Single-Agent Oral Etoposide in Patients With Relapsed or Refractory Extensive Small-Cell Lung Cancer

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Abstract

Objective: To evaluate the effectiveness and toxicity of prolonged low-dose oral etoposide in patients with relapsed or refractory extensive small-cell lung cancer.

Patients and Design: Thirty-one patients with relapsed or refractory extensive SCLC were treated with oral etoposide 50 mg (25 mg bid) for 14 days every 3 weeks. Response, duration of response, survival and toxicity were evaluated.

Setting: Departments of Pulmonary Medicine and Medical Oncology, School of Medicine, Ege University.

Results: Partial response was observed in 32.3% of patients. Complete response was not observed. Median duration of response was 16 weeks. Median survival was 16 weeks (range, 4-48 weeks). Two patients developed grade 3 leukopenia and 6 had grade 1-2 leukopenia. Two patients had grade 1-2 thrombocytopenia. One patient developed grade 2 nausea/vomiting, and one patient grade 2 diarrhea.

Conclusion: Prolonged administration of low-dose oral etoposide is well tolerated in relapsed or refractory SCLC and has therapeutic efficacy.

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Key words: *Oral etoposide, small-cell lung cancer and second-line chemotherapy.*

Introduction

Small-cell lung cancer, which represents approximately 20-25% of all new cases of primary lung cancer, is the most responsive of all lung cancers to cytotoxic chemotherapy and radiotherapy (1). Up to 90% of patients respond to cisplatin plus etoposide (PE), and this combination is considered to be the most effective form of all combination therapies (2).

Single-agent therapy with intravenous (IV) etoposide has clearly demonstrated that this agent is among the most effective therapies in the management of SCLC (3). In clinical trials with oral etoposide in patients with SCLC conducted in 1990s, response rates ranging between 48% and 76% were observed with prolonged administration of oral etoposide in doses ranging from 50 mg/m^2/d to 100 mg/m^2/d (4,5).

Etoposide is both phase-specific and schedule dependent. The bioavailability is approximately 50% for a single oral dose of 100 mg and has been shown to decrease for higher doses.

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Bioavailability has been shown to be high even with low doses such as 50 mg. Efficacy depends on maintaining a certain minimal plasma concentration (1 μg/mL) as long as possible (6).

Katoh et al. (7) performed a pharmocokinetic study and observed that mean peak plasma concentration in patients who were given 50 mg/d (25 mg bid) oral etoposide for the 14 consecutive days of a 4-week course was 1.24 + 0.12 μg/mL. The study suggests that prolonged administration of oral etoposide in a dose of 25 mg twice a day has strong cytotoxic activity. Etoposide shows dose -and schedule-dependent toxicity and high cumulative doses increase the risk of toxicity (6). Thus, oral etoposide given in an effective low dose provides an additional advantage of preventing toxicity.

Despite initial chemosensitivity, the majority of patients eventually relapse and over 90% of all SCLC patients become candidates for some form of second-line chemotherapy. However, there is no ideal second-line chemotherapy regime. Oral etoposide, administered in a dose of 50 mg/m^2/day as a second-line chemotherapy, was reported to have a moderate effect (8,9).

In this study, we evaluated the effectiveness and toxicity of prolonged low-dose oral etoposide in patients with relapsed or refractory extensive small-cell lung cancer. The dose administered (25 mg bid) was lower than that used in previous studies.

Materials and Methods

Thirty-one patients were included in this study conducted between January 1997 and November 1999. Eligibility criteria were as follows: cytologically or histologically proved extensive stage small-cell lung cancer, prior treatment with at least one combination chemotherapy regimen, Karnofsky performance status 50% or higher, total leukocyte count above 3 000/μL, a platelet count greater than 100 000/μL, a serum creatinine level less than 2.0 mg/dL, and a serum bilirubin level less than 2.0 mg /dL.

Before receiving oral etoposide and every three weeks after the onset of treatment, complete blood cell (CBC) counts, biochemical profile, and chest X-ray were performed. CBC counts were repeated in the middle of each cycle (day 10).

The patients were treated with oral etoposide 50 mg (25 mg capsules bid) for 14 days with intervals of 3 weeks between each course. Antiemetics were not routinely used. Response was evaluated after two courses of treatment with chest X-ray and thorax computed tomography. Abdominal and head computed tomography and bone scan were also used for some patients when necessary. Chemotherapy was discontinued if there were signs of progressive disease. Patients who responded received a maximum of six courses. Treatment was continued in patients with stable disease if they had any palliation in their symptoms.

Response and toxicity were assessed according to WHO's criteria. A complete response required total resolution of all measurable lesions for at least 4 weeks. Partial response required a greater than 50% reduction in the sum of the products of the maximum perpendicular diameters of all measurable lesions without the development of any new lesions. Stable disease was defined as less than 50% regression or less than 25% progression of lesions. All others were considered to have progressive disease.

Time to response was calculated from the first dose of etoposide to the first objective evidence of tumor regression or progression. Similarly, survival was calculated from the first dose of etoposide to death. Survival curves were plotted according to the Kaplan-Maier method.

