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ORIGINAL ARTICLE

Phase II study of combined belotecan and cisplatin as first-line chemotherapy in patients with extensive disease of small cell lung cancer

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Abstract
Purpose To determine the efficacy and safety of belotecan in combination with cisplatin as first-line chemotherapy for extensive disease of small cell lung cancer (ED SCLC).
Methods Patients with chemotherapy-naïve ED SCLC were eligible if the following criteria were met: age ≥18 years; a measurable lesion; Eastern Cooperative Oncology Group Performance Status (PS) 0–2; and adequate organ function. Each cycle consisted of belotecan (0.5 mg/m^2/day) on days 1–4 and cisplatin (60 mg/m^2) intravenously on day 1. The cycle was repeated every 3 weeks until the completion of the 6th cycle, disease progression, or intolerable toxicity.
Results Thirty-five patients (median age, 68 years) were enrolled: 32 males (91.4%); and PS = 0 (n = 3), PS = 1 (n = 18), and PS = 2 (n = 14). The median number of cycles delivered was 5 (range, 1–6). The relative dose intensity was 70.1% for belotecan and 83.0% for cisplatin. Of 30 evaluable patients, objective response rate was 71.4% (95% confidence interval [CI], 55.7–87.2) by the intent-to-treat principle. The median duration of follow-up was 14.3 months. The median progression-free survival was 5.7 months (95% CI, 3.9–7.5) and the median overall survival was 10.2 months (95% CI, 9.3–11.1). The frequently reported grade 3 or 4 toxicities included neutropenia in 24 patients (68.6%), thrombocytopenia in 10 (28.6%), and anemia in 7 (20.0%). There was no grade 3 or 4 non-hematologic toxicity except three patients (8.6%) with fatigue.
Conclusions Belotecan and cisplatin combination therapy showed significant efficacy in ED SCLC with improved non-hematologic toxicities.

Keywords Belotecan · Cisplatin · Small cell lung carcinoma · Chemotherapy

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases [1]. SCLC is a more aggressive disease than non-small cell lung cancer (NSCLC); specifically, SCLC has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastasis [2]. Two-thirds of patients with SCLC are initially diagnosed with extensive disease (ED) [2]; thus, tumors are beyond the field of chest irradiation. There has been almost no improvement in survival in patients with ED SCLC since the mid-1980s; the median overall survival (OS) of patients with ED SCLC has remained approximately 10 months [3–6]. Therefore, more effective novel chemotherapeutic agents are needed.

Belotecan (Camtobell®, CKD602, 7-[2(N-isopropylamino)ethyl]-(20S)-camptothecin; Chong Keun Dang Corp., Seoul, Korea) is a new camptothecin derivative with increased water solubility and activity by modifications on the B- and E-rings of the camptothecin [7, 8]. With use of a cleavable complex assay, a preclinical study showed that belotecan was 3 times and slightly more potent than

topotecan and camptothecin, respectively, as a topoisomerase inhibitor [7]. Belotecan also has a significantly higher antitumor index (ATI; defined as the area under the %IR versus time curve plotted from 0 to 240 min as obtained by an ex vivo pharmacodynamic assay and calculated by the trapezoidal rule) than topotecan against 12 human cancer cell lines. The ATI values of belotecan were >twofold higher than those of topotecan in breast, ovarian, and lung carcinoma cell lines [7]. The combination of cisplatin with belotecan showed therapeutic synergy against human gastric cancer cell lines [9].

In a phase I study [8], the maximum tolerated dose of belotecan was 0.7 mg/m^2/day when administered daily for 5 consecutive days every 3 weeks: the dose-limiting toxicity was neutropenia. Two phase II studies [10, 11] reported the activity and tolerability of belotecan monotherapy in patients with ED SCLC. Lee et al. [9] conducted a phase I study involving belotecan in combination with cisplatin in patients with previously untreated ED SCLC. Lee et al. [9] reported the maximal tolerable dose and recommended the dose of belotecan for phase II studies to be 0.5 mg/m^2/day on days 1–4 in combination with 60 mg/m^2 of cisplatin on day 1 every 3 weeks.

Based on these results, we performed a phase II study involving belotecan and cisplatin to determine the efficacy and tolerability of combination chemotherapy in patients with ED SCLC.

