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ORIGINAL ARTICLE

Combination of topotecan and etoposide as a salvage treatment for patients with recurrent small cell lung cancer following irinotecan and platinum first-line chemotherapy

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Abstract
Purpose The efficacy and safety of a combined regimen of topotecan and etoposide was tested in patients with relapsed or refractory small-cell lung cancer.
Patients and methods From October 2003 to May 2005, 23 patients who have failed to the previous irinotecan and platinum chemotherapy received intravenous topotecan 1 mg/m^2 (day 1–5) and etoposide 80 mg/m^2 (day 1–3). Treatment was repeated every 21 days for a maximum of 6 cycles.
Results Twelve patients were refractory to first-line chemotherapy. Seventeen patients (73.9%) were male and the median age was 63 years. ECOG performance status was 0–1 in 13 (56.5%) patients. The median cycles of chemotherapy was three. Twenty-one patients were assessable for response evaluation. The overall response rate was 17.4% (0 CR, 4 PR, 7 SD, 10 PD) under the intent-to-treat analysis. Two sensitive case patients and two refractory case patients achieved partial response. After a median follow-up of 20.8 months, median progression free survival was 4.7 months and median overall survival was 9.5 months. The estimated 1-year survival rate was 38.7%. All patients were assessable for toxicity and major toxicities were myelosuppression. Grade 3/4 neutropenia and thrombocytopenia occurred in 18 (78.3%) and 12 (52.2%) patients, respectively. Grade 3/4 febrile neutropenia occurred in two patients (8.7%) and infection in three patients (13.0%). There was one treatment-related death due to pneumonia.
Conclusion This salvage regimen showed modest efficacy and manageable toxicities. Further study will be required in recurrent SCLC patients pretreated irinotecan and platinum.

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Introduction

Small cell lung cancer (SCLC) is highly responsive to chemotherapy and radiotherapy. However, despite this high response rate, almost 80% of limited disease-small cell lung cancer (LD-SCLC) and nearly 100% of extensive disease-small cell lung cancer (ED-SCLC) will relapse or progress [1]. Patients relapsing at least 3 months after the completion of first-line therapy (sensitive relapse) have a good prognosis and a favorable response rate to second-line therapy. Patients who relapse earlier than 3 months after first-line therapy are categorized as "refractory relapsed" and have a low probability of responding to subsequent treatment. Although many clinical trials on salvage chemotherapy for recurrent SCLC have been reported, the results have been disappointing until now [2].

Topotecan is a campotothecin and a topoisomerase-I inhibitor. In a randomized phase III trial compared to the best supportive care, oral topotecan showed significant prolongation of survival in patients with relapsed SCLC [3]. In another phase III trial which compared topotecan with cyclophosphamide, doxorubicin, and vincristine (CAV) in patients with recurrent SCLC, topotecan showed a response rate of 24.3% versus 18.3% for CAV, with improved symptom

palliation [4]. Progression free survival, overall survival, and 1-year survival rates were similar between the two treatment modalities (3.1, 5.8 months, and 14.2%, respectively, for topotecan; 2.8, 5.7 months, and 14.4%, respectively, for CAV). Based on these results, topotecan in monochemotherapy has been the standard treatment in second-line setting of SCLC patients.

Etoposide, a topoisomerase II inhibitor, is a well-known part of the standard regimen for SCLC [5]. Etoposide has a synergistic effect in vitro and no cross-resistance with topotecan [6, 7]. Pretreatment with topotecan increases topoisomerase II mRNA in cells. Additionally, cellular overexpression of topoisomerase II may increase the cytotoxicity of topoisomerase II inhibitors [8, 9]. Clinical effectiveness of a combination of topoisomerase I and II inhibitors was also demonstrated in several trials [10].

Based on these data, we investigated the efficacy and toxicity of topotecan and etoposide combination chemotherapy as salvage treatment in sensitive or refractory recurrent SCLC patients.

Patients and methods

Patients

Patients with histologically or cytologically confirmed SCLC were enrolled in this trial. Additional eligibility criteria were as follows: (1) 75 years old or younger; (2) a performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale; (3) recurrent or refractory disease after previous irinotecan and platinum chemotherapy; (4) at least one bidimensionally measurable lesion; (5) adequate bone marrow function (absolute neutrophils <1,500 g/dl, hemoglobin <10 g/dl, platelets <100,000/dl), adequate renal function (serum creatinine <1.5 mg/dl), and adequate hepatic function (total bilirubin <1.5 mg/dl and serum transaminase values <3 times normal values); and (6) written informed consent. Patients were not eligible for this study if they had serious concomitant medical problems or active infections: symptomatic brain metastases, and massive pleural or pericardial effusion. Prior etoposide or topotecan chemotherapy was not allowed.

