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Belotecan and Cisplatin Combination Chemotherapy for Previously Untreated Extensive-Disease Small Cell Lung Cancer

Purpose: Belotecan (Camtobell®; Chong Keun Dang Co., Seoul, Korea) is a new camptothecin analog that inhibits topoisomerase I. We evaluated the efficacy and toxicity of belotecan combined with cisplatin in patients with previously untreated extensive-disease small cell lung cancer (ED-SCLC) and who were without evidence of brain metastases. **Materials and Methods:** Twenty patients with previously untreated ED-SCLC were treated with belotecan (0.5 mg/m^2/day) on days 1～4 and with cisplatin (60 mg/m^2/day) on day 1 of a 3-week cycle. **Results:** Of the 19 assessable patients, 16 had an objective tumor response, including two complete responses, for an overall response rate of 84.2%. Toxicity was evaluated in all 20 patients who received a total of 106 cycles (median cycles/patient, 5.5; range, 1～9). The major grade 3/4 hematologic toxicities were neutropenia (67.9% of cycles), anemia (19.8% of cycles) and thrombocytopenia (33.9% of cycles). No grade 3/4 non-hematologic toxicities were observed. No treatment-related deaths occurred. The median progression-free and overall survivals were 7.06 months (95% confidence interval [CI], 3.98～10.14 months) and 9.96 months (95% CI, 6.12～13.80 months), respectively. **Conclusion:** Combination chemotherapy with belotecan plus cisplatin is an effective treatment for ED-SCLC with acceptable hematologic and non-hematologic toxicities. **(J Lung Cancer 2010;9(1):15－19)**

Key Words: Belotecan, Extensive disease, Small cell lung carcinoma, Cisplatin, First-line

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INTRODUCTION

Camptothecin (CPT) is a potent antineoplastic molecule obtained from extracts of the Chinese tree *Camptotheca acuminanata*. The cytotoxic activity of CPT is attributed to a novel mechanism of action involving the nuclear enzyme type I DNA topoisomerase (1), and two derivatives, topotecan and irinotecan, have successfully entered the market and are used as topoisomerase I inhibitors in clinical practice.

Belotecan (Camtobell®; Chong Keun Dang Co., Seoul, Korea), a water-soluble CPT analog also known as CKD-602, was introduced to treat small cell lung cancer (SCLC). In preclinical studies, belotecan was more potent as a topoisomerase I inhibitor and had more antitumor activity than camptothecin or topotecan (Hycamtin®; GlaxoSmithKline, Brentford, UK) in six human tumor xenografts (2,3). Recently, a phase II study using the single agent belotecan in chemotherapy naïve patients with extensive disease (ED)-SCLC showed a promising response rate of 53.2%. The median overall survival was 10.4 months, the median time to progression was 4.6 months, and the 1-year survival rate was 49.9% (4). The most common toxicity was hematologic (grade 3/4 neutropenia, 71.0% of patients; grade 3/4 thrombocytopenia, 12.9%) (4).

Potent antitumor activity against SCLC was noted in a phase I study of belotecan plus cisplatin, with a response rate of 76.5%, a median survival of 15.9 months, and reasonable

non-hematologic toxicities (5). Based on these findings, we investigated the efficacy and toxicity profile of this regimen in previously untreated patients with ED-SCLC.

MATERIALS AND METHODS

1) Eligibility criteria

Patients from two centers, Chungnam National University Hospital and Konkuk University Hospital, were enrolled in the study. All patients had histologically or cytologically confirmed SCLC with evidence of ED, excluding brain metastases.

