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ORIGINAL ARTICLE

Salvage treatment with topotecan in patients with irinotecan-refractory small cell lung cancer

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Abstract
Purpose Although the efficacy of topotecan as a second-line chemotherapy for small-cell lung cancer (SCLC) has been consistently demonstrated in phase II/III clinical trials, the choice of irinotecan as the first-line therapy prevented the use of evidence-based option. This pilot study was conducted to determine the activity and safety of topotecan in SCLC patients refractory to first-line therapy with irinotecan and platinum.
Methods Patients with primary refractory (no response, or progression during or ≤90 days after last chemotherapy) SCLC after treatment with a combination of irinotecan and platinum, received topotecan 1.5 mg/m^2 per day as a 30-min infusion daily for 5 days, every 3 weeks.
Results Of 17 eligible patients, ten patients were previously treated with irinotecan plus cisplatin and 7 were treated with irinotecan plus carboplatin. The median age was 68 years (range 44–75) and the median interval from the last chemotherapy was 50 days (range 21–89). A total of 33 chemotherapy cycles were delivered (median 2; range 1–5). All 17 patients discontinued therapy due to disease progression and 5 patients had progressive disease before second cycle. Toxic effects were mainly hematologic (grade ≥3 neutropenia in 65% of patients) and fatigue (grade 3 in 47%). In an intent-to-treat analysis, two (12%) patients had a confirmed partial response and two patients achieved stable disease. Median progression-free and overall survivals were 1.7 months (95% CI, 1.5–1.9) and 3.4 months (95% CI, 1.7–5.0), respectively.
Conclusions Topotecan monotherapy for patients with irinotecan-refractory SCLC does not appear highly active but the observation of some responses merits further study in patients with chemosensitive disease.

Keywords Small-cell lung cancer · Refractory · Chemotherapy · Topotecan

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Introduction

Small-cell lung cancer (SCLC) is a highly chemosensitive disease and systemic chemotherapy is the treatment of choice for extensive stage [1]. Standard drugs available for the treatment of SCLC include cyclophosphamide, doxorubicin, methotrexate, etoposide, vincristine and platinum compounds. Despite its marked sensitivity to chemotherapy, SCLC is characterized by high relapse rates and a subsequent poor prognosis.

As the first-line therapy for SCLC, the superiority of cisplatin-based chemotherapy over anthracycline-based regimens was demonstrated by a randomized study [2]. Patients who were treated with etoposide and cisplatin achieved a

significant survival benefit over those treated with a combination of cyclophosphamide, epirubicin and vincristine (overall survival, 10.2 vs. 7.8 months; $P < 0.01$). Given the impact of platinum-based chemotherapy, a number of combination regimens have been explored to consolidate this benefit [3]. In a randomized phase III study conducted by Japanese investigators [4], a combination of irinotecan and cisplatin significantly improved the survival when compared with the combination of etoposide and cisplatin (12.8 vs. 9.4 months; $P < 0.01$). This led to the current use of irinotecan plus platinum combination as one of the most important first-line chemotherapy regimens in Korea and Japan.

However, the treatment of SCLC patients after failure with irinotecan-based first-line chemotherapy remains debatable. The vast majority of SCLC patients will progress after first-line therapy. Currently, commonly used second-line approaches include re-induction with first-line therapy for chemosensitive disease, or single-agent topotecan. Although the efficacy of topotecan as second-line chemotherapy for SCLC has been consistently demonstrated in a number of clinical trials [5, 6], the choice of irinotecan as first-line therapy prevented the use of evidence-based option such as topotecan. Topotecan and irinotecan are cytotoxic agents that inhibit the same intracellular pathway, namely topoisomerase I, which is an enzyme involved in DNA replication and RNA transcription. Moreover, SCLC patients with primary refractory disease (who failed to respond or had relapse within 3 months of their last treatment) have a grim prognosis and a standard salvage treatment is not available.

