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A multicenter phase II study of belotecan, new camptothecin analogue, in patients with previously untreated extensive stage disease small cell lung cancer

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ABSTRACT

Belotecan (Camtobell, CKD602) is a new camptothecin derivative antitumor agent that belongs to the topoisomerase inhibitors. The aim of this phase II study was to evaluate the efficacy and safety of single agent belotecan in patients with small cell lung cancer (SCLC).

Patients with previously untreated extensive stage disease (ED) SCLC were entered into the study. Belotecan was given by daily intravenous infusion at 0.5 mg/m^2/day for 5 consecutive days, every 3 weeks.

62 patients were enrolled in this study. The overall response rate to chemotherapy on an intention-to-treat basis was 53.2%. The median overall survival was 10.4 months, the median time to progression 4.6 months, and the 1-year survival rate 49.9%. The most common toxicity was hematologic. Grade 3/4 neutropenia occurred in 71.0% of patients and grade 3/4 thrombocytopenia 12.9%. Non-hematologic toxicity of grade 3 or 4 was low.

The results suggest that belotecan is relatively active and well tolerable as single agent in patients with ED SCLC. Further investigations with platinum or other active agents are needed.

1. Introduction

Small cell lung cancer (SCLC) is extremely aggressive, frequently associated with distant metastases, and has the poorest prognosis of all lung neoplasms. In two-thirds of cases it presents initially as extensive stage disease (ED). Combination chemotherapy is a mainstay treatment of ED SCLC, and the combination of etoposide and cisplatin remains the most widely used regimen. Initial response rate is high but few survive beyond 2 years [1]. Clearly, new and more effective agents against SCLC are needed.

Belotecan (Camtobell; CKD602, 7-[-2(N-isopropylamino)ethyl]-(20S)-camptothecin, Chong Keun Dang Corp., Seoul, Korea) is a new camptothecin analogue, and a potent topoisomerase I inhibitor [2]. In the preclinical studies, belotecan had a more potent activity and lower toxicity than other camptotecin anticancer agents [3,4]. In a phase I study of belotecan, the maximum tolerated dose was 0.7 mg/m^2/day when administered daily for 5 consecutive days every 3 weeks and dose-limiting toxicity was neutropenia without other severe toxicity [4].

We conducted a multicenter phase II study to investigate the efficacy and toxicity profile of single agent belotecan in patients with previously untreated ED SCLC.

2. Patients and methods

2.1. Eligibility

The main eligibility criteria included histologically confirmed SCLC, previously untreated patients with extensive stage disease at the diagnosis and ECOG performance status ≤2. The other inclusion criteria were as follows: age ≥18; at least one unidimensionally measurable lesion; adequate bone marrow, hepatic and renal functions defined as absolute neutrophil count (ANC) ≥1500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9 g/dl, alanine aminotransferase/aspartate aminotransferase ≤2.0 times the upper normal limit, serum bilirubin ≤1.5 mg/dl, and serum cre-

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atinine ≤1.5 mg/dl. All patients gave a written informed consent approved by the Institutional Review Board or Ethical Committee of all participating institutions. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Study design

This was an open-label, multicenter, phase II study of single belotecan for patients with ED SCLC. Belotecan was to be diluted in a total volume of 100 ml of 5% dextrose water and administered i.v. for 30 min once a day on days 1–5 of a 3-week course. The dose of belotecan was 0.5 mg/m^2/day at the first cycle, but a dose adjustment for the subsequent cycles would be made according to the greatest degree of toxicity developed during the first cycle. However, after the dose adjustment would be made, further dose increment or reduction would not be allowed. The dose would be adjusted as follows: the dose would be decreased to 0.4 mg/m^2/day when (i) ANC nadir of <500/mm^3 for 4 days or more, (ii) febrile neutropenia, (iii) platelet nadir of <50,000/mm^3 for 4 days or more, (iv) thrombocytopenia associated with bleeding episode or requiring transfusion, or (v) grade 3 or higher non-hematologic toxicity except alopecia, nausea and vomiting; the dose would be increased to 0.6 mg/m^2/day when ANC nadir of ≥1000/mm^3, platelet nadir of ≥75,000/mm^3 and no grade 3 or higher non-hematologic toxicity; otherwise, the same dose of 0.5 mg/m^2/day was given. A new scheduled cycle could be administered if ANC was ≥1500 mm^3, platelets was ≥100,000/mm^3, and all non-hematologic toxic effects except alopecia, nausea and vomiting recovered to grade 0 or 1. Otherwise, a new cycle should be delayed for up to 2 weeks. The treatment could be given until progressive disease (PD), unacceptable toxicity including treatment interruption for >2 weeks, or patient's withdrawal.

