

## Clinical Efficacy of Belotecan (CKD-602), Newly Developed Camptothecin Analog, in the 2nd Line Treatment of Relapsed Small Cell Lung Cancer

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### 재발된 소세포폐암환자에서 이차 약제로 사용되는 Belotecan (CKD-602)의 임상적 효용성

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**연구배경:** Belotecan (Camtobell, CKD-602, Chongkundang Pharm., Korea)은 camptothecin의 치환체로 topoisomerase I 효소를 억제하여 항암효과를 나타내는 것으로 알려져 있다. 이에 2차 항암화학요법에 치료제로써 Belotecan의 효과, 생존율 및 부작용에 대해 연구하였다.

**방 법:** 이에 소세포폐암에서 etoposide와 platinum을 사용한 1차 항암화학요법에서 실패한 49명의 환자들을 대상으로 2차 항암화학요법에 Belotecan을 투약하였다.

**결 과:** 전체 반응률은 25%였으며, 11명의 환자에서 partial response를 보였다. 또한 1차 항암화학요법 이후 90일 이내에 재발한 군과 90일 이상 경과한 군간에 유의한 차이는 보이지 않았다. 전체 환자의 중증생존기간은 10.3개월(290일)이었고, 비반응군에서는 186일(95% CI; 67~305)로 반응군의 471일(95% CI; 234~568)에 비해 생존기간의 감소 유의하게 있음을 확인하였다(p=0.07).

**결 론:** 2차 항암화학요법의 치료제로써 Belotecan의 효능과 부작용에 대해서는 향후 무작위 비교 연구가 필요할 것으로 사료된다.

**Key Words:** Belotecan, Camptothecin, Small cell lung carcinoma, Relapse

### Introduction

Small cell lung cancer (SCLC) accounts for 14% of new lung cancer cases, or about 77,000 of the estimated 550,000 lung cancers in the USA and Europe in 2004<sup>1</sup>. Chemotherapy is the main treatment option for patients

with SCLC, leading to a 5-year survival of about 20% in limited disease (LD), and less than 5% in extensive disease (ED). Although initial tumor response rate to Etoposide and Cisplatin combination (EP) chemotherapy is very high<sup>2</sup>, the vast majority of SCLC patients relapses in approximately 4 months in ED and 12 months in LD after completion of first-line chemotherapy<sup>3</sup>.

These relapsed small cell lung cancers have been treated by camptothecin analogues and Topotecan has been extensively tested in the second-line therapy of SCLC. In a phase II Study of Topotecan, overall response rate and median survival were 6.4% and 4.7

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months in refractory relapse, 37.8% and 6.9 months in sensitive relapse patients<sup>4</sup>. Belotecan (Camtobell, CKD-602, Chongkundang Pharm., Seoul, Korea), newly developed camptothecin analog derived from *Camptotheca acuminata*, is a semi-synthetic and total synthetic water-soluble agent with targeting to topoisomerase I and activity various human tumor cell lines. Phase I studies, involving many different schedules of administration, have identified neutropenia as the dose-limiting toxicity and enabled identification of 0.5 mg/m<sup>2</sup>/d intravenously daily for 5 days repeated every 21 days, as the recommended dose and schedule for phase II studies. But, the clinical results of belotecan have not been published sufficiently. To aim of this study is to assess response rate, hematologic and non hematologic toxicity and overall clinical experiences of belotecan.

