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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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. 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, the vast majority of SCLC patients relapses in approximately 4 months in ED and 12 months in LD after completion of first-line chemotherapy.

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. Belotecan (Camtobell, CKD-602, Chongkundang Pharm., Seoul, Korea), newly developed camptothecin analog derived from *Camptotheca acuminate*, 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/m²/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 3,500×10⁹/L, absolute granulocyte count ≥1,500×10⁹/L, hemoglobin ≥9.0 g/dl, platelet ≥100×10⁹/L, 9) total bilirubin level ≤1.5 mg/dl, AST and ALT ≤two times the upper normal limit in absence of liver metastasis, creatinine level ≤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/m²/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 1.5×10⁹/L, the platelet count was more than or equal to 100×10⁹/L and recovery to Common Toxicity Criteria (CTC) grade I nonhematologic toxicity had occurred. Belotecan dose reduction 0.1 mg/m²/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/m² 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, x² 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.