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SHORT COMMUNICATION

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Is there a circadian variation in plasma concentrations of etoposide given by prolonged continuous infusion?

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Abstract The prolonged continuous infusion of low-dose etoposide is a new approach to treating cancer. Whether or not a circadian variation in the plasma levels of etoposide existed was investigated in nine patients with non-small-cell lung cancer. Etoposide was infused for 14 days and blood samples were obtained every 4 h for 1 day. There was no significant circadian variation, and the observed small within-day variations seemed to lack clinical significance.

Key words Etoposide · Circadian variation · Low-dose infusion · Lung cancer

Introduction

Antineoplastic agents, such as the fluoropyrimidines, oxaliplatin, 4′-*O*-tetrahydropyranyl doxorubicin and cisplatin, exhibit a circadian variation in plasma levels and cytotoxicity [1, 2, 7, 8, 11]. Accordingly, chronotherapy, in which these agents are administered at carefully selected times of the day, has been developed to reduce toxicity while improving antitumor efficacy [6]. However, a circadian variation in pharmacokinetics has been clearly demonstrated only for 5-flurouracil (5-FU) [11]. The effects of chronotherapy in the other agents have been evaluated only by pharmacodynamic outcomes without the assessment of plasma levels.

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Etoposide is a semisynthetic derivative of podophyllotoxin that is effective in treating small-cell lung cancer, testicular cancer, malignant lymphoma, and leukemia [10]. It may also be effective against non-small-cell lung cancer [5, 10]. Clinical studies have shown that the effect of etoposide is schedule-dependent [3, 5, 13]. Prolonged exposure to low concentrations of the drug is important to maximize its antitumor efficacy [5]. The administration of divided doses of etoposide is more effective than administering the same amount as a single dose [13]. Recently, the prolonged administration of a low dose of etoposide, orally or intravenously, has been found to be effective [5]. Within-day variation of the plasma concentration of etoposide administered in this manner, which would result in the need for chronotherapy, has not been reported.

We sought to determine whether there is a circadian variation in the plasma level of etoposide when administered by prolonged low-dose infusion.

Patients and methods

We studied nine Japanese patients with non-small-cell lung cancer [six men and three women aged 56 to 71 (median 65) years; Table 1] who were scheduled to receive a continuous infusion of etoposide monotherapy for 14 days. Seven patients had adenocarcinoma, one, squamous cell carcinoma, and one, large cell carcinoma. The performance status was 0 in two patients, 1 in four patients, and 2 in three patients. The clinical stage was IIIB in two patients, and IV in six patients, and one patient was in postoperative relapse. The mean creatinine clearance was 66 ± 13 ml/min. For inclusion in the study, the patients had to fulfil the following criteria: no prior chemotherapy, no other serious medical disease, estimated life expectancy $\geq$6 weeks, leukocyte count $\geq$3500/μl, platelet count $\geq$100 000/μl, hemoglobin $\geq$10 g/dl, serum creatinine $\leq$2.0 mg/dl, serum transaminases $\leq 2 \times$ upper limit of normal, total bilirubin $\leq$2.0 mg/dl, and albumin $\geq$3.0 g/dl. Each patient provided informed consent for participation.

All patients were treated in hospital. Each received a continuous infusion of etoposide for 14 days, with the infusion started at a dose of 40 mg/m^2 per day. Etoposide was diluted in a 5% glucose solution and was infused via a central venous line at a constant rate using a drip pump. The infusion was started at 0600 hours on day 1. Based on the plasma concentration of etoposide obtained 24 h after initiating the infusion, the rate of infusion was modified by 30 h (day 2) to achieve a

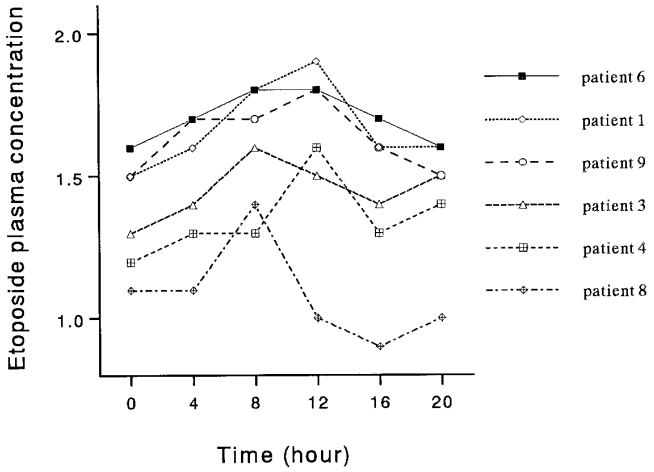

Fig. 1 Six patients showed a maximum plasma concentration of etoposide in the morning (0800 or 1200 hours)

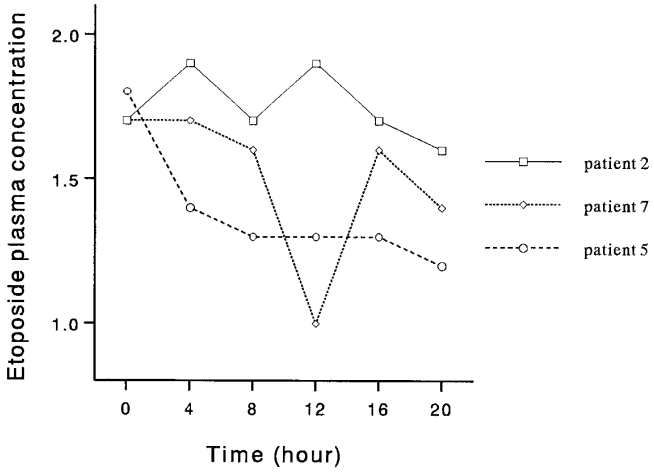

Fig. 2 One patient (patient 5) had a maximum plasma concentration of etoposide at time 0 (2400 hours), while two patients exhibited other patterns

plasma concentration of 1.5 μg/ml. The concentration of etoposide in the solution was changed so that the total volume infused ranged from 700 to 1500 ml/day. Otherwise, the concentration of etoposide in the solution and the rate of infusion in each patient remained unchanged until day 14.