## Materials and Methods

### 1. Patients

The eligible patients for this study were required to meet all of the following criteria: 1) Histologically or cytologically confirmed SCLC, 2) progressive disease after one first-line chemotherapy not including camptothecin analogues, 3) age 18~80 years inclusive, 4) ECOG Performance score below 2, 5) life expectancy above 3 months, and 6) written informed consent, 7) presence of at least one bidimensionally measurable disease, 8) WBC count greater than  $3,500 \times 10^9/L$ , absolute granulocyte count  $\geq 1,500 \times 10^9/L$ , hemoglobin  $\geq 9.0$  g/dl, platelet  $\geq 100 \times 10^9/L$ , 9) total bilirubin level  $\leq 1.5$  mg/dl, AST and ALT  $\leq$  two times the upper normal limit in absence of liver metastasis, creatinine level  $\leq 1.5$  mg/dl and a calculated creatinine clearance  $>60$  ml/min. Patients with increased bilirubin (up to 2.5 times the upper normal limit) because of liver metastases were also considered eligible. Patients must have been off all previous systemic chemotherapy at least 3 weeks before study entry and must have recovered from the side effects of prior therapy. Patients with brain metastases were eligible provided that neurologic symptoms were under control with radiotherapy or steroid

treatment, and the brain was not the only site of assessable disease.

### 2. Treatment

Belotecan (CKD-602) was administered intravenously, 0.5 mg/m<sup>2</sup>/d (diluted in 100 ml of 5% dextrose water) as a 30-minute infusion for 5 consecutive days. Chemotherapy treatment schedule were repeated every 3 weeks if neutrophil count was more than or equal to  $1.5 \times 10^9/L$ , the platelet count was more than or equal to  $100 \times 10^9/L$  and recovery to Common Toxicity Criteria (CTC) grade I nonhematologic toxicity had occurred. Belotecan dose reduction 0.1 mg/m<sup>2</sup>/d was to be performed in case of grade IV neutropenia complicated by fever or lasting 7 days or longer, grade III neutropenia lasting beyond day 21 of the treatment cycle, or grade IV thrombocytopenia. Also same dose reduction were applied to grade III or IV nonhematologic toxicity (excluding grade III Nausea), or the patient could be withdrawn from the study.

### 3. Response, toxicity and survival evaluation

To evaluate the Responses of tumor lesions and toxicity profiles, we monitored chest radiography, computed tomography (CT) scans, complete blood cell counts, and blood chemistries. The response could be evaluated in 42 patients who were treated with belotecan above 1 cycle. And we observed overall response rate, survival and toxicities of belotecan monotherapy (0.5 mg/m<sup>2</sup> for 5 days every 21 days) after failure of etoposide and platinum (EP).

### 4. Statistical analysis

Statistical analyses were done using SPSS for Window version 12.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, frequency tables,  $\chi^2$  tests were used.

Survival time and time to progression were recorded as days from the beginning of belotecan treatment. Kaplan-Meier method was used to calculate survival and time to progression according to predictors were done using a log-rank test.

## Results

### 1. Patients demographics

From Aug 2004 to Oct 2006, the 49 patients were entered onto the study and 44 patients could be evaluated the response and toxicity profiles. 5 patients could not follow up on the response. Reason for loss to follow-up were death and poor physical status. The characteristics of enrolled patients are summarized in Table 1. The mean age of  $64.5 \pm 7.6$  (mean  $\pm$  SD) years. All of patients were treated by etoposide and platinum combination chemotherapy (EP) as first-line chemotherapy. Responses to previous first-line chemotherapy (etoposide/platinum) were partial remission (PR) in 29, stable disease (SD) in 7, progression (PD) in 9, and not evaluable in 4 cases. 21 patients showed relapse more than 90 days after prior EP therapy (sensitive relapse, SR) and 28 patients relapsed within 90 days after prior chemotherapy (refractory relapse, RR).

### 2. Dose intensity

Dose intensity was calculated as the sum of the daily doses delivered during the course divided by the dura-

tion of the course in weeks. Relative dose intensity was  $78 \pm 15\%$  in responders and  $83 \pm 13\%$  in non-responders ( $p=0.03$ ).

### 3. Clinical response of belotecan treatment

Within the 49 eligible patients, 5 patients could not be evaluated for response because of inadequate radiologic assessment. After receiving belotecan above at least 1 cycle of the 44 assessable patients, 11 patients showed partial remission, 19 patients remained stable, and 10 patients showed progression of their disease. The overall response rate was 25% (11/44) and the disease control rate (partial remission+stable disease) was 75%. There were no significant difference in response rate between sensitive and refractory patients group (6 PRs, 10 SDs and 4 PDs in sensitive relapses; 5 PRs, 12 SDs and 7 PDs in refractory patients).