As a baseline, all patients underwent a complete history and physical examination, including documentation of concomitant medications, performance status and history of smoking, laboratory tests (complete blood count, biochemistry profile, and urinalysis), and electrocardiogram within 14 days before the study entry. Chest X-ray, computed tomography scans of chest (including upper abdomen), magnetic resonance imaging of brain, and radionuclide bone scan were carried out within 4 weeks before the study entry.

2.3. Response and toxicity assessment

Tumor responses were classified every three cycles according to the following response evaluation criteria in solid tumors (RECIST) guidelines [5]; complete response (CR), the disappearance of all target lesions; partial response (PR), a decrease of at least 30% in the sum of the longest diameters of the target lesions; progressive disease (PD), an increase of at least 20% in the sum of the longest diameters of the target lesions or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0. Overall survival (OS) was defined as the interval between the date treatment started and the date of death due to any cause. Time to progression (TTP) was defined as the interval between the date treatment started and the date of documented disease progression or death from any cause.

2.4. Statistical analysis methods

This trial was designed to detect a response rate of 70% as compared to a minimal, clinically meaningful response rate of 50%. This trial used a two-stage optimal design, as proposed by Simon [6], with a 80% power to accept the hypothesis and 5% significance to reject the hypothesis. Allowing for a follow-up loss rate of 20%, the total sample size was 62 patients with a measurable disease. Survival curves were calculated and graphically presented using the Kaplan–Meier method. Median survival time, median time to progression and the 1-year survival rate were obtained from the Kaplan–Meier survival curves. Statistical analyses were performed using the statistical packages SAS for Windows Version 8.02.

3. Results

3.1. Patients' characteristics

From January 2005 to June 2007, a total of 62 patients were entered into the study. The characteristics of the patients are listed in Table 1. Out of 62 patients, 53 were assessable for overall response rate. However, all patients received at least one cycle were assessable for toxicity. The dose for the subsequent cycles was adjusted to 0.6 mg/m^2/day in 6 patients, 0.5 mg/m^2/day in 37 patients, and 0.4 mg/m^2/day in 10 patients.

3.2. Response and survival outcome

Nine patients were not assessable; three of them were lost during follow-up; three were non-compliant; one died as a result of sudden developed asphyxia; one who had previously bronchiectasis died due to severe hyponatremia and acute right heart failure which might be due to myocardial infarction; one died due to sepsis initially not related with neutropenia. Of 53 patients assessable, 33 had an objective tumor response, including one CR, for an overall response rate of 53.2% (Table 2). From the total enrolled 62 patients, the median overall survival was 10.4 months and the median time to progression was 4.6 months (Fig. 1). The 1-year survival rate was 49.9%.

Table 1
Patient characteristics.

Characteristic	No. of patients	%
Total enrolled	62	100
Eligible for response	53	85.4
Age (years)		
Median (range)	65.5 (36–86)	
Gender		
Male	49	79.0
Female	13	20.9
Performance status (ECOG)		
0	8	12.9
1	48	77.4
2	6	9.6
Prior therapy		
No	62	100

ECOG: Eastern Cooperative Oncology Group.

Table 2
Overall response for treatment (intention-to-treat analysis).

	No. of patients
Total number of patients	62
Complete response (CR)	1 (1.6%) 95% CI 0.08–9.83%
Partial response (PR)	32 (51.6%) 95% CI 38.68–64.34%
Stable disease (SD)	10 (16.1%) 95% CI 8.41–28.12%
Progressive disease (PD)	10 (16.1%) 95% CI 8.41–28.12%
Not evaluable (NE)	9 (14.5%)
Overall response rate (CR + PR)	33 (53.2%) 95% CI 40.21–65.83%