Patients and methods

Patients

Patients with histologically- or cytologically-confirmed ED SCLC were enrolled in this study, which was conducted in a single institution (Gachon University Gil Hospital [GUGH]). The eligibility criteria included the following: (1) age ≥18 years; (2) at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria [12]; (3) no previous chemotherapy or radiotherapy; (4) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) between 0 and 2; and (5) adequate organ and marrow function (absolute neutrophil count ≥1,500/μL, hemoglobin ≥9 g/dL, platelet ≥100,000/μL, total bilirubin ≤1.5 mg/dL, aspartate and alanine aminotransferase levels both ≤twofold the upper limit of normal, and serum creatinine ≤1.5 mg/dL or a calculated creatinine clearance ≥60 mL/min). Patients with an uncontrolled co-morbid illness, an active infection, or a second malignancy were ineligible. The study was reviewed and approved by the Institutional Review Board of GUGH. Written informed consent was obtained from all patients prior to study entry.

Treatment

Belotecan (0.5 mg/m^2/day) mixed with 100 ml of 5% dextrose was administered over 30 min intravenously on days 1–4. Additionally, cisplatin (60 mg/m^2) mixed with 150 ml of normal saline was intravenously infused over 1 h on day 1 with adequate hydration and anti-emetics. Treatment was repeated every 3 weeks. A total of six cycles were administered unless there was documented disease progression, unacceptable toxicity, or patient refusal.

Dose adjustments at the start of a new cycle were based on the worst toxicity observed during the previous cycle. If the patient had an absolute neutrophil count (ANC) >1,000/μL and ≤1,500/μL and/or a platelet count >75,000/μL and ≤100,000/μL, the patient had a 25% reduction in belotecan (0.375 mg/m^2/day). Treatment was delayed for 1 week if the absolute ANC was ≤1,000/μL and/or the platelet count was ≤75,000/μL. If a patient had grade 4 neutropenia (ANC ≤500/μL) with fever, the patient had a 25% dose reduction in belotecan in the next cycle. Primary prophylactic granulocyte colony-stimulating factor (G-CSF) was not given. Secondary G-CSF prophylaxis was administered with subsequent cycles in patients who developed grade 3 or 4 neutropenia or febrile neutropenia. Cisplatin was reduced by 50% if the creatinine clearance was ≤60 ml/min. If the creatinine clearance was ≤40 ml/min, cisplatin was discontinued and the patients were dropped from the study. Subsequent cycles were started when toxicity measurements satisfied the following criteria: neutrophil count >1,500/μL; platelet count >75,000/μL; and recovery of non-hematologic toxicities to ≤grade 2. If the delay period exceeded 3 weeks, patients were withdrawn from the study.

Assessment of tumor response and toxicity

A safety evaluation, including an assessment of laboratory data and any clinical adverse events, was performed after the completion of each cycle. Treatment response was evaluated every two cycles by chest computed tomography (CT) with a comparable protocol in all patients. CT of body areas other than the chest, magnetic resonance imaging, or bone scintigraphy could be used to follow pre-existing measurable or evaluable lesions or to detect any new lesion if clinically indicated. Tumor response was measured unidimensionally according to the RECIST 1.0 criteria and responses were confirmed at least 4 weeks after initial assessment. To record adverse events, the National Cancer Institute Common Toxicity Criteria (version 3.0) was used.

Statistical analysis

The primary endpoint of the study was to evaluate response rate and safety of belotecan and cisplatin combination