### 4. Survival time

Median survival time (MST) from the beginning of belotecan treatment was 10,3 months (290 days). MST of non-responders were 186 days (95% CI; 67~305), while responders were 401 days (95% CI; 234~568,  $p=0.07$ ) (Figure 1). MST was not different between SR (290

Table 1. Characteristics of subjects

Number (N) of patients	49
Age (mean $\pm$ SD, range, yr)	$64.5 \pm 7.6$
N < 65 (yr)	21
N $\geq$ 65 (yr)	28
Sex (Male/Female)	41/8
Smoking history	
Never-smoker	8
Ex-smoker	4
Current smoker	37
Response to first-line chemotherapy	
PR / SD / PD / not evaluable	29/7/9/4
Initial stage	
Limited stage	21
Extensive stage	28
Interval between end of prior chemotherapy and start of belotecan, months	
> 3	21
< 3	28

PR: partial remission; SD: stable disease; PD: progression.

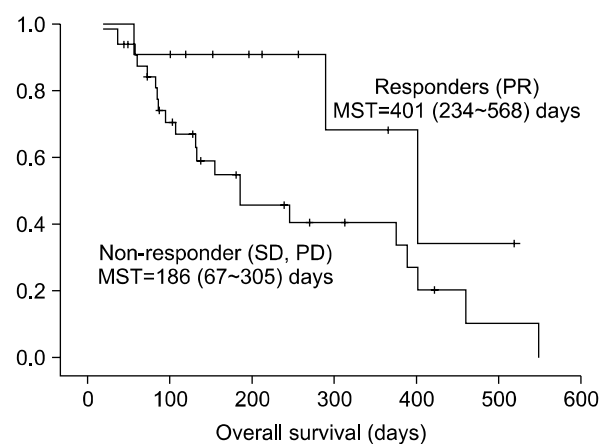
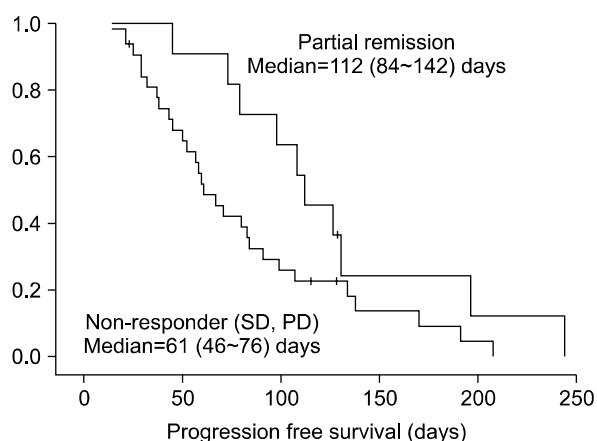


Figure 1. Overall survival in responders. The figure showed better overall survival in responders with belotecan compared to in non-responders: mean survival time of non-responders was 186 days (95% CI; 67~305), while was 401 days in responders (95% CI; 234~568,  $p=0.07$ ).



**Figure 2.** Progression free survival showed tendency of better survival in responders: median progression free survival of responders was 112 days in contrast to 61 days of non-responders ( $p=0.06$ ).

days) and RR (376 days). Median progression free survival (MPFS) was 73 days (95% CI; 48~98 days). MPFS of responders was 112 days in contrast to 61 days of non-responders ( $p=0.06$ , Figure 2). MPFS was not different between SR (79 days) and RR (67 days).

## 5. Toxicity

Grade III~IV neutropenia, anemia, and thrombocytopenia were experienced by 59.6%, 12.8% and 23.4% of belotecan patients. And the severity of non-hematologic toxicity is generally mild. In our study, the grade III~IV nausea, vomiting, and myalgia have not been experienced.