Although their mechanism of action is similar, the preclinical and clinical data of these two drugs have some notable differences. Topotecan and irinotecan have different spectra of anti-tumor activity in various models of human cancer. Clinical data also support that these agents may have different spectra of activity; irinotecan has demonstrated activity against colorectal cancer [7], whereas topotecan does not have any significant activity against the disease [8]. The differences in anti-tumor activities may also reflect the different mechanisms of resistance. Resistance to camptothecin analogues can result from the reduction of cellular topoisomerase I activity [9], structural mutation of DNA topoisomerase I [10], or altered cellular accumulation of the topoisomerase I inhibitor [11, 12], including active efflux mechanisms. However, there may be specific mechanisms of resistance to each drug, and resistance to one drug may be associated with sensitivity to the other. In human tumor xenograft models, irinotecan maintained essentially full activity against lines selected for primary resistance to topotecan and maintained very high activity in a tumor cross resistant to topotecan [13]. These data suggest that different mechanisms of resistance may develop and indicate that tumors with acquired resistance to one topoisomerase I inhibitor may respond to an alternative agent. Furthermore, topotecan and irinotecan have different limiting toxicities (myelosuppression and diarrhea, respectively).

Based on these considerations, we conducted a pilot phase II study with topotecan monotherapy on patients with irinotecan-refractory SCLC to determine its antitumor activity and tolerability.

Patients and methods

Patients were required to have histologically or cytologically proven SCLC with refractory disease to prior irinotecan-based chemotherapy. Refractory disease was defined as no response to prior chemotherapy, or progression during or ≤90 days after the last chemotherapy. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, age between 18 and 75 years, no active brain or leptomeningeal metastases, and adequate hematologic, hepatic and renal functions. At least one lesion had to be measurable. Exclusion criteria included pregnant or lactating women, patients with active infection, and extensive radiotherapy within the previous 4 weeks, or previous other malignancies with the exception of adequately treated non-melanoma skin cancer or in situ cervical cancer. Patients were also excluded from the study if they had any severe comorbid illness, a known history of anaphylaxis of any origin, or a history of severe adverse events to the drug used in this study. The study protocol was reviewed and approved by the Gil Medical Center (Incheon, Korea) institutional review board. We obtained informed consents after the nature of the study was fully discussed before the initiation of treatment, including an explanation of the risk and the possibility of discomfort, as well as the potential benefits.

Topotecan 1.5 mg/m^2 per day was administered as a 30-min intravenous infusion for five consecutive days. Each cycle of chemotherapy was given every 3 weeks if the patient's blood count had returned to normal and non-hematologic toxic effects had resolved. Treatment was repeated until disease progression and/or unacceptable toxicity was detected. Dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. All patients received standard supportive regimen including blood products and anti-emetics. The use of hematopoietic growth factors was not allowed during treatment, except for patients with febrile neutropenia or grade 4 myelosuppression, at the investigators' discretion.

Baseline evaluation included a complete medical history and physical examinations, blood counts, serum chemistry,

chest X-ray, and computed tomography (CT) scan of chest and upper abdomen. Follow-up history, physical examinations and toxicity assessments were performed before each 3-week cycle of therapy. Tumor response was evaluated every two cycles according to the response evaluation criteria in solid tumor (RECIST) criteria, and was assessed by chest CT scan and the same tests used initially to stage the tumor. Progression in non-measurable lesions leading to deterioration of the patient's status was classified as progressive disease, regardless of the status of the measurable lesions. Toxicity grading was based on the National Cancer Institute criteria (NCI-CTCAE version 3).

The primary endpoints were response rate and safety. Two-stage design based on both response and progression was applied to allow for early closure if the study arm was inactive [14]. A response rate ≤10% was considered inadequate to warrant further evaluation of single-agent topotecan in this study. In the first stage of enrolling 18 patients, accrual was stopped with the conclusion that topotecan was inactive in this patient population if we observed (1) ≤1 response, (2) two responses with ≥4 cases of early progression, (3) four responses with ≥7 cases of early progression, or (4) 5 responses with ≥8 cases of early progression. If the study went on to the second stage, a total of 30 patients would be studied. All analyses were performed on the intent-to-treat population, defined as all registered patients who signed informed consent and fulfilled the main inclusion criteria.