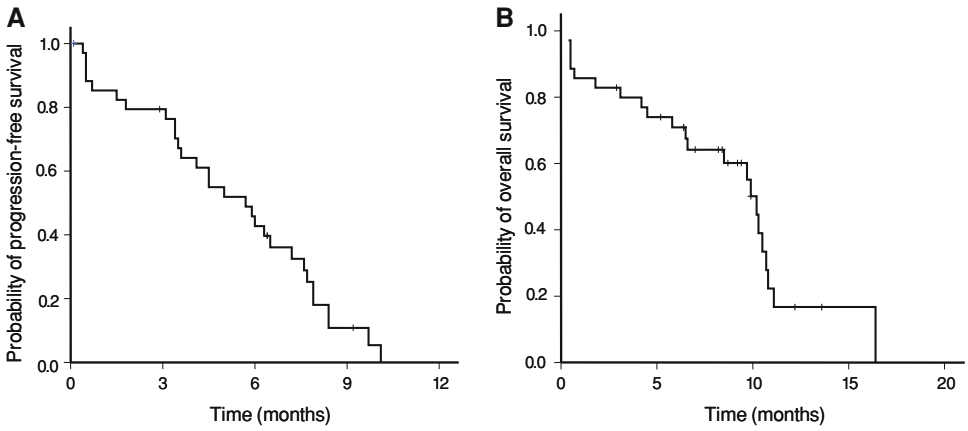

Fig. 1 Kaplan–Meier estimates of **a** progression-free survival and **b** overall survival

chemotherapy. Secondary endpoints were the evaluation of progression-free survival (PFS) and OS.

According to Simon's minimax two-stage design, at least 28 eligible patients were required on the basis of a null hypothesis with a <50% response rate versus a ≥75% response rate (85% power with an $\alpha = 0.05$). The first stage of the study required 11 patients, and if at least six objective responses were observed, the second stage required a total of 28 patients. If at least 19 patients responded after the second accrual stage, treatment was considered promising. In the assumption of 20% falling off during enrollment, a total of 34 patients was the target sample size. PFS and OS were analyzed by the Kaplan–Meier method. All values were two-sided and statistical significance was accepted at the $P < 0.05$ level. Safety was analyzed in all patients who received at least one dose of study medications. SPSS (version 15.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics

Between January 2008 and June 2010, 35 patients were enrolled. Among the 35 patients, 30 were evaluable for response: two patients died of neutropenic septic shock and three patients withdrew the consent after the first cycle of the chemotherapy. The baseline patient characteristics and clinical features are summarized in Table 1. During a median duration of follow-up of 14.3 months (range, 2.9–32.8 months), 30 patients experienced an event for PFS analysis and 20 patients died. The median number of cycles delivered was 5 (range, 1–6).

Treatment outcomes

Of 30 evaluable patients, the best overall response was a partial response (PR) in 25 (83.3%), stable disease (SD) in 2 (6.7%), and progressive disease (PD) in three patients (10%). The overall RR was 71.4% (95% confidence interval [CI], 55.7–87.2) in an intent-to-treat analysis and 83.3% (95% CI, 69.2–97.5%) among the evaluable patients (Table 2). The median PFS was 5.7 months (95% CI, 3.9–7.5 months) and the median OS was 10.2 months (95% CI, 9.3–11.1 months; Fig. 1).

Table 1 Patient characteristics

No. of patients	35
Median age (range)	68.0 (range 51–77)
Gender	
Male	32 (91.4%)
Female	3 (8.6%)
ECOG performance status	
0	3 (8.6%)
1	18 (51.4%)
2	14 (40.0%)
Lactose dehydrogenase	
Within the normal range	16 (45.7%)
Elevated	19 (54.3%)
Weight loss	
No	26 (74.3%)
Yes	9 (25.7%)
Site of metastasis[a]	
Lung (other lobe)	6
Pleura	17
Liver	9
Bone	11
Central nervous system	3
Adrenal gland	6
Bone marrow	2
Other	2
1 or 2 sites of metastasis	22 (62.9%)
≥3 sites of metastasis	13 (37.1%)

ECOG Eastern Cooperative Oncology Group

[a] Patient may have two or more metastatic locations

Table 2 Analysis of treatment response

	Number of patients (%)
Best overall response	
Complete response	0
Partial response	25 (71.4%)
Stable disease	2 (5.9%)
Progressive disease	3 (8.8%)
Not evaluable	5 (14.7%)
Overall response rate	% (95% CI)
By intent-to-treat analysis	71.4 (55.7–87.2)
By per protocol analysis	83.3 (69.2–97.5)

