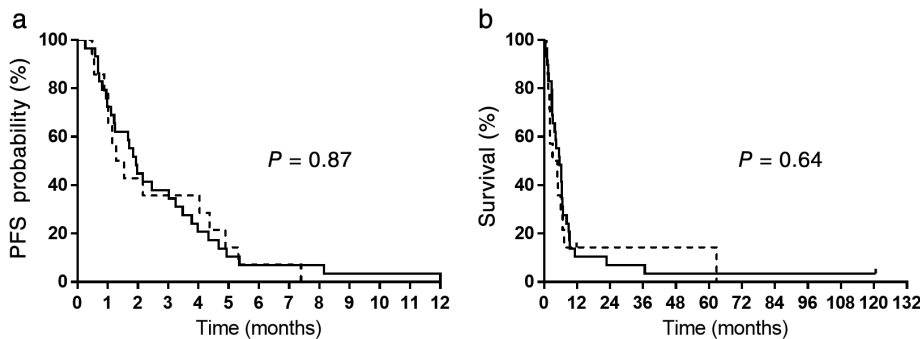


Figure 2 Kaplan–Meier survival estimates for the study population based on type of small cell lung cancer. (a) The median progression-free survival (PFS) rates in the sensitive and refractory-relapsed patients were 1.9 and 1.4 months, respectively (P = 0.87). (b) The median overall survival rates of sensitive and refractory-relapsed patients were 5.5 and 4.0 months, respectively (P = 0.64). —, Sensitive (n=29); ---, Refractory (n=14).

Table 3 Univariate and multivariate analyses of progression-free survival and overall survival

Factors	Median PFS (months)	Univariate analysis PFS			Multivariate analysis PFS			Median OS (months)	Univariate analysis OS			Multivariate analysis OS		
		HR	95% CI	P	HR	95% CI	P		HR	95% CI	P	HR	95% CI	P
Gender														
Male/female	1.9/1.1	0.56	0.22–1.89	0.31	—	—	—	5.0/4.2	0.82	0.32–2.78	0.72	—	—	—
Disease extent at diagnosis														
LD/ED	3.3/1.2	0.49	0.25–0.94	0.03	0.44	0.21–0.89	0.02	6.2/4.2	0.54	0.27–1.03	0.06	0.6	0.29–1.17	0.13
Efficacy of first-line treatment														
PR/non-PR	1.9/0.9	0.61	0.29–1.45	0.25	—	—	—	5.4/1.8	0.74	0.34–1.84	0.49	—	—	—
Non-PD/PD	1.8/2.6	1.08	0.43–3.66	0.87	—	—	—	5.0/4.1	1.08	0.38–4.50	0.89	—	—	—
Relapse pattern														
Sensitive/refractory	1.9/1.4	0.94	0.50–1.86	0.87	—	—	—	5.5/4.0	0.85	0.45–1.71	0.64	—	—	—
Age (years) at the timing of TOP														
70–74/≥ 75	3.6/1.1	0.47	0.24–0.88	0.01	0.63	0.32–1.21	0.16	6.2/3.2	0.5	0.25–0.97	0.04	0.55	0.27–1.08	0.08
ECOG-PS at the time of TOP treatment														
0–1/2–3	2.0/1.0	0.34	0.16–0.74	0.008	0.27	0.12–0.62	0.003	5.8/3.2	0.56	0.28–1.19	0.12	—	—	—
Line of treatment														
Second line/≥ third line	3.4/1.6	0.55	0.27–1.07	0.08	0.56	0.27–1.09	0.09	5.4/4.5	0.71	0.34–1.40	0.33	—	—	—
Starting dose (mg/m ² /day)														
0.8/1.0	1.2/2.5	1.65	0.84–3.13	0.13	—	—	—	3.1/5.8	1.37	0.70–2.58	0.33	—	—	—
Efficacy of TOP														
PR/non-PR	5.0/1.7	0.43	0.06–1.43	0.19	—	—	—	6.4/4.8	0.99	0.16–3.34	0.99	—	—	—
Non-PD/PD	4.0/1.6	0.66	0.29–1.35	0.27	—	—	—	5.0/5.1	1.22	0.51–2.55	0.62	—	—	—
Administration of AMR														
Yes/no	1.6/2.9	1.69	0.86–3.57	0.12	—	—	—	5.0/5.0	1.35	0.67–2.94	0.4	—	—	—

Bold value indicates $P < 0.05$ are statistically significant. AMR, amrubicin; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status (score); ED, extensive disease; HR, hazard ratio; LD, limited disease; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; TOP, topotecan.

