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Phase II Study of Topotecan and Etoposide as Second-line Treatment in Chemotherapy-refractory Small-cell Lung Cancer

Chul Kim, M.D.[1], **Joo Hyuk Sohn**, M.D.[1], **Joo Hang Kim**, M.D.[1], **Se Kyu Kim**, M.D.[2], **Young Sam Kim**, M.D.[2], **Joon Chang**, M.D.[2] and **Jae Yong Cho**, M.D.[3]

[1]Yonsei Cancer Center, Department of Internal Medicine, [2]The Institute of Chest Disease, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Medical Oncology, Yong-Dong Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Purpose: **Refractory small-cell lung cancer (SCLC) has a poor prognosis, and current salvage chemotherapy for refractory SCLC, such as CAV (cyclophosphamide, adriamycin, vincristine) or topotecan, has an unsatisfactory outcome, with a response rate and overall survival of less than 10% and 6 months, respectively. This phase II study evaluated the role of topotecan combined with etoposide in SCLC patients that have progressed, or relapsed, within 3 months following completion of the initial chemotherapy.**

Materials and Methods: **Twenty-seven patients were entered into this study. Eligible patients had an ECOG performance status of less than, or equal to, 2, at least one bidimensionally measurable lesion and adequate end organ function. IV topotecan, 1.0 mg/m^2/d for 5 consecutive days, and etoposide, 100 mg/m^2/d through days 1 to 3, were administered every 3 weeks until disease progression or undue toxicity.**

Results: **The major toxicity was myelosuppression. Grade 3/4 anemia, granulocytopenia, and thrombocytopenia occurred in 14.2, 34.8, and 27.3% of cycles, respectively. There was no treatment-related death, and other non-hematologic toxicities were generally mild. Four patients achieved partial responses, with a response rate RR of 14.8%. The progression-free survival PFS ranged from 1 to 7 months, with a median of 2.0 months (95% confidence interval 1.22～2.78 months). Twenty-five patients died, with a median overall survival of 5.5 months (ranging from 1 to 21 months, 95% CI 4.32～6.68 months), and the 6-month survival rate was 32.1% (95% confidence interval 14.4～49.8%).**

Conclusion: **The combination of topotecan and etoposide chemotherapy showed a modest response rate, but failed to prolong survival of refractory SCLC patients compared to topotecan monotherapy.** ***(Cancer Research and Treatment 2002;34:334-338)***

Key Words: **Lung neoplasm, Small cell carcinoma, Combination chemotherapy, Topotecan, Etoposide**

INTRODUCTION

Small-cell lung cancer (SCLC) comprises approximately 20% of all primary malignancies of the lung (1,2). Although SCLC responds favorably to current chemotherapy and radiation treatment initially, the overall prognosis remains very poor, with 5-year survival of less than 5% due to the short response duration, high relapse rate and intrinsic or acquired drug resistance (3,4). The response of recurrent, or progressed, SCLC to second-line chemotherapy depends on the interval between the completion of the first chemotherapy and appearance of the progressive disease (5,6). For patients who develop tumor progression during, or shortly after, the initial chemotherapy, the response to salvage chemotherapy remains very poor, with SCLC being almost uniformly fatal. Hence, there is a strong need for non-cross-resistant therapeutic options in the salvage settings.

CAV (Cyclophosphamide, Adriamycin and Vincristine) has been used as a second-line treatment in relapsed SCLC patients who were primarily treated with a platinum containing regimen (7～9). Other agents reported to be active as second-line treatments include carboplatin, ifosfamide and paclitaxel, although their reported response rates have been variable, and generally unsatisfactory (10～12).

Topotecan is a water-soluble, semisynthetic analogue of the alkaloid *camptothecin* and exerts a tumoricidal effect through inhibition of the nuclear enzyme DNA topoisomerase I. This compound has been found to be active against a number of tumor models *in vitro* and in animal xenografts, and has been introduced into clinical use for cisplatin-refractory ovarian cancer. After the Eastern Cooperative Oncology Group conducted a phase II trial on topotecan in extensive stage SCLC, which reported an overall response rate and median survival of

Correspondence: Jae Yong Cho, Department of Medical Oncology, Yong-Dong Severance Hospital, Yonsei University College of Medicine, 146-92 Dogok-dong, Kangnam-gu, Seoul 135-720, Korea. (Tel) +82-2-3497-3310, (Fax) +82-2-3463-3882, (E-mail) chojy@yumc.yonsei.ac.kr

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39% and 10 months, respectively (13), there have been many investigations on the efficacy and toxicities of topotecan in the primary and second-line treatment of SCLC (6,14).

The response to topotecan in the treatment of chemosensitive, relapsed SCLC is at least comparable to other second-line treatments (15,16), but is disappointing in primarily refractory or early-relapse patients, with a response rate of less than 11% and a survival of less than 20 weeks, respectively (17). So another approach, such as its combination with other chemotherapeutics, is needed. Etoposide is a topoisomerase II inhibitor, with intrinsic activity against SCLC, and preclinical studies have shown that combined or sequential use of topoisomerase I and II inhibitors can increase the activity of chemotherapy (18～20). Therefore, we evaluated the therapeutic role and toxicities of topotecan and etoposide in combination in the treatment of refractory or early-relapse SCLC.