Safety and dose intensity

The toxicity profile is summarized in Table 3. Hematologic toxicities were more prominent than non-hematologic toxicities in patients with ED SCLC who received combination chemotherapy. The frequently observed toxicities were anemia (77.1%), neutropenia (74.3%), anorexia (57.1%), fatigue (48.6%), and thrombocytopenia (37.1%). Severe (grade 3 or 4) toxicities of anemia, neutropenia, and thrombocytopenia were reported in 7 (20.0%), 24 (68.6%), and 10 patients (28.6%), respectively. Grade 4 neutropenia was reported in 19 patients (54.3%), 8 of whom had febrile neutropenia. All eight patients had no definite focus of infection and five were culture-negative. Six of the eight patients recovered after intravenous antibiotic therapy while the other two patients (5.7%) experienced treatment-related mortality (neutropenic septic shock) during the second stage of patient accrual. One of the two patients, a 72 year-old male patient with an ECOG PS of two, weight loss >10% within 6 months, and an elevated serum lactose dehydrogenase (LDH) level died during the 1st cycle without response to broad spectrum antibiotics. The other patient was a 73 year-old male with an ECOG PS of one and an elevated LDH level who had a treatment-related death. He denied weight loss, but his serum albumin was <3.0 g/dL before the treatment.

The median delivered dose intensity (DI) of belotecan and cisplatin was 0.47 and 16.6 mg/m^2/week, respectively. The relative DI was 70.1% for belotecan and 83.0% for cisplatin.

Salvage treatment

Among the enrolled patients, 13 received 2nd-line salvage chemotherapy; four patients achieved a PR, one patient had SD, and six patients had PD. One patient declined further 2nd-line chemotherapy after the first cycle, and another patient was recently reported to have PD and just began

Table 3 Toxicity profile

Event	Number of patients (n = 35)						
	Grade by Common Toxicity Criteria for Adverse Event (CTCAE) version 3.0						
	1	2	3	4	5 (death)	≥3, %	≥4, %
Anemia	5	14	6	1	0	20.0	2.9
Leucopenia	1	4	6	9	0	42.9	25.7
Neutropenia	1	1	5	19	0	68.6	54.3
Thrombocytopenia	1	2	5	5	0	28.6	14.3
Febrile neutropenia[a]	–	–	6	0	2	22.9	22.9
Anorexia	12	8	0	1	0	2.9	2.9
Nausea	9	4	1	0	0	2.9	2.9
Vomiting	6	3	0	0	0	0	0
Stomatitis	5	1	0	0	0	0	0
Diarrhea	2	2	0	0	0	0	0
Constipation	7	4	0	0	0	0	0
Neuropathy	4	2	0	0	0	0	0
Alopecia	5	1	–	–	–	–	–
Fatigue	7	7	2	1	0	8.6	2.9
Elevated serum creatinine	2	0	0	0	0	0	0
Elevated AST or ALT	1	0	0	0	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

[a] Febrile neutropenia is defined as a fever of unknown origin without a clinically- or microbiologically-documented infection with an absolute neutrophil count <1,000/μL and a fever ≥38.5 in the CTCAE (version 3.0)

Table 4 Comparison of the patient characteristics and clinical outcomes among combination regimens in studies in chemotherapy naïve extensive disease small cell lung cancer

	Combination regimen	*n*	Median age	ECOG PS (0,1 vs. 2)	Response rate (%)	Progression-free survival	Overall survival
Eckardt et al. [3]	Topotecan + Cisplatin	389	59.7 (31–80)	87% vs. 13%	63	Not reported	39.3 weeks
	Etoposide + Cisplatin	395	59.6 (28–80)	87% vs. 12%	69	Not Reported	40.3 weeks
Hanna et al. [4]	Etoposide + Cisplatin	110	62 (38–83)	92.3% vs. 7.2%	43.6	4.6 months (as TTP)	10.2 months
	Irinotecan + Cisplatin	221	63 (37–82)	88.2% vs. 10.9%	48	4.1 months (as TTP)	9.3 months
Lara et al. [5]	Etoposide + Cisplatin	324	63 (35–86)	100% vs. 0%[a]	57	5.2 months	9.1 months
	Irinotecan + Cisplatin	317	62 (22–85)	100% vs. 0%[a]	60	5.8 months	9.9 months
Noda et al. [6]	Etoposide + Cisplatin	77	63 (40–70)	87% vs. 13%	52	4.8 months	9.4 months
	Irinotecan + Cisplatin	77	63 (30–70)	92% vs. 8%	65	6.9 months	12.8 months
Lee et al. [17]	Belotecan + Cisplatin	30	59.5 (42–73)	90% vs. 10%	70	6.9 months	19.2 months
Current study	Belotecan + Cisplatin	35	68 (51–77)	60% vs. 40%	71.4	5.7 months	10.2 months

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ; creatinine

TTP time to progression

[a] Only patients with ECOG PS 0 or 1 were included in this study

2nd-line chemotherapy. Only two patients received 3rd-line palliative chemotherapy.