Table 4 Incidence of drug-related adverse events†

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade \geq 3	%
Leukopenia							
Total	8	9	12	4	—	16	37.2
Dose of 0.8 mg/m ² /day	2	3	4	1	—	5	45.4
Dose of 1.0 mg/m ² /day	6	6	8	3	—	13	40.6
Neutropenia							
Total	3	8	13	9	—	22	51.1
Dose of 0.8 mg/m ² /day	0	4	4	2	—	6	54.5
Dose of 1.0 mg/m ² /day	3	4	9	7	—	16	50.0
Anemia							
Total	15	17	3	0	0	0	0
Dose of 0.8 mg/m ² /day	7	1	3	0	0	0	0
Dose of 1.0 mg/m ² /day	8	16	0	0	0	0	0
Thrombocytopenia							
Total	8	10	13	1	—	14	32.5
Dose of 0.8 mg/m ² /day	4	3	3	0	—	3	27.2
Dose of 1.0 mg/m ² /day	4	7	10	1	—	11	34.3
Febrile neutropenia							
Total	—	—	4	0	0	4	9.3
Dose of 0.8 mg/m ² /day	—	—	1	0	0	1	9.0
Dose of 1.0 mg/m ² /day	—	—	3	0	0	3	9.3
Nausea/vomiting	7	5	1	0	0	1	2.3
Anorexia	7	9	3	0	0	3	6.9
Malaise	5	11	—	—	—	—	—
Constipation	3	5	0	0	0	0	0
Aspartate transaminase	0	3	0	0	—	0	0
Alanine transaminase	1	2	0	0	—	0	0
Pneumonitis	0	0	1	0	0	1	2.3

†According to Common Terminology Criteria for Adverse Events version 4.0.

counterparts, some studies suggest that such patients may be at a greater risk for more severe adverse events than younger patients.^{22,23} Therefore, non-cisplatin-based regimens, such as carboplatin and etoposide, have been a standard first-line therapy for elderly patients with SCLC.²⁴ However, treatment options for elderly patients with SCLC following relapse remain unclear. While topotecan monotherapy is often administered to patients with relapsed SCLC, its safety in elderly patients previously treated for SCLC has not been assessed. Ours is the first study of the efficacy and safety of topotecan monotherapy for elderly patients with previously treated SCLC.

Resistance to chemotherapy is common following early-line treatment for SCLC, and there are few subsequent chemotherapeutic options.²⁵ The efficacy of second-line chemotherapy usually depends on whether the tumor being subjected to first-line chemotherapy is sensitive or refractory. To that end, topotecan and amrubicin have been shown to be effective in the second-line setting.^{26,27} In a Japanese randomized phase II study comparing topotecan with amrubicin, Inoue *et al.* showed that the response rate in the topotecan arm was better in the sensitive (21%) than in the refractory (0%) group. Moreover, the disease control rate with topotecan was also better in the sensitive (63%)

than in the refractory group (18%).²⁶ They also reported that topotecan monotherapy produced median PFS and OS rates of 3.0 and 11.7 months in the sensitive group and 1.5 and 5.4 months in the refractory group, respectively. Furthermore, the aforementioned European phase II study by Ardizzoni *et al.* revealed that topotecan treatment at a dose of 1.5 mg/m² produced a more favorable response rate, disease control rate, and median OS in sensitive patients (37.8%, 68.9%, and 6.9 months, respectively) than in refractory patients (6.4%, 57.6%, and 4.7 months, respectively).¹⁵ Likewise, in a randomized phase III study comparing topotecan with amrubicin, the response rate, median PFS, and median OS with topotecan monotherapy were more favorable in sensitive (23.1%, 4.3 months, and 9.9 months, respectively) than in refractory (9.4%, 2.6 months, and 5.7 months, respectively) patients.²⁷

Considering that refractory patients are extremely resistant to chemotherapy, the efficacy of topotecan monotherapy is fairly encouraging. Takeda *et al.* performed a single-arm phase II study of topotecan 1.0 mg/m² for relapsed SCLC, and found that the ORR, median time to progression, and median OS were 26.0%, 4.3 months, and 8.6 months, respectively (although they did not distinguish between patients with sensitive and refractory relapses).²⁸

Overall, the response and survival rates of patients with refractory disease were unsatisfactory in the aforementioned trials investigating the efficacy of single-agent regimens. However, the disease control rate in our refractory group was 42.8%, which was relatively promising even though our investigation was retrospective. The reason that the disease control rate in sensitive patients (20.6%) was lower than in refractory patients may be because a higher percentage of patients in the refractory group were only on their second-line treatment (42.9% vs. 24.1%); the sensitive group had a greater proportion of patients already on their third-line treatment (65.5%).