Patients had to meet the following criteria: at least one unidimensionally measurable or assessable lesion; age ≥18 years, Eastern Cooperative Oncology Group performance status (PS) ≤3, absolute neutrophil count ≥1,500/mm^3, hemoglobin >10.0 g/dL, platelet count ≥100,000/μL, aspartate and alanine aminotransferase levels ≤2-fold the upper limit of normal, bilirubin ≤1.5 mg/dL, creatinine ≤1.5 mg/dL, or a calculated creatinine clearance >60 mL/min. Patients were not eligible for the study if they had any of the following: active infection, history of myocardial infarction within the last 6 months, congestive heart failure or significant arrhythmia, uncontrolled pleural or pericardial effusion or ascites, or a second primary cancer. The pretreatment assessment included chest radiography, computed tomography of the thorax and brain, a radionuclide bone scan, positron-emission tomography/computed tomography, and fiberoptic bronchoscopy. Pulmonary function studies and arterial blood gas measurements were also conducted when signs or symptoms of respiratory insufficiency were present. This study was approved by the ethics committees of the two participating centers. Written informed consent was obtained from all patients before the study.

2) Treatment

Chemotherapy consisted of cisplatin (60 mg/m^2) on day 1 and belotecan (0.5 mg/m^2/day) on days 1 to 4 for 3 weeks. The dose and schedule were based on a study conducted previously (5). Cisplatin was diluted to 150 mL in normal saline and administered as a 60-min intravenous infusion on day 1. Patients received standard intravenous hydration with 1,000 mL of 5% dextrose or normal saline for 2 hours before and after cisplatin administration. A standard antiemetic combination of 10 mg dexamethasone and 8 mg dolasetron was administered by intravenous infusion before the cisplatin administration. Belotecan was diluted in 100 mL of 5% dextrose in water for injection and was immediately administered in a 30-min intravenous infusion once per day on days 1 to 4.

During the treatment cycle, belotecan combined with cisplatin treatment was delayed for 1 week if any of the following conditions were present on day 1 of the planned treatment: absolute neutrophil count (ANC) <1,500/mm^3, platelet count <100,000/mm^3, or non-hematologic toxicity > grade 2. If any of the following conditions were present, the chemotherapy dose was reduced to 80% of the planned dosage: ANC nadir of <500/mm^3 for 4 or more days, febrile neutropenia, platelet nadir count of <50,000/mm^3 for 4 or more days, thrombocytopenia associated with a bleeding episode, or non-hematologic toxicity ≥grade 4. Treatment interruptions or delays due to unacceptable toxicity were not allowed for ≥2 weeks. Prophylactic use of granulocyte-colony-stimulating factor was not allowed, but it could be used therapeutically. The treatments were given for ≥6 cycles, unless disease progression or unacceptable toxicity occurred.

3) Response and toxicity criteria

Tumor responses were assessed every two cycles according to the Response Evaluation Criteria in Solid Tumors. A complete response (CR) was defined as the disappearance of all target lesions, while a partial response (PR) was defined as a decrease of ≥30% in the sum of the greatest dimensions of the target lesions taken as a reference of the baseline sum for the greatest dimensions and/or the persistence of one or more nontarget lesion(s). Progressive disease (PD) was defined as an increase of ≥20% in the sum of the greatest dimensions using the smallest sum of the greatest dimensions recorded since starting treatment as a reference, or the appearance of one or more new lesions, and/or unequivocal progression of existing nontarget lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify as PR nor a sufficient increase to qualify as PD using the smallest sum of the greatest dimensions observed since starting treatment as the reference.

Descriptive statistics are reported as proportions and medians. Overall survival (OS) was defined as the time from treatment initiation to death or to the last known follow-up. Progression-free survival (PFS) was defined as the time between treatment initiation and disease progression, death, or

last known follow-up, whichever occurred first. Toxicities were monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

RESULTS

From August 2006 to July 2008, 20 patients from Chungnam National University Hospital and Konkuk University Hospital participated in the study. The patient characteristics are listed in Table 1. The patient age at diagnosis ranged from 49 to 76 years (median, 65.5 years) and the male : female ratio was 3 : 1 (15 : 5). Of the 20 patients, 19 were assessable for response rate, and all patients were assessable for toxicity.

In the 19 assessable patients, the objective tumor response rate was 84.2% (16/19), including two CRs (Table 2). One patient was not eligible for response evaluation because he refused further treatment after one cycle of chemotherapy due to financial difficulties.