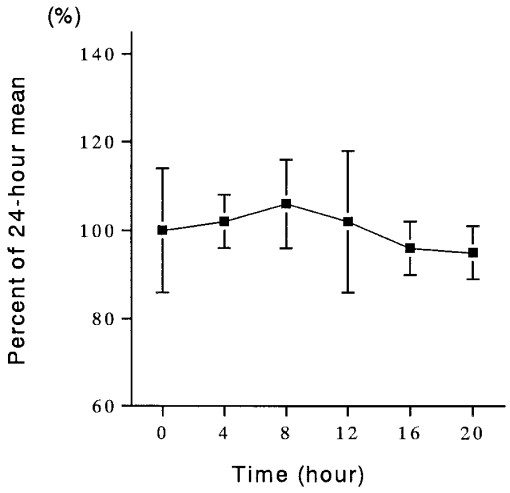

Fig. 3 Circadian variation in plasma concentrations of etoposide in the nine patients with non-small-cell lung cancer given a continuous low-dose infusion of this drug. Data are expressed as mean ± SD of the percentages of each patient's 24-h mean plasma value at each time. Differences were not statistically significant (one-way ANOVA; $P = 0.370$)

Blood sampling and assay for etoposide

To avoid the influence of the dose modification on day 2 on the plasma concentrations of etoposide, blood was sampled from all nine patients after day 4. The day selected for study was based on clinical convenience. Heparinized blood samples were obtained via a peripheral venous catheter every 4 h for 20 h, i.e. at 0, 4, 8, 12, 16, and 20 h. Plasma was immediately separated by centrifugation and stored at –20 °C until assayed. The plasma concentration of etoposide was determined by high-performance liquid chromatography, performed by Sumitomo Metal Bio-Science, Inc. (Sagamihara, Japan). The limit of detection was 0.05 μg/ml. The intra- and interassay coefficients of variation (CV) were each below 5%.

Statistical analysis

Because there was an interpatient difference in 24-h mean plasma concentrations of etoposide, data on plasma concentrations of the drug were adjusted by converting the data to a percentage of the 24-h mean concentration for each patient. The CV was defined as standard deviation (SD)/mean × 100. Circadian variation was evaluated by one-way analysis of variance (ANOVA). The *P*-value was two-sided, and values <0.05 were considered to be significant.

Table 1 The 24-h mean plasma concentrations of etoposide administered as a low-dose continuous infusion in nine patients with non-small-cell lung cancer (*BSA* body surface area, *SD* standard deviation, *CV* within-day coefficient of variation

Patient	Age (years)	Sex	BSA (m^2)	Dose (mg/m^2/day)	24-h mean ± SD (range) (μg/ml)	CV (%)
1	66	F	1.32	30	1.67±0.15 (1.5–1.9)	9
2	60	M	1.70	32	1.75±0.12 (1.6–1.9)	7
3	61	M	1.67	35	1.45±0.10 (1.3–1.6)	7
4	69	F	1.32	29	1.35±0.14 (1.2–1.6)	10
5	71	M	1.35	35	1.38±0.21 (1.2–1.8)	15
6	56	M	1.62	46	1.70±0.09 (1.6–1.8)	5
7	64	M	1.54	55	1.50±0.27 (1.0–1.7)	18
8	65	F	1.40	29	1.08±0.17 (0.9–1.4)	16
9	69	M	1.52	40	1.63±0.12 (1.5–1.8)	7

Results

Overall, the 24-h mean plasma concentration of etoposide was 1.5±0.2 μg/ml (range 1.1–1.8 μg/ml). The mean within-day CV was 11±5% (range 5–18%). Six of the nine patients showed a maximum plasma concentration of etoposide in the morning at 0800 or 1200 hours (Fig. 1). The other three patients did not show such a pattern (Fig. 2). While there was a trend toward a higher plasma concentration of the drug in the morning than the evening, the difference was not statistically significant (P = 0.370, Fig. 3).

Two patients developed WHO grade 3 leukopenia, and one developed WHO grade 4 leukopenia. The within-day CVs of the plasma concentrations of etoposide were 7% in the two WHO grade 3 patients and 15% in the one WHO grade 4 patient. There was no relationship between the within-day CV of the plasma concentrations of etoposide and the severity of leukopenia or the other toxic effects observed.

Discussion

We observed no statistically significant within-day variation in the plasma concentrations of low-dose etoposide given as a continuous infusion. If we investigated more patients, the statistical evaluation might reach significance. However, the between-day CV previously reported in studies of the infusion of low doses of etoposide is approximately 15% [9, 12]. Therefore, the within-day CV of 11% observed in the present study lacked clinical significance.

Nevertheless, our results do not exclude the possibility of a circadian variation in the pharmacodynamics of etoposide. Focan compared two timings of etoposide administration, giving a dose of 100 mg/m^2 at 6 a.m. or at 6 p.m. in combination with cisplatin (100 mg/m^2, at 4 to 6 p.m.) [4]. The results obtained in 76 patients given 261 courses showed a lower hematologic toxicity of etoposide given at 6 a.m., although there were no differences in dose intensity, clinical response or survival.

Thus, we found no indication of a circadian variation in plasma concentrations of etoposide administered by continuous low-dose infusion.

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