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A phase I study of 3-day topotecan and cisplatin in elderly patients with small-cell lung cancer

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Abstract *Purpose*: The aim of this phase I study was to determine the maximum-tolerated dose (MTD) in elderly patients with small-cell lung cancer (SCLC). *Patients and methods*: Patients aged over 75 years with previously untreated SCLC were enrolled in this study. Both topotecan and cisplatin were administered on days 1–3 and repeated every 3 weeks. The starting dose of topotecan was 0.5 mg/m^2/day, while cisplatin was fixed at the dose of 20 mg/m^2/day. Patients with limited disease (LD) SCLC received thoracic irradiation after the completion of chemotherapy. *Results*: Twenty-one elderly patients were enrolled in this study and received a total of 59 cycles. The major hematological toxicity was neutropenia and non-hematological toxicities including diarrhea were generally mild and reversible. The MTD of topotecan was determined as 1.2 mg/m^2/day. The recommended phase II study dose of topotecan was determined as 1.0 mg/m^2/day with cisplatin 20 mg/m^2/day daily for 3 days. An objective response was observed in 6 of 10 patients (60%) with LD-SCLC and 6 of 11 (55%) with extensive disease (ED) SCLC. The median survival time in patients with LD-SCLC and those with ED-SCLC were 16.0 and 11.0 months, respectively. *Conclusion*: The combination chemotherapy of 3-day topotecan and cisplatin appears to be tolerable and effective in elderly patients with SCLC.

Keywords Small-cell lung cancer · Elderly patients · Topotecan · Cisplatin · Phase I study · 3-day schedule

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Introduction

The standard chemotherapy for extensive disease small-cell lung cancer (ED-SCLC) has been considered to be a combination of etoposide and cisplatin [1, 9, 11]. Recently, a randomized phase III study comparing a combination of irinotecan, one of the topoisomerase I inhibitors, and cisplatin with a standard combination of etoposide and cisplatin in patients with previously untreated ED-SCLC, demonstrated a significant survival benefit in a combination with irinotecan and cisplatin [18]. Thus, the combination of a topomerase-I inhibitor and cisplatin is an attractive strategy for the treatment of SCLC.

However, elderly patients were excluded from these previous trials [11, 18]. In general, elderly patients are

considered to have an increased risk of chemotherapy-related morbidity and mortality due to comorbid diseases, deterioration of organ functions, or poor performance status (PS) [6, 21]. In addition, frequent dose reductions due to excessive toxicities may be required in elderly patients because of poor functional reserves, resulting in an insufficient dose-intensity of the chemotherapy [27]. Regarding the toxicity profile of the irinotecan and cisplatin combination, one of the major toxicities seems to be high incidence of diarrhea (grade 2 or more: 44% [18]), which may lead to low treatment compliance in the elderly patients. Therefore, it is desirable to establish the optimal treatment for elderly patients with SCLC.

Topotecan is a semi-synthetic derivative of camptothecin, which is a potent inhibitor of the topoisomerase I enzyme and involved in DNA unwinding needed for DNA replication and transcription [8]. In the previous phase II monotherapy trial in the 5-day administration schedule, the overall response rate for previously untreated SCLCs was 39% [25]. Non-hematological toxicities were relatively mild. In particular, diarrhea has been reported to be rare, which is the dose-limiting toxicity (DLT) of irinotecan [14, 17]. Additionally, the safety and efficacy of a 3-day topotecan regimen have recently been reported in patients with ovarian cancer [4, 13], and this modified regimen seemed to be less toxic than a 5-day topotecan regimen [7] with a comparable antitumor activity in patients with ovarian cancer [4, 13]. These findings suggest that a 3-day topotecan might be safely administered to elderly patients with SCLC.

Based on these background data, we designed a phase I study of topotecan administered for three consecutive days in combination with cisplatin, a key drug for SCLCs in elderly patients with SCLC. The primary objective was to determine the maximum-tolerated dose (MTD) for each drug, with a secondary objective of assessing antitumor activity.