Topotecan monotherapy showed favorable disease control in both sensitive and refractory groups in our analysis. OS was not significantly different between these two groups; furthermore, the PFS in the refractory group was similar to that in the sensitive group (1.9 vs. 1.4 months; $P = 0.87$). The response and median PFS rates of the elderly SCLC patients in our study appeared to be consistent with those in previous studies; however, our OS rates were slightly lower than those previously reported.^{15,26,27} These differences might be explained by variations in demographic characteristics or by other biases. Furthermore, as mentioned above, our refractory group had a higher proportion of patients undergoing second-line treatment than the sensitive group; previous studies of topotecan monotherapy for relapsed SCLC, which comprised a large percentage of patients undergoing second-line treatment, included only a small proportion of subjects with poor PS or at advanced age. The median OS rates in the sensitive and refractory groups in our study were similar. These results suggest that topotecan monotherapy is beneficial for elderly patients with refractory SCLC. Notably, our outcome data for elderly patients are not inferior to those of previous studies of non-elderly patients.

Multivariate analysis demonstrated that the extent of disease at diagnosis (limited vs. extensive disease) and PS (0–1 vs. 2–3) were independent predictors of PFS in patients administered topotecan monotherapy, which indicates that this regimen might be useful for elderly relapsed SCLC patients with limited disease at diagnosis and good PS.

The toxicity profile of topotecan monotherapy revealed in our study was tolerable, and was consistent with the findings of previous phase II and III trials that noted myelosuppression as a major toxic influence.^{15,26,27} However, the difference in the standard dose between Western countries and Japan should be considered. Non-hematologic toxicities were generally mild. The frequencies of grade ≥ 3 hematologic toxicities that occurred in patients administered 1.0 mg/m²/day versus 0.8 mg/m²/day were identical; however, dose reduction was more frequent in patients receiving the former (28%) than the latter (10%). Although

the PFS and OS rates of patients administered 1.0 mg/m²/day tended to be longer than those of patients receiving 0.8 mg/m²/day, univariate analysis showed that the initial dose did not significantly influence either survival measure. Thus, an initial dose of 1.0 mg/m² may be suitable. These findings demonstrate that the toxicity profile of topotecan monotherapy might be suitable for the treatment of relapsed SCLC in elderly individuals.

The study has several limitations. First, this was a retrospective study comprising a select group of patients. Second, the planned chemotherapy was reduced, skipped, or delayed at the attending physician's discretion. To minimize this bias, all consecutive patients who were treated at our institutions were included in our analysis, and the patients' original charts were thoroughly reviewed. Third, the use of topotecan as a treatment for recurrence as well as the selection of first and subsequent-line treatments were decided at the discretion of the treating physician. These decisions may have been affected by selection bias, which may have influenced survival rates. Finally, the population of our study was relatively small; larger prospective studies are needed to verify the applicability of our findings in clinical practice.

In conclusion, our retrospective analysis provides evidence that topotecan monotherapy is an effective and tolerable regimen for patients aged ≥ 70 years with previously treated SCLC. The data presented should assist in therapy decision-making for elderly patients with SCLC who have already received one or more chemotherapy regimens.

Acknowledgments

We thank Drs. Tomohiro Tamura, Sakae Fujimoto, and Takeshi Hisada for their assistance in preparing this manuscript.

Disclosure

No authors report any conflict of interest.

References

- Govindan R, Page N, Morgensztern D *et al.* Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006; **24**: 4539–44.
- Johnson BE, Jänne PA. Basic treatment considerations using chemotherapy for patients with small cell lung cancer. *Hematol Oncol Clin North Am* 2004; **18**: 309–22.
- Demedts IK, Vermaelen KY, van Meerbeek JP. Treatment of extensive-stage small cell lung carcinoma: Current status and future prospects. *Eur Respir J* 2010; **35**: 202–15.