Discussion

Single agent or combination chemotherapy has been shown to extend survival in SCLC. In this phase II study, belotecan and cisplatin combination chemotherapy for ED SCLC showed a significant RR. Considering the reported RRs of combination etoposide and cisplatin (44–69%) [3–6] and combination irinotecan and cisplatin (48–84%) [4–6] in previous phase III studies (Table 4), the RR of belotecan with cisplatin in the current study was comparable to currently used combination regimens. It was also reported 54–89% in phase II or III studies of irinotecan and carboplatin for ED SCLC [13–16].

There is only one prior report of a phase II study of combination belotecan and cisplatin in patients with newly diagnosed ED SCLC. Lee et al. [17] conducted a multicenter phase II study to evaluate the efficacy and safety of belotecan combined with cisplatin for the treatment of chemotherapy-naïve patients with ED SCLC ($n = 30$). Lee et al. [17] reported that the RR was 70% (95% CI, 50.6–85.3%), the median PFS was 6.9 months (95% CI, 6.3–7.5 months), and the median OS was 19.2 months (95% CI, 13.3–25.2 months). The RR was similar with our study (>70% in the intent-to-treat analysis and >80% in the per-protocol analysis). The OS in the current study was not as promising as the study conducted by Lee et al. [17]. This observation may have resulted from the difference in baseline patient characteristics. In our study, the median age of the enrolled patients was older (median, 68.0 vs. 59.5 years) and the number of patients with ECOG PS 2 was greater (14 of 35 patients [40%] vs. 3 of 30 patients [10%]). Furthermore, while only 13 of 35 patients (37.1%) received subsequent second-line chemotherapy, greater than one-half of the patients (17 of 30 patients [56.6%]) who participated in the phase II study conducted by Lee et al. [17] received second-line chemotherapy. Although these two phase II studies could not be compared directly, we postulate that a high response rate can be achieved by combination belotecan and cisplatin in patients with ED SCLC. Considering median ages were mostly the early 60 s and more patients with ECOG PS 0 or 1 were enrolled in previous larger studies (Table 4), combination belotecan and cisplatin warrants further investigation for improvement in OS in patients with newly diagnosed ED SCLC.

Non-hematologic toxicities were mild and manageable. There was no grade 3 or 4 stomatitis, diarrhea, and neuropathy. Grade 2 alopecia was only 2.8%. Compared to combination etoposide and cisplatin, which resulted in 32.1% of grade 2 alopecia in a previous phase III study [4], combination belotecan and cisplatin relieved fears of total hair loss in patients with ED SCLC. With respect to hematologic toxicities, neutropenia was the most frequent toxicity. Grade 4 neutropenia occurred in 54.3% of the patients: 2 of 35 patients died of sepsis. Considering the similar incidence of grade 4 neutropenia (53%) and febrile neutropenia (30%), but no occurrence of treatment-related deaths in the previous study by Lee et al. [17], this is most likely a consequence of the age and PS of the patients in the study. Indeed, the dose and schedule in the current study may be optimal and more appropriate for patients of a younger age and good PS. As more than half of the patients experienced grade 4 neutropenia, use of prophylactic G-CSF should be considered [18]. Otherwise, the dose of belotecan combined with cisplatin is recommended to 25% dose reduction, 0.5 mg/m^2 for 3 days, because relative DI was 70.1% for belotecan and 83.0% for cisplatin.

In conclusion, combination belotecan and cisplatin showed significant RR and improved non-hematologic toxicities in patients with previously untreated ED SCLC. A larger, randomized phase III trial comparing this combination with currently available standard treatment, etoposide with cisplatin is warranted. The phase III COMBAT study comparing belotecan plus cisplatin to etoposide plus cisplatin in patients with ED SCLC (NCT00826644) is ongoing.

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