## Discussion

The overall survival of small cell lung cancer patients has not been increased in spite of high response rate to initial chemotherapy<sup>5</sup>. In the relapsed patient after first-line chemotherapy, survival for patients on supportive care is not sufficiently long. But world-wide used second line chemotherapeutic agents showed somewhat improving survival and cancer related symptoms<sup>6</sup>.

Belotecan, novel camptothecin derivative agent, is a cytotoxic alkaloid that is extracted from leaves of *Camptotheca acuminata*, which is a tree endemic in

China. The preclinical studies showed the equivalent or superior to those of camptothecin and topotecan in the tumor cell cytotoxicity<sup>7</sup>.

In phase II study of topotecan, the overall response rate was 37.8% and median survival of 5.4 months<sup>4,5</sup>. Ardizzoni et al.<sup>4</sup> also reported 74.9% of grade III/IV neutropenia, 29.5% of grade III/IV thrombocytopenia and mild nonhematologic adverse events. Also, von Pawel et al.<sup>8</sup> reported the overall response of 54% and median survival of 25 weeks.

Irinotecan is the other available topoisomerase I inhibitor. In the phase II clinical trials, irinotecan appears the 33.3% in the relapsed small cell lung cancer after first-line chemotherapy, also showed the major toxicities in hematologic complications and diarrhea.

In our study, the result of belotecan showed 25% of overall response rate and 75% of disease control rate in chemo-sensitive and resistant groups. This result was no inferiority compared with other topoisomerase I inhibitors.

The median survival and progression free survival (MPFS) of all patients was 10.3 months (290 days) and 73 days. We have analyzed the MST and MPFS to chemo-sensitive and resistant groups. The MST and MPFS show no significant differences between SR and RR. Eckardt et al.<sup>9</sup> reported an overall survival time of 30 weeks in the pooled analysis of 3 trials in which patients with chemo-sensitive SCLC were treated with topotecan. The median survival of these two studies showed the more reliable result in Belotecan treatment group. And we are following up survival time of remained responders.

In the other phase II clinical trials, Belotecan appears the 24% of overall objective response rates in the relapsed small cell lung cancer after first-line chemotherapy. Median follow-up duration of 6.3 months, median time to progression was 4.4 months (95% CI; 2.6~6.3) and median overall survival wasn't reached<sup>10</sup>. Overall response rate was not different with our results.

In conclusion, this result of belotecan, new camptothecin derivative, showed possibility of development of new chemotherapeutic agent in small cell lung cancer,

which warrants the comparative study between belotecan and other camptothecins.

### Summary

**Background:** Belotecan (Camtobell, CKD-602, Chongkundang Pharm., Korea), a camptothecin derivative, has anticancer effects by inhibiting topoisomerase I such as topotecan. This study observed the response, survival and toxicity of belotecan monotherapy after the failure of etoposide and platinum (EP).

**Methods:** Forty nine small cell lung cancer (SCLC) patients (M/F=41/8; age,  $64.5 \pm 7.6$  (mean  $\pm$  SD) years), who failed in their first line chemotherapy were enrolled in this study. Twenty one SCLC patients showed relapsed lung cancer more than 90 days after their prior EP chemotherapy (sensitive relapse group, SR) and 28 patients relapsed within 90 days (refractory relapse group, RR).

**Results:** The response rate was 25%. Eleven patients showed partial responses and 5 patients could not be checked. The response rate of the SR and RR patients was similar. The relative dose intensity was lower in the responders ( $78 \pm 15\%$ ) than non-responders ( $83 \pm 13\%$ ,  $p=0.03$ ). The median survival time (MST) was 10.3 months (290 days). The MST of the non-responders and responders was 186 days (95% CI; 67~305) and 401 days (95% CI; 234~568,  $p=0.07$ ), respectively. The median progression free survival (MPFS) was similar in the SR (79 days) and RR (67 days) patients. Grade 3~4 neutropenia, anemia, and thrombocytopenia were observed in 59.6%, 12.8% and 23.4% of patients, respectively.

**Conclusion:** The efficacy and survival were demonstrated in the second-line setting. However, a randomized comparative trial with topotecan will be needed.

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