Results

The first patient was entered in September 2004. In September 2006, after 17 patients had been enrolled, accrual was held pending assessment of response and progression in the first cohort. When the criteria for closure were met (two responses and five early progression), the study was then closed. All patients were assessable for toxicity and response. The characteristics of the patients are listed in Table 1. The median age was 68 years (range 44–75 years) and a majority of patients (94%) had symptomatic (ECOG performance status 1 or 2) disease. All the 17 patients had been treated with first-line irinotecan and platinum. Three patients, who had limited stage SCLC at the time of initial diagnosis, had been previously treated with thoracic radiotherapy. Nine patients had initially responded to irinotecan-based first-line chemotherapy and subsequently progressed, and the other eight patients failed to respond to first-line chemotherapy. The sites of metastases at the enrollment were: contralateral lung in six patients, liver in eight patients, adrenal in five patients, bone in five patients, pleural effusion in four patients, brain in two patients and bone marrow in two patients.

Table 1 Patient characteristics

	No.	%
Age, years		
Median (range)	68 (44–75)	
Male gender	16	94
ECOG performance status		
0	1	6
1	13	77
2	3	18
Disease extent at diagnosis		
Limited	3	18
Extensive	14	82
No. of metastatic sites		
1	5	29
>1	12	71
Interval from the last chemotherapy, days		
Median (range)	50 (21–89)	
Prior chemotherapy		
Irinotecan plus cisplatin	10	59
Irinotecan plus carboplatin	7	41
Best response to prior chemotherapy		
CR	1	6
PR	8	47
SD	3	18
PD	5	29

A total of 33 treatment cycles was given (median 2; range 1–5), and 11 (33%) of the planned cycles were delayed because of toxic effects. Dose reduction was required in four (12%) cycles. No patient stopped topotecan therapy before disease progression. Twelve (71%) patients received at least two cycles of chemotherapy and the remaining five patients had progressive disease before completing two cycles of therapy. All eligible patients were evaluable for toxic effects (Table 2). The most frequently

Table 2 Maximum grade toxic effects per patients

	All grades		Grade ≥3	
	No.	%	No.	%
Leukopenia	16	94	7	41
Netropenia	15	88	11	65
Thrombocytopenia	10	59	5	29
Anemia	13	77	2	12
Nausea	4	24	1	6
Vomiting	3	18	0	
Fatigue	12	71	8	47
Stomatitis	1	6	0	
Anorexia	4	24	2	12
Diarrhea	2	12	0	

encountered toxic effects were neutropenia and fatigue, which were managed with rest, dose reduction, or treatment discontinuation. Although difficult to differentiate from the symptoms of the underlying disease, grade 3 fatigue was observed in eight (47%) patients. Even if all the patients were pretreated with cytotoxic chemotherapy, only two episodes of febrile neutropenia occurred. Besides fatigue, non-hematologic toxicities were infrequent. One patient experienced transient elevation in liver transaminase during the treatment. In one patient, a period of inotropic support was required for symptomatic congestive heart failure. Two patients, who were previously known to have an ECOG performance status of 2, died of respiratory failure shortly after receiving the first cycle of chemotherapy. These two deaths were thought to be related to the progression of SCLC.

We obtained two partial responses [12%; 95% confidence interval (CI), 0–27%] which maintained for 5.7 and 6.0 months. Two other patients had stable disease. At a median follow-up of 17.1 months, the median progression-free survival was 1.7 months (95% CI, 1.5–1.9 months) and the median overall survival was 3.4 months (95% CI, 1.7–5.0 months). The progression-free survival was significantly higher in patients with objective response (7.6 months for responders vs. 1.7 months for non-responders; $P = 0.01$). There was a trend toward, although statistically insignificant, longer overall survival in responders (8.3 months vs. 3.3 months; $P = 0.29$). At the time of present analyses, 14 patients (82%) died. Although not specified in the protocol, third-line chemotherapy was offered to five patients after failure. Palliative radiotherapy was given to three patients with symptomatic progression in lung, bone, or brain.

Discussion

With few exceptions, it is generally conceived that salvage chemotherapy is relatively ineffective in chemotherapy-refractory SCLC [15]. However, there are some patients with no further treatment options who have progressed while receiving first-line therapy and there is a need to develop better treatments for patients with relapsed SCLC. With the demonstrated benefits of topotecan as salvage therapy [6], there is a potential rationale to use topotecan after the failure of irinotecan. Therefore, this pilot phase II study was designed to investigate the efficacy and tolerability of topotecan given as second-line chemotherapy in patients with irinotecan-refractory SCLC. Topotecan second-line therapy was tolerated in patients with irinotecan-refractory SCLC. Two patients (12%) had partial responses and 24% of patients had a response or stable disease. However, the high incidence of early progression resulted in the closure of the study as per the multinomial phase II stopping rules used [14].