Patients and methods

Eligibility

The eligibility criteria for entry into this study were as follows: (1) pathologically proven SCLC, (2) age of 76 years or more, (3) no prior anticancer therapy,(4) PS of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale [20], (5) presence of evaluable lesions, (6) adequate reserves of hematological function (white blood cell [WBC] count $\geq$ 4,000/μl, neutrophil count $\geq$ 2,000/μl, hemoglobin level $\geq$ 9.5 g/dl, platelet count $\geq$ 10×10^4/μl), renal function (serum creatinine $\leq$ 1.5 mg/dl), hepatic function (total bilirubin $\leq$ 1.5 mg/dl, serum transaminases $<$ 2.5×upper limit of normal range) and pulmonary function ($PaO_2 \geq 60$ Torr at rest), and (7) acquisition of a written informed consent. Patients with symptomatic brain metastasis were excluded from the study. The baseline pretreatment evaluations included a complete history, physical examination, laboratory tests, a chest radiograph, computed tomography (CT) scans of the chest and abdomen, fibreoptic bronchoscopy, magnetic resonance imaging (MRI) of the brain, and a radionuclide bone scan, if medically indicated. The protocol was approved by the institutional review board of each participating institute.

Treatment scheme

Topotecan, diluted in 100 ml of physiological saline, was intravenously administered for 30 min on days 1–3. After the completion of the topotecan infusion, a fixed dose of cisplatin (20 mg/m^2/day), diluted in 300 ml of physiological saline, was intravenously administered over 1 h on the same days. The treatment was repeated every 3 weeks and six dose levels were planned (Table 1).

Four cycles of chemotherapy were planned. Patients were treated with at least two cycles of chemotherapy unless there was a disease progression, unacceptable toxicity in the first cycle, or withdrawal of their consent. Initiation of the next cycle of chemotherapy was delayed until recovery of the WBC count to 3,000/μl, the neutrophil count to $\geq$ 1,500/μl, the platelet count to $\geq$ 10×10^4/μl, hemoglobin $\geq$ 8.0 g/dl, and resolution of non-hematologic toxicities to $\leq$ grade 1. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was noted, the use of granulocyte colony-stimulating factor (G-CSF) was permitted. Patients with limited-disease (LD)-SCLC received thoracic irradiation at a total of 45 Gy in 25 fractions after the completion of chemotherapy. In addition, patients achieving complete response received prophylactic cranial irradiation.

Assessment of toxicity and dose escalation

Toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria Version 2.0. All treatment cycles were analyzed to determine DLT, although the decision to elevate the dose level was based on the toxicities in the first cycle. The DLT was defined as development of at least one of the following toxicities: any non-hematological toxicities $\geq$ grade 3 other than nausea, vomiting, and alopecia; grade 4 neutropenia or leukopenia lasting for 4 days or more; platelet count $\leq$ $1–10^4$/μl. At least three patients were scheduled to enter the study at each dose level and if all three patients developed the DLT, the dose level was determined to be

Table 1 Planned dose level

Dose levels	Cisplatin (mg/m^2/day)	Topotecan (mg/m^2/day)
1	20	0.5
2	20	0.65
3	20	0.8
4	20	1.0
5	20	1.2
6	20	1.4

the MTD. If one or two of the three patients experienced the DLT, three additional patients were subjected to the same dose level. The MTD was defined as a dose level that produced any of the DLTs developed in three or more patients among a maximum of six patients, and further dose escalation was not permitted. Dose escalation in the individual patient was not allowed. The recommended dose was defined as the dose level below the MTD for safe administration of the both drugs.

Assessment of efficacy

The response was evaluated according to the Standard Response Evaluation Criteria in Solid Tumors [28]. The time to progression and the overall survival time were calculated from the date of registration to this trial until the first document of disease progression and death, respectively, using the Kaplan–Meier method. Statistical analyses were performed using the STATVIEW 5.0 program (Brainpower, Calabasas, CA).

Results

Patient characteristics

Between November 2001 and September 2004, a total of 21 elderly SCLC patients were enrolled in this study (Table 2). In ED-SCLC patients, most frequent metastatic sites were the liver and adrenal gland. A total of 59 cycles were administered, with median number of three cycles per patients (range 1–4). Seven of the 10 LD-SCLC patients received thoracic irradiation after completion of chemotherapy with a median-delivered dose of 45 Gy. One patient received only one cycle of chemotherapy because of withdrawal of consent. All patients and cycles were assessable for toxicity and response.