Treatment schedule

Topotecan was administered using a 30-min intravenous infusion at a dose of 1.0 mg/m^2 for 5 consecutive days. Etoposide was administered after topotecan using a 120-min intravenous infusion at a dose of 80 mg/m^2 on days 1–3. Treatment was repeated every 21 days. Patients continued therapy for up to six cycles until unacceptable toxicities or disease progression occurred. No prophylactic granulocyte colony-stimulating factor (G-CSF) was administered. Treatment was delayed if the neutrophil count was <1,500 cells/mm^3, if the platelet count was <100,000 cells/mm^3, or if there was a persistent non-hematologic toxicity of grade 2 or higher. The dosage of topotecan and etoposide was reduced when the platelet count was less than 50,000 cells/mm^3 or if febrile neutropenia or severe non-hematologic toxicity occurred. The next cycle of topotecan was administered for 4 consecutive days along with a reduced dose of etoposide (60 mg/m^2).

Assessment of patients

All patients underwent a medical history taking, physical examination, ECOG PS and clinical tumor assessment at screening, after each cycle of treatment, and at follow-up. Pretreatment laboratory evaluation consisted of complete blood count (CBC) with differential, serum chemistry profile (total bilirubin, AST, ALT, alkaline phosphatase, blood urea nitrogen, creatinine and electrolytes) and urinalysis. Chest X-ray, computed tomography (CT) of the chest and upper abdomen, radionuclide bone scan, brain magnetic resonance imaging (MRI) were conducted if brain metastasis was suspected. Additionally, a bone marrow study was conducted if bone marrow metastasis was suspected. All of these were utilized to determine the stage of the disease at screening. Chest X-ray, CBC with differential, and complete biochemical profile were obtained on day 1 of each cycle. Toxicities were evaluated before each cycle according to the National Cancer Institute's (NCI) common toxicity criteria version 3.0. Response was assessed, using CT scan of the chest and upper abdomen, and/or bone scan after every third cycle of chemotherapy. Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [11].

Endpoint evaluation

In this study the primary endpoint was the response rate. The secondary endpoints such as the overall survival (OS), progression free survival (PFS) and toxicity were also evaluated. Intent-to-treat analysis was applied to all the evaluations of primary and secondary endpoints. OS was defined as the interval between the start of treatment and the date of death or the last follow-up. PFS was defined as the time from the commencement of treatment to the date of progression or the last follow-up. Survival curves were estimated using the Kaplan–Meier method. Survival differences between the subgroups were compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox regression analysis model to identify prognostic factors and the risks associated with them. SPSS software (version 12.0) was used to run the analyses.

Simon's optimal two-stage design was used to determine the sample size and decision criteria [12]. Assuming that a response rate of 25% in eligible patients would indicate a potential efficacy of the regimen, and that a rate of 5% would be the lower limit of interest with an alpha-error of 5% and a beta-error of 20%, the estimated number of required patients was 18 patients. It was determined that at least 20 patients were required for the study, taking into account an expected drop-out rate of 10%.

Results

Patient characteristics

Between October 2003 and May 2005, a total of 23 patients were enrolled in the trial. The demographics of these patients are listed in Table 1. Ten (43.5%) patients had an ECOG PS of 2, and all the patients were pretreated with a median chemotherapy of six cycles (irinotecan 50–60 mg/m^2 on days 1,8, and 15 and cisplatin 40 mg/m^2 on days 1 and 8 or carboplatin AUC 5 mg/m^2 ml on day 1 every 4 weeks). Eleven (47.8%) patients were considered to have sensitive relapse.

