Efficacy and Toxicity of Belotecan for Relapsed or Refractory Small Cell Lung Cancer Patients

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Introduction: Belotecan (Camtobell, CKD602) is a new camptothecin-derivative antitumor agent that belongs to the topoisomerase inhibitors. The aim of this study was to evaluate the efficacy and safety of belotecan monotherapy as a second-line therapy in patients with relapsed or refractory small cell lung cancer (SCLC).

Methods: Between June 2008 and August 2011, a total of 50 patients with relapsed or refractory SCLC were treated with belotecan 0.5mg/m^2 for 5 consecutive days, every 3 weeks. We evaluated the overall response rate (ORR), the progression-free survival (PFS), and the overall survival (OS), and toxicity according to sensitivity to initial chemotherapy.

Results: The median age was 66 years (range, 43–84 years) and Eastern Cooperative Oncology Group performance was 0 or 1 in 34 patients (68%) and 2 in 16 patients (32%). Twenty patients (40%) had sensitive relapse and 30 patients (60%) had refractory disease. The ORR, PFS, and OS for sensitive patients were 20% (95% confidence interval [CI], 8–40), 2.8 months (95% CI, 0.53–5.06), and 6.5 months (95% CI, 1.58–11.42), respectively. In the refractory group, the ORR, PFS, and OS were 10% (95% CI, 1–21), 1.5 months (95% CI, 1.25–1.75), and 4.0 months (95% CI, 3.40–4.60), respectively. Most commonly reported grade-3 or -4 adverse events included neutropenia (54%), thrombocytopenia (38%), and anemia (32%).

Conclusion: Belotecan showed modest activity with an acceptable safety profile as a second-line therapy in patients with relapsed or refractory SCLC.

Key Words: Belotecan, Relapsed, Refractory, Small cell lung cancer.

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Small cell lung cancer (SCLC) comprises approximately 15% of all lung cancers and is strongly associated with smoking.[1] SCLC is highly responsive to initial chemotherapy or radiotherapy. However, approximately 80% of the limited-stage and nearly all extensive-stage patients develop recurrence. The patients who relapse after initial chemotherapy have a poor prognosis. The median survival is 2 to 3 months for the patients who do not receive salvage therapy.[2] The results of second-line chemotherapy are also disappointing, with low response rates and short survival times.[3]

The efficacy of salvage chemotherapy depends on the response and the duration of the response to initial chemotherapy. The patients who recur more than 3 months after completion of the initial therapy are often termed as "sensitive relapse" patients. In contrast, the patients whose tumor does not respond or progress through treatment or who develop a recurrence within 3 months after completion of initial therapy are considered to be "refractory or resistant relapse" patients. Refractory patients have a dismal prognosis, with a survival of 3 to 5 months and overall response rates (ORRs) of approximately 10% or less.[4]

Currently, topotecan is the only drug approved for single-agent second-line SCLC treatment in the United States and is considered the standard second-line regimen in many countries. Topotecan showed an ORR of 24% and a median overall survival (OS) of 6 months in sensitive patients. However, topotecan seems to have only minimal activity in refractory disease, producing ORRs of 4 to 12% and an OS of 3.4 to 5.8 months.[4-6] In terms of toxicity, topotecan showed significant adverse events, including grade-3 or -4 myelosuppression (neutropenia, 86–89%, thrombocytopenia, 43–57%, and anemia 31–40%), diarrhea (6–8%), and fatigue (5–8%).[4-8] More recently, amrubicin has shown favorable efficacy in relapsed SCLC patients (ORR, 17–60%, median survival, 5.3–12 months) and is also currently in phase-III clinical evaluations.[9-12] Therefore, the development of new strategies for the management of this disease is urgently needed.

Belotecan (Camtobell, CKD602, 7-[-2(N-isopropylamino)ethyl]-(20S)-camptothecin, Chong Keun Dang Corp., Seoul, Korea) is a new camptothecin analog, in which a water-solubilizing group is introduced at the position of the B ring.[13] In the preclinical studies, belotecan was a more potent topoisomerase-I inhibitor and had superior antitumor activity compared to other camptothecin agents including topotecan.

Recently, several phase-II trials showed that belotecan was active and well tolerated as a single agent or in combination with cisplatin in untreated patients with SCLC.[14,17] Two phase-II trials of belotecan in second-line treatment of SCLC also showed modest efficacy and tolerable toxicity.[18,19] However, these two studies had a small number of patients and had little data for refractory patients. One had only sensitive-relapsed patients (n = 27) and the other study (n = 25) had no information on the type of relapse. Therefore, we evaluated the efficacy and toxicity of belotecan as a second-line chemotherapy for a relatively large number of patients with relapsed or refractory SCLC.