Hematological toxicity

The hematological toxicities in 21 patients are listed in Table 3. The main toxicity was neutropenia, which was observed in 54 (91.5%) of 59 cycles. G-CSF was required in 34 (58%) cycles for grade 4 neutropenia (31 cycles) or febrile neutropenia (three cycles). Grade 4 anemia was observed in seven (12%) cycles, and blood transfusion was required in four cycles at dose levels 3 and 5. Grade 2 or 3 thrombocytopenia was frequently observed and platelet transfusion was required in one cycle at dose level 5, however, no severe hemorrhage complications were experienced.

Table 2 Patient characteristics

No. of patients	21
Age	
Median (range)	78 (76–82)
Gender	
Male	19
Female	2
Performance status	
0	5
1	13
2	3
Stage	
Limited disease	10
Extensive disease	11

Non-hematological toxicity

Table 4 shows non-hematological toxicities of grade 2 or greater in all treatment cycles. Diarrhea was extremely mild and grade 1 diarrhea occurred in 7 (12%) of 59 cycles and no grade 2 or more diarrhea was observed in this study. Febrile neutropenia was experienced in one and two cycles at dose levels 3 and 5, respectively, however, it was reversible with appropriate supportive care including G-CSF and antibiotics. Grade 3 hepatic dysfunction and grade 4 hyponatremia occurred in one cycle each, and these toxicities were considered to be the DLT. However, these conditions spontaneously recovered. There were no treatment-related deaths.

Maximum-tolerated dose

Dose limiting toxicity was observed in one of six patients at dose level 3 (hepatic toxicity), and in three of six patients at dose level 5 (febrile neutropenia, persistent neutropenia, and hyponatremia). Thus, we determined the MTD of 3-day topotecan and cisplatin to be 1.2 and 20 mg/m^2/day, respectively (dose level 5). The recommended doses were considered to be 1.0 mg/m^2/day for topotecan and 20 mg/m^2/day for cisplatin (dose level 4).

Antitumor activity

An objective response was observed in 6 (60%) of 10 patients with LD-SCLC and 6 (55%) of 11 patients with ED-SCLC. The median follow-up time of the surviving patients was 11.0 months, and the median survival time was 12.8 months. When stratified by disease extent, the median survival times in patients with LD-SCLC and those with ED-SCLC were 16.0 and 11.0 months, respectively.

Discussion

The present phase I study demonstrated that the combination chemotherapy of 3-day topotecan and cisplatin was well tolerated in elderly SCLC patients. The major toxicity in our study was myelosuppression, whereas diarrhea was rarely observed. All the toxicities were reversible and no life-threatening toxicities occurred.

Table 3 Hematological toxicity of grade 2 or greater (all cycles)

		Dose levels				
		1	2	3	4	5
No. of treated patients		3	3	6	3	6
No. of cycles evaluated		9	5	19	7	19
	Grades	No. of cycles (%)				
Leukopenia	2	4 (44)	2 (40)	7 (37)	4 (57)	10 (53)
	3	1 (11)	1 (20)	10 (53)	0	6 (32)
	4	0	0	0	0	2 (11)
Neutropenia	2	0	1 (20)	2 (11)	1 (14)	0
	3	4 (44)	3 (60)	6 (32)	1 (14)	9 (47)
	4	3 (33)	1 (20)	10 (53)	3 (43)	10 (53)
Anemia	2	3 (33)	0	6 (32)	2 (29)	3 (16)
	3	1 (11)	2 (40)	3 (16)	2 (29)	3 (16)
	4	0	0	2 (11)	0	5 (26)
Thrombocytopenia	2	3 (33)	2 (40)	4 (21)	0	2 (11)
	3	2 (22)	2 (40)	6 (32)	0	11 (58)
	4	0	0	0	0	0

Table 4 Non-hematological toxicity of grade 2 or greater (all cycles)

		Dose levels				
		1	2	3	4	5
No. of treated patients		3	3	6	3	6
No. of cycles evaluated		9	5	19	7	19
	Grades	No. of cycles (%)				
Nausea/vomiting	2	2 (22)	1 (20)	2 (11)	2 (29)	2 (11)
	3	2 (22)	0	6 (32)	0	2 (11)
Fatigue	2	1 (11)	1 (20)	0	0	0
	3	0	0	0	0	8 (42)
Hepatotoxicity	2	0	0	0	1 (14)	0
	3	0	0	1 (5)	0	0
Infection	3	1 (11)	0	2 (11)	1 (14)	2 (11)
Febrile Neutropenia	3	0	0	1 (5)	0	2 (11)
Hyponatremia	4	0	0	0	0	1 (5)

The MTDs for topotecan and cisplatin were determined to be 1.2 and 20 mg/m^2/day, respectively (dose level 5), and this regimen yielded a favorable antitumor activity.