- 4 Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2191–7.
- 5 Pallis AG, Shepherd FA, Lacombe D, Gridelli C. Treatment of small-cell lung cancer in elderly patients. *Cancer* 2010; **116**: 1192–200.
- 6 Okamoto H, Watanabe K, Nishiwaki Y *et al.* Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. *J Clin Oncol* 1999; **17**: 3540–5.
- 7 Sekine I, Fukuda H, Kunitoh H, Saijo N. Cancer chemotherapy in the elderly. *Jpn J Clin Oncol* 1998; **28**: 463–73.
- 8 Gridelli C, Shepherd FA. Chemotherapy for elderly patients with non-small cell lung cancer: A review of the evidence. *Chest* 2005; **128**: 947–57.
- 9 Chrischilles EA, Pendergast JF, Kahn KL *et al.* Adverse events among the elderly receiving chemotherapy for advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 620–7.
- 10 Li J, Chen P, Dai CH, Li XQ, Bao QL. Outcome and treatment in elderly patients with small cell lung cancer: A retrospective study. *Geriatr Gerontol Int* 2009; **9**: 172–82.
- 11 Ebi N, Kubota K, Nishiwaki Y *et al.* Second-line chemotherapy for relapsed small cell lung cancer. *Jpn J Clin Oncol* 1997; **27**: 166–9.
- 12 Giaccone G, Donadio M, Bonardi G, Testore F, Calciati A. Teniposide in the treatment of small-cell lung cancer: The influence of prior chemotherapy. *J Clin Oncol* 1988; **6**: 1264–70.
- 13 Jackman DM, Johnson BE. Small-cell lung cancer. *Lancet* 2005; **366**: 1385–96.
- 14 Kim YH, Mishima M. Second-line chemotherapy for small-cell lung cancer (SCLC). *Cancer Treat Rev* 2011; **37**: 143–50.
- 15 Ardizzoni A, Hansen H, Dombernowsky P *et al.* Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: A phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of cancer early clinical studies group and new drug development office, and the lung cancer cooperative group. *J Clin Oncol* 1997; **15**: 2090–6.
- 16 von Pawel J, Schiller JH, Shepherd FA *et al.* Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999; **17**: 658–67.
- 17 Garst J, Buller R, Lane S, Crawford J. Topotecan in the treatment of elderly patients with relapsed small-cell lung cancer. *Clin Lung Cancer* 2005; **7**: 190–6.
- 18 Goldstraw P, Crowley J, Chansky K *et al.* International Association for the Study of Lung Cancer International Staging Committee, Participating Institutions. The IASLC lung cancer staging project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2007; **2**: 706–14.
- 19 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
- 20 Stephens RJ, Johnson DH. Treatment and outcomes for elderly patients with small cell lung cancer. *Drugs Aging* 2000; **17**: 229–47.
- 21 Sekine I, Yamamoto N, Kunitoh H *et al.* Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. *Cancer Treat Rev* 2004; **30**: 359–68.
- 22 Oshita F, Kurata T, Kasai T *et al.* Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. *Jpn J Cancer Res* 1995; **86**: 1198–202.
- 23 Jara C, Gómez-Aldaraví JL, Tirado R, Meseguer VA, Alonso C, Fernández A. Small-cell lung cancer in the elderly—Is age of patient a relevant factor? *Acta Oncol* 1999; **38**: 781–6.
- 24 Okamoto H, Watanabe K, Kunikane H *et al.* Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007; **97**: 162–9.
- 25 Nagy-Mignotte H, Guillem P, Vignoud L *et al.* Multidisciplinary Thoracic Oncology Group. Outcomes in recurrent small-cell lung cancer after one to four chemotherapy lines: A retrospective study of 300 patients. *Lung Cancer* 2012; **78**: 112–20.
- 26 Inoue A, Sugawara S, Yamazaki K *et al.* Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan lung cancer study group trial 0402. *J Clin Oncol* 2008; **26**: 5401–6.
- 27 von Pawel J, Jotte R, Spigel DR *et al.* Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2014; **32**: 4012–9.
- 28 Takeda K, Negoro S, Sawa T *et al.* A phase II study of topotecan in patients with relapsed small-cell lung cancer. *Clin Lung Cancer* 2003; **4**: 224–8.