Eighty (75.5%) of 106 cycles were conducted without a dose reduction. Ten (50.0%) of the 20 patients completed six cycles with a median follow-up time of 9.26 months, and a median OS and PFS of 9.96 months (95% confidence interval [CI], 6.12～13.80 months), and 7.06 months (95% CI, 3.98～10.14 months), respectively (Fig. 1). One patient with CR received five cycles of combination chemotherapy without a dose reduction. The other patient with CR received eight cycles, with six 20% dose reductions of the planned dose. At the time of this report, the former patient has lived for 40.4 months without recurrence.

Ten patients received retreatment with etoposide plus cisplatin (EP) after recurrence. Five patients achieved PR, three patients had SD, and two patients had PD.

Toxicity was evaluated in all 20 patients, who received 106 treatment cycles (median cycles/patient, 5.5; range, 1～9). The major toxicities observed were hematologic (Table 3). Grade 3

Table 1. Patient Characteristics

Characteristic	No. of patients (%)
Total number enrolled	20
Eligible for response evaluation	19
Age, median (range), yr	65.5 (49～76)
Gender	
Male	15 (75.0)
Female	5 (25.0)
Performance status	
1	13 (65.0)
2	6 (30.0)
3	1 (5.0)
Metastatic site	
Bone	15 (53.5)
Liver	4 (14.3)
Lung	3 (10.7)
Adrenal gland	3 (10.7)
Other	3 (10.7)

Table 2. Tumor Responses

Response	n (%)
Complete response	2 (10.5)
Partial response	14 (73.7)
Stable disease	2 (10.5)
Progressive disease	1 (5.3)
Objective response	16/19 (84.2)
Total	19

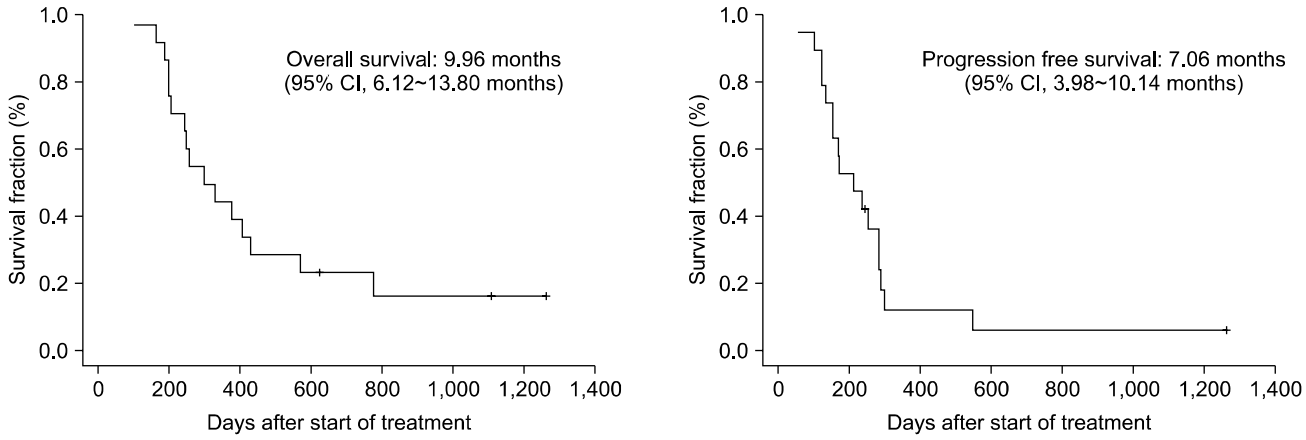

Fig. 1. Kaplan-Meier estimates of survival outcomes are illustrated. Tick marks indicate censored data.