PATIENTS AND METHODS

Data Source and Analytic Variables

Between June 2008 and August 2011, we identified 56 patients who received belotecan monotherapy for refractory or relapsed SCLC at the Yonsei Cancer Center, Seoul, Korea. We excluded one patient who received the first-line chemotherapy after surgery and those who received a belotecan as third-line or later-line settings. Thus, 50 patients were left for analysis. We retrospectively collected and analyzed the data of these patients.

Patient characteristics were sex, age, performance status, stage at diagnosis, initial chemotherapy regimen, the response of the initial chemotherapy, and the duration of the response to initial chemotherapy. A complete history of the treatment each patient had received for SCLC was recorded, including the start and stop dates of chemotherapy, dose of chemotherapy agents, reason for discontinuation, best response, and date of progressive disease (PD). The study was approved by the Institutional Review Board of the Severance Hospital.

Treatment

Belotecan was administered intravenously for more than 30 minutes once a day on days 1 to 5 for every 3 weeks. The dose of belotecan was 0.5 mg/m^2/d during the first cycle, but a dose adjustment for the subsequent cycles was made according to the greatest degree of toxicity developed during the previous cycle. The dose was adjusted as follows: the dose would be decreased to 0.4 mg/m^2/d in the event of (1) absolute neutrophil count nadir of less than 500 /mm^3 for 4 days or more (2) febrile neutropenia (3) platelet nadir of less than 50,000 /mm^3 for 4 days or more (4) thrombocytopenia associated with bleeding episode or requiring transfusion or (5) grade-3 or higher nonhematological toxicity except alopecia, nausea, and vomiting. Dose increment was not allowed. The next cycle of treatment was started when absolute neutrophil count was 1500/mm^3, platelet count was 100,000/mm^3, and all nonhematologic toxicity except alopecia, nausea, and vomiting recovered to grade 2 or less. Otherwise, the next cycle would be delayed for up to 3 weeks. Granulocyte colony-stimulating factor was used as a therapeutic intervention for neutropenia but not used as a prophylactic. Treatment was continued until one of the following events occurred: PD, termination of treatment by the physician, and unacceptable toxicity which makes treatment interruption for more than 3 weeks.

Evaluation

All patients underwent a history-taking and physical examination, including documentation of concomitant medications, performance status, and history of smoking, laboratory tests (complete blood count, biochemistry profile, and urinalysis), and computed tomography scans of chest and abdomen electrocardiogram before the start of belotecan monotherapy. Tumor assessments were carried out once every two cycles. Toxicity was assessed twice every cycle (D+1 and D+14). Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors version 1.0.

Statistical Consideration

We analyzed the ORR, PFS, OS, and toxicity profiles. The distribution of baseline patient characteristics and a relapse pattern was evaluated by using Mantel-Haenszel χ^2 tests for categorical variables and analysis of variance for continuous variables. We performed univariate and multivariate logistic regressions to evaluate the association between the patient characteristics and the efficacy. Survival curves were generated using the Kaplan Meier method and compared by the log rank test. Logistic regression and Cox's proportional hazard model were used to determine the contribution of the clinico-pathological factors to response and survival, respectively. All tests were two-sided, with a p-value of less than 0.05 being considered statistically significant. The data were presented with 95% CIs and calculated using standard methods based on a binomial distribution. Data analysis was done by the SPSS software (version 18.0).

RESULTS

Patient Characteristics

From June 2008 to August 2011, a total of 50 patients were treated with belotecan monotherapy as a second-line treatment for relapsed or refractory SCLC. The baseline characteristics of the patients are listed in Table 1. Four patients were women and 46 were men, and their median age was 66 years (range, 43–84 years). Among the 50 patients, 34 (68%) had a PS of 0 or 1 before belotecan monotherapy. Sixteen patients (32%) had limited disease at diagnosis. Thirteen patients had received thoracic irradiation simultaneously with first-line chemotherapy. Twenty patients (40%) had sensitive relapse and 30 patients (60%) had refractory relapse. Almost all the patients (98%) had received etoposide-containing chemotherapy and two patients had received an irinotecan-based regimen.

Treatment Delivery

Two patients died during the first cycle of treatment because of PD. Therefore, 48 patients received more than one cycle of treatment. In total, 130 cycles of treatment (68 cycles for sensitive group and 62 cycles for refractory group) were administered, with a median of two cycles (range, one to nine cycles). The median duration of treatment was 6.5 weeks