It is of note that diarrhea was extremely mild in our regimen without any grade 2 or over. Diarrhea was a major toxicity in the irinotecan and cisplatin arm of the

Table 5 Response

	Dose level					Total
	1	2	3	4	5	
LD-SCLC						
No. of patients evaluated	1	2	3	1	3	10
CR	1	0	2	1	0	4 (40%)
PR	0	0	0	0	2	2 (20%)
NC	0	2	1	0	0	3 (30%)
PD	0	0	0	0	1	1 (10%)
ED-SCLC						
No. of patients evaluated	2	1	3	2	3	11
CR	0	0	0	0	0	0 (0%)
PR	1	0	2	1	2	6 (55%)
NC	1	1	0	1	1	4 (36%)
PD	0	0	1	0	0	1 (9%)

LD-SCLC limited disease small-cell lung cancer, *ED-SCLC* extensive disease small-cell lung cancer, *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease

recent randomized phase III study. Indeed, grade 2 or more diarrhea occurred in 44% of the evaluable patients [18]. Topotecan has the advantage of a lower incidence of diarrhea compared to irinotecan when combined with cisplatin. However, Lilenbaum et al.[12] also demonstrated in a phase I study of topotecan combined with cisplatin that grade 2 diarrhea occurred in 3 (9.7%) of 31 patients despite the fact that no grade 3 or 4 diarrhea was experienced. In addition, Ardizzoni et al.[3] reported grade 3 or 4 diarrhea to be 4% in a phase II trial of topotecan with cisplatin. Accordingly, the 3-day administration schedule in the present study may be superior to prevent diarrhea.

In the previous phase I studies of topotecan and cisplatin, the major toxicity was myelosuppression [12, 16, 22–24]. In a phase I study of 5-day topotecan with cisplatin conducted by Miller et al.[16], dose-limiting grade 4 neutropenia lasting for more than 7 days occurred in three (30%) of nine patients, whereas our 3-day-schedule regimen did not show such a durable toxicity. Additionally, in a phase II study comparing a 3-day regimen of topotecan and cisplatin with a 5-day regimen, the incidence of grade 3 or more leukopenia was somewhat lower in the former regimen (22 and 33%, respectively) [26]. These observations suggest that a 3-day topotecan regimen may be less toxic than a 5-day one, although other clinical factors possibly affected the difference of the toxicity profiles. Furthermore, the frequency of neutropenia in our trial was almost comparable with that in the irinotecan and cisplatin arm of the randomized trial [18], and that in the combination chemotherapy of carboplatin and etoposide in elderly patients with SCLC [19]. Thus, our regimen is considered to be safely administrable in terms of both hematological and non-hematological toxicity when compared with the previous results.

With regard to the efficacy, our regimen seems to have potential antitumor activity in elderly patients with SCLC, with response rates of 60% in LD-SCLC and 55% in ED-SCLC. In addition, the median survival times for LD- and ED-SCLC were 16.0 and 11.0 months, respectively. In the previous clinical trials, median survival times in the treatment of elderly LD- and ED-SCLCs were reported to be 12–15 and 9–11 months, respectively, with combination chemotherapy consisting of carboplatin and etoposide [5, 10, 15, 19]. Ardizzoni et al.[2] recently conducted a phase II study of cisplatin and etoposide in elderly patients with LD- and ED-SCLC. They demonstrated that the overall response rate and survival time were 60.0% and 9.5 months, respectively. The clinical outcome in our study seems to be comparable with these studies, suggesting that this regimen has considerable antitumor activity in elderly patients with SCLC. Because of the small sample size in this study, it is necessary to verify the efficacy of this regimen in a subsequent phase II study.

In conclusion, combination chemotherapy consisting of topotecan and cisplatin on days 1–3 is well tolerated for elderly patients with SCLC, which seems to show reasonable efficacy. The phase II study of this regimen is now under investigation.

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