Efficacy

A total of 23 patients were included in the analysis of tumor response and survival. No patients achieved a complete response (CR); however, 4 (17.4%) had a partial response (PR) for an overall response rate of 17.4% (95% CI, 10.4–34.9). Seven patients showed stable disease (SD), and ten demonstrated progressive disease (PD). Two patients were not assessable for response because of self-withdrawals and an adverse event after initiation of treatment. Patients with sensitive relapse and two patients with refractory relapse achieved a partial response. The median response duration was 6.4 months (range 2.8–7.6 months). Twelve (52.2%) patients received third-line chemotherapy. The median follow-up was 21.6 months. The median progression-free survival was 4.7 months (95% CI 1.8–7.7 months). The median overall survival was 9.5 months (95% CI, 3.9–15.1 months) with an estimated 1-year survival rate of 38.7% (Fig. 1). Patients with sensitive relapse showed a more favorable overall survival time (14.5 months) than those with refractory relapse (6.5 months), but the difference was not significant ($P = 0.14$). Median overall survival time significantly differed between patients with ECOG PS 1 (15.0 months) and PS 2 (6.2 months) ($P = 0.001$).

When we compared the survival profile with the clinical parameters (age, ECOG PS, initial stage, relapse pattern, number of lesion, tumor response, and third-line treatment) using the Cox's proportional regression hazard model, only

Table 1 Patient characteristics

Number of patients (%)	
Total number of patients	23
Median age (years)	63 (Range 48–72)
Sex	
Male	17 (73.9)
Female	6 (26.1)
ECOG performance status	
0–1	13(56.5)
2	10(43.5)
Initial stage at diagnosis	
Limited disease	10 (43.5)
Extensive disease	13 (56.5)
Previous chemotherapy	
Irinotecan/cisplatin	10 (43.5)
Irinotecan/carboplatin	13 (56.5)
Cycle of previous chemotherapy	
Median	6 (Range 3–6)
Previous radiotherapy	
Thorax	13 (56.5)
Brain[a]	8 (34.8)
Bone	1 (4.3)
Initial response of the previous chemotherapy	
CR	5 (21.7)
PR	15 (65.2)
SD	3 (13.1)
Relapse pattern	
Sensitive relapse	11 (47.8)
Refractory relapse	12 (52.2)
Number of lesion	
1	9 (39.1)
≥2	14 (60.9)

ECOG Eastern Oncology Cooperative Group

[a] Six patients received prophylactic cranial irradiation were included

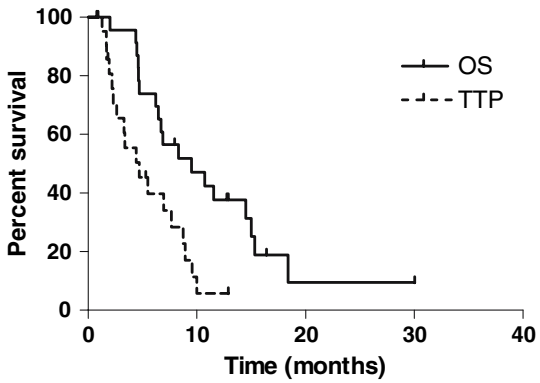

Fig. 1 Kaplan–Meier curves for time to progression and overall survival for the intent to-treat population ($n = 23$)

the ECOG PS was found to be significant in overall survival ($P < 0.01$).

Adverse events

All of the patients were assessed for toxicity with myelosuppression being most frequent. The maximum toxicity experienced during treatment is summarized in Table 2. Grade 3/4 neutropenia and thrombocytopenia were observed in 18 (78.3%) and 12 (52.2%) patients, respectively. Grade 3/4 neutropenic fever was reported in two (8.3%) patients, and grade 3/4 infection occurred in three (13.0%) patients. *Herpes zoster* infection occurred in one patient, and pneumonia in two patients. All of the hematologic and non-hematologic toxicities resolved without any significant complications, except for one patient who died of pneumonia after the third cycle of chemotherapy.

Compliance with treatment

A total of 82 cycles of chemotherapy were administered, with a median of 3 cycles per patient (range 1–6 cycles). Eight (34.7%) patients completed six cycles of chemotherapy. Six patients required dose reductions in topotecan and etoposide due to neutropenia. Mean actual dose intensity of topotecan was 1.49 mg/m^2 week (range 0.78–1.67) and etoposide was 73.84 mg/m^2 week (range 48–80 mg/m^2 week). The relative dose intensities of topotecan and etoposide were 0.89 and 0.92, respectively.