MATERIALS AND METHODS

The primary objective of this study was to evaluate the response and time to progression of limited and extensive SCLC, in patients who were classified as refractory to initial chemotherapy, when treated with IV topotecan and etoposide. Refractory patients were defined as those who relapsed within 3 months of the completion of first-line chemotherapy or whose condition progressed during chemotherapy. The secondary objective was to evaluate the survival, hematological and non-hematological toxicities, in patients treated with this regimen.

Patients of both sexes, aged over 20 years, with limited or extensive, histologically proven SCLC, whose condition had progressed or relapsed within 3 months of completion of the first chemotherapy, were entered into this study. At least one lesion had to be bidimensionally measurable by computed tomography, magnetic resonance imaging, radiograph or physical examination. Other criteria for eligibility included an ECOG performance status of less than or equal to 2, hemoglobin more than 9.0 g/dl, a WBC count more than, or equal to, 3.5×10^9/l, neutrophils more than, or equal to, 1.5×10^9/l, platelets more than, or equal to, 100×10^9/l, transaminase and alkaline phosphatase levels less than, or equal to, 2.5 times the normal upper limit, bilirubin less than, or equal to, 1.5 times the normal upper limit , and creatinine less than, or equal to, 1.5 mg/dl or creatinine clearance more than, or equal to, 50 ml/min. Patients with symptomatic brain or leptomeningeal metastasis, requiring corticosteroid, were excluded. The presence of other severe uncontrolled medical problems also precluded a patient from entering the study.

Patients were treated with topotecan, 1.0 mg/m^2/d, administered as a 30-minute infusion for 5 consecutive days, and etoposide, 100 mg/m^2/d, infused intravenously for 2 hours through days 1 day 3 every 21 days. Full doses were administered if the treatment day neutrophil count was more than, or equal to, 1.5×10^9/l, the platelet count was more than, or equal to, 100×10^9/l, and the hemoglobin was more than, or equal to, 9.0 g/dl. The duration of treatment depended on the patient's response to therapy, but it was recommended that patients with a stable disease remained on the therapy for at least four cycles providing their tolerability was good.

Lesions were measured by CT or MRI scan and x-ray or physical examination, with the same diagnostic technique being used throughout the study. Radiographic measurements were performed before each alternate course, except for those lesions evaluated by physical examination, which were measured before every course.

Responses were determined according to the World Health Organization criteria, and patients had to have completed at least one 5-day treatment course to be considered for evaluation. A complete response (CR) or partial response (PR) was defined as the disappearance or a decrease of more than 50% in measurable lesions, respectively, lasting at least 4 weeks with no appearance of new lesions. The progression-free, and overall, survivals were measured from the first administration of topotecan, until evidence of progression or death, respectively.

The major treatment-related toxicities were assessed using the National Cancer Institute common toxicity criteria (NCICTC).

The patients who received at least two cycles of treatment underwent assessment for their response, unless they had definite evidence of progression following first cycle. Those patients showing definite progression after one cycle of treatment, but failed to complete the evaluation process, were categorized as having a progressive disease (PD), and those having received at least one cycle of treatment were classed as assessable for toxicity. The actuarial survival was estimated by the product-limit method of Kaplan and Meier, with 95% confidence intervals (CI), and the 6-month survival rate was calculated from the binomial distribution.

RESULTS

1) Patient characteristics

The characteristics of the 27 patients entered into this phase II study are listed in Table 1. They were all pretreated with first-line carboplatin and ifosfamide chemotherapy, and had the progressive disease during, or within, the 3 months from the end of first-line chemotherapy, regardless of their initial responses to the first-line treatment. Sixteen Patients (59.3%) received radiotherapy to the thorax prior to entry to the study. All patients received at least one cycle of chemotherapy and were therefore assessable for toxicity, with 22 receiving at least two cycles of treatment, so were assessable for response. Five patients received at least one cycle of topotecan and etoposide, but failed to complete the post-treatment radiographic evaluation, but all 5 showed clinical evidence of progression.

2) Response to treatment and survival

Of the 27 patients who received at least one cycle of topotecan and etoposide chemotherapy, 22 were assessable for a response in the present study. The five patients not completing the post-treatment radiographic evaluation, but showing clinical deterioration, were all considered as having a progressive disease. There were 4 partial and no complete responses, with a response rate of 14.8% (intend-to-treat). The progression-free survival (PFS) ranged from 1 to 7 months, and

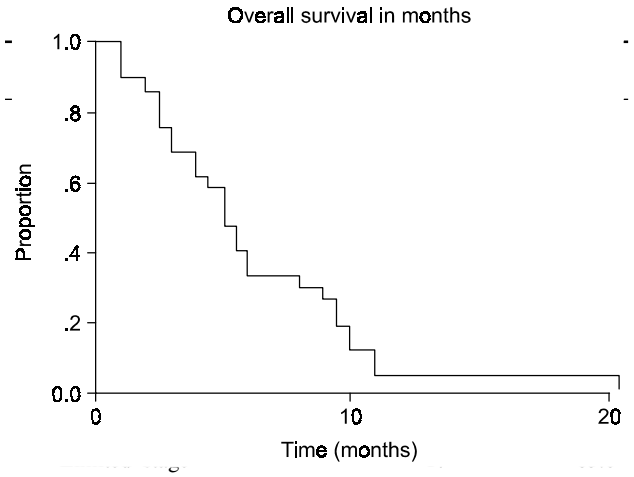

Fig. 1. Survival analysis of SCLC patients treated with topotecan-etoposide chemothearpy who progressed during or early after 1st-line chemotherapy (Kaplan-Meier plot).