Topotecan does appear to have significant antitumor activity in relapsed SCLC [1, 23]. von Pawel et al. [6] reported higher response rate for patients treated with topotecan (24%) compared to cyclophosphamide, doxorubicin and vincristine (18%). Most patients in the study who received platinum-based first-line chemotherapy had responded to first-line therapy, relapsed more than 60 days after last chemotherapy, and exhibited good performance status. The result is less relevant in the clinical situations for second-line therapy in Korea and Japan, because SCLC patients are currently treated with first-line irinotecan/platinum combination chemotherapy.

In the second-line therapy of SCLC, treatment outcome depends on many factors, including type of response to first-line therapy, treatment-free interval and performance status [16]. There are two categories (sensitive and refractory/resistant) of previously treated SCLC patients according to their different probability of responding to second-line chemotherapy. The prognosis for SCLC patients receiving second-line therapy depends on the response to first-line chemotherapy [17]. Patients with refractory SCLC have a grim prognosis with very little chance of responding to any type of therapy and a short life expectancy. In the phase II and III studies involving topotecan as second-line chemotherapy [6, 18, 19], the overall response rates were 2–11% in patients refractory to previous chemotherapy. While only 2 out of 17 patients had responded and significant number of patients had early progression with the current regimen, it is interesting to note that the results are identical to the results achieved in the refractory population in European phase II studies [20]. These two responders may serve as proof of principle for the concept of the different mechanisms of resistance between irinotecan and topotecan. We believe that this outcome could be attributed in part to the poor prognosis of SCLC patients refractory to first-line chemotherapy, irrespective of therapy. We cannot completely rule out the possibility that the observed efficacy of second-line topotecan in our study may reflect the natural history of disease rather than the drug's activity. The poor prognostic factors exhibited in our study might explain the poor outcome from second-line topotecan. Refractory disease and a poor performance status are generally recognized as unfavorable prognostic factors, predicting lower response rates and shorter survival in SCLC. Of note, patients with a larger tumor burden had a little chance to achieve a clinical response. The fact that all of the patients in this study had refractory disease and ultimately received less chemotherapy cycles than expected may be a factor in the minimal response seen. In the current study, a majority of patients had symptomatic disease (ECOG performance status 1 or

2) and multiple metastases, including liver and bone marrow.

The objective response rate of 12% and five early progressions observed in this study calls into question the use of single-agent topotecan in irinotecan-refractory patients with SCLC. Although the efficacy outcomes achieved were thought comparable to those seen in other studies, the predesigned criteria for continuing the study were not met. A possible explanation may rest on the selection of primary endpoint employed in our study. We chose early discontinuation due to any causes, which is difficult to distinguish toxicity from early progression, as a primary endpoint. In the current study, five patients with early discontinuation stopped therapy due to progressive disease. Furthermore, a study arm for patients with irinotecan-sensitive SCLC, which is more interesting and frequent situation, would have been useful to determine the respective role of topotecan when used in salvage therapy. In retrospect, considering the poor prognosis of patients with refractory SCLC, our presumptions seem to be too enthusiastic. Although the results presented here are from a relatively small phase II study and the study was not designed to draw strong conclusions, the results suggest that topotecan after failure with irinotecan is tolerated. Topotecan monotherapy does not appear to be highly active in refractory SCLC but the observation of some responses merits further evaluation in patients with sensitive disease. The unfavorable outcomes observed in this study and others, raise the possibility that combination chemotherapy may be a preferred option when the disease is refractory to first-line therapy. In one study [21], topotecan in combination with cisplatin has shown a promising response rate of 24% in refractory SCLC. In addition, adequate assessment of performance status is important when evaluating treatment options for refractory SCLC patients, because patients with poor performance status rarely respond to second-line therapy. The disappointing efficacy results indicate that second-line chemotherapy in refractory SCLC patients with poor performance status should be given with caution and consideration should be warranted to exclude such patients from future clinical trials.

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