Table 2 Toxicity profiles

NCI-CTC grade	G 1	G 2	G3	G 4	G5	G3–5 (%)	
Hematological toxicities ($N = 23$)							
Neutropenia	3	2	3	15	0	18	(78.3)
Leukopenia	5	4	10	3	0	13	(56.5)
Anemia	9	10	2	0	0	2	(8.7)
Thrombocytopenia	5	3	7	5	0	12	(52.3)
Nonhematological toxicities ($N = 23$)							
Anorexia	5	3	0	0	0	0	
Nausea	5	6	0	0	0	0	
Vomiting	4	4	0	0	0	0	
General weakness	4	6	1	0	0	1	(4.3)
Diarrhea	2	0	0	0	0	0	0
OT/PT elevation	0	0	0	0	0	0	0
Febrile neutropenia	0	0	1	1	0	2	(8.7)
Infection	1	2	2	0	1	3	(13.0)
Pain	1	1	0	0	0	0	

NCI-CTC The National Cancer Institute's Common Toxicity Criteria

Discussion

Irinotecan plus platinum chemotherapy has been one of the most commonly used regimens for SCLC as a first-line treatment in Asia [13, 14]. A demand for active salvage regimen after irinotecan and platinum is currently increasing. Accordingly, we evaluated the combination chemotherapy of topotecan and etoposide as second -line treatment in SCLC. Moreover, this is the first clinical study that explored an efficient regimen for patients with recurrent SCLC who were pretreated with irinotecan and platinum.

In this study, 4 of the enrolled 23 patients responded to the treatment. Although Calver et al. [15] reported that in irinotecan-resistant xenografts, transient cross-resistance is observed with topotecan, irinotecan and topotecan may have different mechanisms of cross-resistance in a clinical setting due to distinctive clinical toxicity profiles which are used in a different tumor spectrum [16]. Interestingly, in this study, 2 of 12 irinotecan-refractory patients showed objective responses, which suggests that there is some degree of non-cross-resistance between topotecan and irinotecan. Otherwise synergistic cytotoxic effects caused by combination of topotecan and etoposide could overcome cross-resistance.

We achieved a median PFS of 4.7 months with a median OS of 9.6 months. These survival results are comparable with those reported by other studies. In general, the performance status, relapse pattern, and response are considered to be prognostic factors in recurrent SCLC [17]. Although this study included only a small population, the significant factor for overall survival was performance status in multivariate analysis.

The rationale for the combination of topoisomerase I and II inhibitors was based on the preclinical and clinical data. Such a combination might result in more potent cytotoxicity, because one topoisomerase has the compensatory activity for the deficiency of the other. As a salvage treatment in recurrent SCLC, this combination demonstrated the clinical effectiveness. Masuda et al. [10] reported a synergistic effect when combining irinotecan and etoposide for the treatment of refractory or recurrent SCLC. Shivayama et al. [18] evaluated the clinical benefit of a combination of amrubicin (topoisomerase II inhibitor) and topotecan. Additionally, as first-line therapy in ED-SCLC, Reck et al. [19] investigated topotecan (1 mg/m^2) administered intravenously on days 1–5, followed by etoposide (75 mg/m^2) administered intravenously on days 8–10 every 4 weeks. The confirmed tumor response was 46.4% and the median overall survival was 29.9 weeks.

Several studies have reported that in a combination of comptotecin and topoisomerase II inhibitors, the treatment schedule is critical for efficacy. Sequential administration

of camptotecins followed by topoisomerase II inhibitors may lead to synergistic cytotoxicity [9]. In clinical studies, sequential or concurrent administration may be also effective [20]. Therefore, the clinical efficacy of the two drugs may be independent of the sequence of administration.

The hematologic toxicities were predictable by those previously described in topotecan studies. Grade 3/4 neutropenia developed in 78.3% of patients and neutropenia-related adverse events occurred somewhat frequently. About half of the enrolled patients in this study had an ECOG 2 performance status, and this could explain the frequent incidence of neutropenic fever and infection. These toxicities can potentially be overcomed by giving G-CSF to the patients prophylactically. When assessing the value of anticancer treatment in a palliative setting, it is important to consider the impact on quality of life, which is mainly determined by the toxicity of chemotherapy. It has recently been reported that weekly scheduled topotecan shows a favorable hematologic toxicity profile when compared with the 5-day regimen even though maintains or improves antitumor activity [21]. Based on this report, the treatment schedule should be adjusted if this specific combination will be used in future studies.

In conclusion, the results of this study suggest that a combination of topotecan and etoposide may have a modest efficacy and manageable toxicities. Further studies with larger numbers of patients will be required to evaluate the efficacy of new regimens and the proper treatment schedule for patients with recurrent SCLC who have been treated with irinotecan and platinum.

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