Table 3. Toxicity Profile by Cycles

Adverse event	No. of toxicities/Total cycles (%) (total cycles=106)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity, n (%)				
Leukopenia	39 (36.8)	17 (16.0)	28 (26.4)	22 (20.7)
Neutropenia	28 (26.4)	6 (5.7)	17 (16.0)	55 (51.9)
Anemia	40 (37.7)	45 (42.5)	16 (15.1)	5 (4.7)
Thrombocytopenia	59 (55.7)	11 (10.4)	21 (19.8)	15 (14.1)
Non-hematologic toxicity, n (%)				
Alopecia	69 (65.1)	37 (34.9)	0 (0)	0 (0)
Anorexia	92 (86.7)	14 (13.2)	0 (0)	0 (0)
Nausea/vomiting	97 (91.5)	9 (8.5)	0 (0)	0 (0)
Constipation	106 (100)	0 (0)	0 (0)	0 (0)
Diarrhea	104 (98.1)	2 (1.9)	0 (0)	0 (0)

or 4 neutropenia developed in 72 cycles (67.9%), and grade 3 or 4 thrombocytopenia developed in 36 cycles (33.9%). No grade 3 or 4 non-hematologic toxicity occurred, including diarrhea, and no treatment-related death took place.

DISCUSSION AND CONCLUSION

The present study showed a high response rate (84.2%) and acceptable toxicities for treatment with belotecan plus cisplatin. The results were similar to those of a phase I study with a response rate of 76.5% (5). However, accepting the median OS and PFS was difficult because of the small sample size.

The major observed toxicities were grade 3 or 4 neutropenia in 67.9% of the treatment cycles (72/106) and grade 3 or 4 thrombocytopenia in 33.9% (36/106). Similarly, the toxicities of the belotecan plus cisplatin regimen were similar to those observed with other camptothecin derivatives plus cisplatin (6,7).

In a randomized phase III study conducted by the Japanese Cooperative Oncology Group (JCOG), a combination of irinotecan and cisplatin (IP) significantly improved survival when compared to irinotecan and EP (12.8 vs 9.4 months; $p < 0.01$) (6). However, in a subsequent and larger study comparing a modified weekly IP regimen with the EP regimen in patients with chemo-naïve ED-SCLC, the superior results with irinotecan were not reproduced (7). The causes for the different outcomes were a different IP dose and schedule, differences in UDP-glucuronosyltransferase (UGT1A1) polymorphisms, which is an enzyme that metabolizes irinotecan, and the observation that molecular differences exist between Asian and US populations (7). In contrast, Hermes et al. (8) reported on a 2008 randomized phase III study of irinotecan plus carboplatin versus etoposide plus carboplatin in a Scandinavian population with ED-SCLC. Similar to the JCOG data, they found a significantly more favorable OS for patients in the irinotecan-containing regimen. Eckardt et al. (9) reported that oral topotecan with cisplatin provides similar efficacy and tolerability to EP in chemo-naïve patients with ED-SCLC. Taken together, the camptothecin derivatives plus platinum were superior or had a similar efficacy compared to the standard EP regimen.

Topotecan, irinotecan, and belotecan are commercially available and used in therapy for different kinds of tumors including SCLC. Their mechanism of action is similar, but the drug clinical data have some notable differences. Topotecan and irinotecan have different limiting toxicities (myelosuppression and diarrhea, respectively) (10). Diarrhea is a notorious toxicity of the camptothecin derivatives, especially irinotecan.

Irinotecan is a prodrug, which has to be converted to its active SN-38 form. SN-38 is inactivated by conjugation; thus, patients with Gilbert's syndrome and other forms of genetic glucuronization deficiency (UGTA1) are at an increased risk for irinotecan-induced severe diarrhea (1). However, grade 3 or 4 diarrhea was absent in patients receiving belotecan-containing regimens (4,5,10-12).

Recently, a phase II belotecan and cisplatin study in chemotherapy naïve patients (n=30) with ED-SCLC showed promising response rates (70%), PFS (6.9 months), and OS (19.2 months). Grade 3/4 neutropenia was 76%, and no diarrhea occurred. The response rate and the disease control rate with

subsequent second-line therapy (mainly etoposide and platinum) were 23.5% and 52.9%, respectively, which may have led to a better survival outcome (12).

This study showed a high response rate and acceptable toxicities for belotecan plus cisplatin treatment. The results should be reinforced by studies with an increased sample size and longer follow-up time.

Combination chemotherapy with belotecan plus cisplatin was active as a first-line therapy for patients with ED-SCLC, with acceptable hematologic and non-hematologic toxicities.

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