Results

The mean age of the patients was 61.51±9.83 years. Median Karnofsky performance score was 60% (range, 50-80%). Eleven patients had received prior cyclophosphamide, epirubicine, vincristine (CEV), and the remaining 20 had received prior cisplatin plus etoposide (PE). Seven (63.6%) of the patients who had received CEV and 12 (60%) who had received PE had responded to these chemotherapy regimens. Median time to relapse after the last chemotherapy course in these patients was 3 months (range, 1-15 months). In 6 patients who had late relapses (after 3-4 months), the previous treatment was not admin-

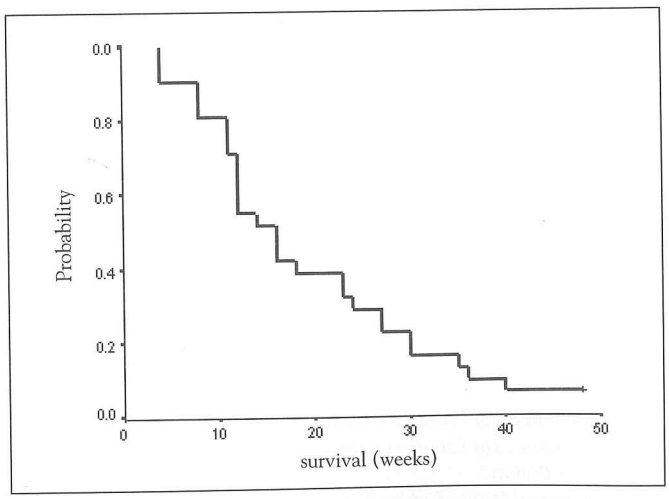

Figure 1. *Survival curves of the patients.*

istered either because the patients refused intravenous treatment or were not eligible. Twelve patients had not responded to any previous chemotherapy, so the treatment was switched to oral etoposide.

Partial response was observed in 10 patients (32.3%). Complete response was not observed in any patient. Median time lapse to response was 16 weeks (6 to 18 weeks). Median survival was 16 weeks, ranging from 4 to 48 weeks. Figure 1 shows the survival curve. Among eight of the patients who were evaluated as having stable disease, three showed improvement in their symptoms, therefore continued to receive chemotherapy. Patient characteristics and response rates are given in Tables 1 and 2.

Table 1. Patients characteristics

Number of patients	31
Mean age (years)	61.51 ± 9.83
Sex (female/male)	(3/28)
Median Karnofsky PS (range)	60% (50-80%)
Previous chemotherapy (n)	31
CEV	11
PE	20

CEV: cyclophosphamide, epirubicine, and vincristine group
PE: cisplatin plus etoposide group

Three of the 11 patients with previous CEV exposure and 7 of the 20 patients who had previously received PE showed some response to etoposide.

A total 112 courses of oral etoposide were administered to our 31 patients (median 3 courses for each). Grade 3 leukopenia developed in two patients and 6 had grade 1-2 leukopenia. Two patients had grade 1-2 thrombocytopenia. One patient developed grade 2 nausea/vomiting, and one patient grade 2 diarrhea. We did not interrupt or delay the treatment of any patient due to toxicity.

Discussion

The second-line therapy in SCLC is a big problem. PE is the most effective regimen if not used before (2). Cyclophosphamide, doxorubicin, and vincristine (CAV) is not an effective combination as a second-line therapy after PE (10,11). Intravenous etoposide is also unsuccessful as a second-line chemotherapy (12,13).

In recent years, clinical trials with new drugs such as docetaxel and topotecan as second-line chemotherapy in SCLC have been conducted. Smyth et al. (14) used 100 mg/m^2 of docetaxel and found a response rate of 25% in 25 patients who had received prior chemotherapy. Pawel et al. (15) reported a response rate of 24.3% in 107 patients treated with topotecan as a second-line chemotherapy. Median survival was 25 weeks. In spite of the moderate effectiveness of these regimens, the cost is very high. One course of docataxel and topotecan cost approximately 1136 $ and 1420 $, respectively. The cost of oral etoposide is very low compared to other agents and has moderate effectiveness in SCLC as a second-line chemotherapy. One course of oral etoposide costs 128 $.

It was shown that prolonged oral etoposide was effective in patients with relapsed or refractory SCLC. In a study by Einhorn et al., 26 refractory SCLC patients were given 50 mg/m^2/d oral etoposide and a response rate of 23% was observed. Median survival was 18 weeks (8). In another second-line oral etoposide study, Johnson et al. treated 23 relapsed or refractory SCLC patients with 50 mg/m^2/d oral etoposide. The overall response rate was 45% and median survival was 3.5 months (9). We observed a similar response rate (32.3%) with even lower doses. Toxicity was also a relatively minor problem in our series.

In our patients, prior chemotherapy (PE or CEV) did not appear to influence the response to oral etoposide. Johnson et al. reported similar results in their study (9). These observations suggest that the effect of etoposide may be different when it is administered orally in low doses over a prolonged period.

The optimal schedule for oral etoposide is not known. In most studies a regimen consisting of a daily dose of 50 mg/m^2 administered for 21 days, with a treatment–free interval of 1-2 weeks between courses, was applied. This regimen was also the basis of the reported maximum tolerated dose (6). Some investigators recommend continuous etoposide treatment, but a dose of 50 mg/m^2/d can prove to be too toxic for continuous treatment (8,16). In a study, a dose of 50 mg/d was administered for a median of 63 days and only three patients had to be withdrawn from the study

Table 2. Response rates in patients

	Complete response	Partial response	Stable response	Progressive disease	Overall response
CEV (11)	0	3	4	4	3
PE (20)	0	7	4	9	7
Total (31)	0	10	8	13	10
		32.3%	25.8%	41.9%	32.3%

CEV: cyclophosphamide, epirubicine, and vincristine group
PE: cisplatin plus etoposide group

because of toxicity (17). To avoid toxicity problems in patients previously treated with aggressive chemotherapy protocols, we prefer to use 50 mg/d of oral eteposide in our clinic. A dose of 50 mg/d provides an effective plasma concentration (above 1 μg/ml).

In conclusion, our experience indicates that as a second line chemotherapy in SCLC, prolonged oral etoposide administered in a dose of 25 mg bid for 14 days with treatment-free intervals of 3 weeks is a low cost regimen with moderate effectiveness and minimal toxicity.

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