Extensive stage	10	37.0
Prior treatment		
Chemotherapy with carboplatin/ifosfamide	27	100.0
Thoracic radiotherapy	16	59.3
Response to first-line chemotherapy		
CR	0	0.0
PR	10	37.0
SD	10	37.0
PD	7	25.9

all assessable patients showed progression during follow-up, with a median PFS of 2.0 months (95% confidence interval 1.22～2.78 months). Twenty-five patients had deceased by the time of this report, with a median overall survival was 5.5 months (range 1 to 21 months, 95% CI 4.32～6.68 months) and a 6-month survival rate of 32.1% (95% CI 14.4～49.8%, Fig. 1).

Table 2. Worst CTC grade hematologic toxicity

Toxicity	NCI CTC grade (% of cycles)	
	Grade 3	Grade 4
Neutropenia	24.2	10.6
Thrombocytopenia	19.7	7.6
Anemia	14.2	0.0

NCI; National Cancer Institute, CTC; Common toxicity criteria

3) Adverse events

Any adverse events related to the treatment were evaluated at each cycle, and a total of 61 cycles of chemotherapy were administered (range 1～6 cycles and a median 2 cycles). The major toxicity was a hematological complication (Table 2), including neutropenia (Grade 3 and 4; 34.8% of all cycles) and thrombocytopenia (Grade 3 and 4; 27.3%). Other toxicities included gastrointestinal (nausea, vomiting), constitutional (fatigue) and neuromuscular (peripheral neuropathy) (Table 3). Generally, topotecan and etoposide were well tolerated, and no patient discontinued treatment due to toxicity related to chemotherapy.

Table 3. Worst CTC grade non-hematologic toxicity

Toxicity	NCI CTC grade (% of cycles)	
	Grade 3	Grade 4
Gastrointestinal	21	<1
Constitutional	12	<1
Neuromuscular	2	<1

NCI; National Cancer Institute, CTC; Common toxicity criteria

DISCUSSION

The treatment outcome and long-term survival of SCLC is still disappointing, with a median overall survival of less than 1 year, and a 5-year survival rate of less than 5% in many clinical trials (3,4). Despite the high response rate to the initial chemotherapy, this notoriously dismal survival is primarily due to the short response duration, and a much poorer response to the second-line chemotherapy.

Topotecan showed modest activity as a second-line chemotherapeutic agent for relapsed SCLC in some trials with oral or IV administration, when used alone, or in combination with other agents. Schiller et al reported no improvement in the overall survival of four cycles of topotecan, in combination with four cycles of etoposide and cisplatin (PE) compared with observations after four cycles of only PE, in SCLC patients (21). The outcome of second-line chemotherapy in SCLC depends on several factors, including the interval between completion of induction chemotherapy and relapse, the extent of tumor regression achieved with the induction regimen and the composition of the induction regimens. In general, patients who relapse at least 3 months after cessation of the front-line chemotherapy retained high response rates to second-line therapy, with longer survival duration. In contrast, those with a disease recurrence within 3 months following the end of the induction chemotherapy, or who did not respond to initial therapy (primarily refractory) had high rates of resistance to second-line treatment, leading to the call for the development of a new non-cross-resistant drug combination. The discrepancy in the response rates reported in various studies may reflect the small, heterogeneous populations tested. The results of second-line chemotherapy, with topotecan, for SCLC patients initially refractory, or with an early relapse, following completion of the first-line chemotherapy, were invariably dismal, with a response rate lower than 10% and a survival of around half a year (6,14,17). Our results showed a modest response rate (14.8%), with similar results for overall survival (5 months) and a 6-month survival rate (32.1%).

The adverse event profile for the topotecan and etoposide combination was generally tolerable and manageable. The most common and serious toxicities were hematological; with grade 3 and 4 neutropenia and thrombocytopenia observed in more

than 25% of cycles. Both the topotecan and etoposide were shown to be non-cumulative in other trial (22), and most patients recovered from the hematological toxicities by means of usual management, and there were no treatment-related deaths in our trial. Non-hematological toxicities were usually mild, with nausea and fatigue being the most common.

CONCLUSIONS

The results of this phase II study, relating to IV topotecan and etoposide chemotherapy in refractory small-cell lung cancer patients, showed a modest response rate, but failed to show survival benefits for refractory SCLC patients compared to topotecan monotherapy. The treatment-related toxicities were mainly hematological, but were generally acceptable and manageable.

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