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Therapeutic Drug Monitoring in 21-Day Oral Etoposide Treatment for Lung Cancer

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We aimed to determine whether or not therapeutic drug monitoring is applicable to 21-day oral etoposide treatment for lung cancer. As the starting dose, a 25-mg capsule of etoposide was taken orally three times daily (75 mg/body). To achieve the target concentration range of 1.0 to 1.5 μg/ml, the dose was changed to two (50 mg/body) or four (100 mg/body) times a day from day 5, depending on the mean concentration obtained on days 3 and 4 (C_{before}). The mean concentration was calculated by use of a limited sampling model we constructed previously. Among 26 courses in 15 patients, two patients experienced grade 4 leukopenia plus neutropenia, and one of them died on day 20. Because nausea/emesis prevented the planned dose escalation in one patient, we excluded two courses of this patient from the pharmacokinetic analysis of dose modification. Among 5 courses with dose reduction, the C_{before} of 1.7±0.1 (μg/ml, mean±SE) was decreased to 1.3±0.2 after day 5 (C_{after}). Among 7 courses with dose escalation, the C_{before} of 0.9±0.0 was increased to the C_{after} of 1.2±0.1. Among the remaining 12 courses without dose modification, the C_{before} and the C_{after} were 1.2±0.0 and 1.3±0.1, respectively. Hematologic toxicities tended to correlate with the drug concentration. TDM is thus applicable to oral etoposide given according to this schedule, and a larger study is now needed to confirm that the therapeutic efficacy is improved by introducing TDM.

Key words: Oral etoposide — Low dose — Drug monitoring — Pharmacokinetics — Lung cancer

Etoposide is a semisynthetic derivative of podophyllotoxin that has proven effective in treating small-cell lung cancer, testicular cancer, malignant lymphoma and leukemia, and may also be effective against non-small-cell lung cancer.[1–3] It has been shown that the clinical effect of etoposide is schedule-dependent.[4–6] Recently, the prolonged administration of a low dose of etoposide, orally or intravenously, has been found effective for several malignancies, including small cell or non-small-cell lung cancer.[7–9] However, the optimal administration schedule of the drug remains to be fully established.

Pharmacodynamic analyses of prolonged low-dose etoposide demonstrated that the duration of exposure to low concentrations (1 μg/ml) is important for its antitumor effect, while the hematologic toxicity is dependent upon exposure to higher concentrations (2 to 3 μg/ml).[6, 10–12] Etoposide concentration after administration of a uniform dose based upon the body surface area varies significantly among patients.[2, 13, 14] Therefore, we previously conducted a study of 14-day infusional etoposide to maintain a steady-state concentration of 1.5 μg/ml using therapeutic drug monitoring (TDM) guided by the concentrations found during the early steady-state.[15] The results indicated that the steady-state concentration of etoposide could be maintained at 1 to 2 μg/ml using TDM, and the inter-patient variability of the steady-state concentration was decreased by the dose modification.

The oral route for prolonged administration of etoposide is easier than intravenous infusion, but because the bioavailability varies considerably among patients,[16] the inter-patient variability in plasma concentration of etoposide might be larger by the oral route than by the infusional method. Therefore, we considered that the TDM would be essential in order to maintain the etoposide concentration within the therapeutic range in the case of oral administration. Recently, we studied 21-day, low-dose, oral etoposide administration using a small capsule (25 mg) three times daily (hyper-fractionated).[17] The results demonstrated that a stable, low blood level of etoposide could be obtained by this regimen of oral administration.

Based on these findings, we conducted a trial of 21-day, low-dose, hyper-fractionated oral etoposide using TDM. The targeting range of the mean etoposide concentration was from 1.0 to 1.5 μg/ml. The objectives of this study were to determine whether TDM is applicable to oral etoposide given according to this schedule.

PATIENTS AND METHODS

Patient eligibility and evaluation Patients had to fulfill all of the following criteria: histologic or cytologic proof of lung cancer; no other serious disease, including uncontrollable pleural or pericardial effusion, heart failure, or infection; age ≤75 years; estimated life expectancy ≥4 weeks; a performance status ≤3 on the Eastern

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Cooperative Oncology Group scale; leukocyte count $\geq 3500/\mu l$; platelets $\geq 100000/\mu l$; serum creatinine ≤ 2.0 mg/dl; total bilirubin ≤ 2.0 mg/dl; albumin ≥ 3.0 g/dl; and no anti-neoplastic treatment during the 4 weeks before the trial. Patients with non-small-cell lung cancer had inoperable cancers or postoperative relapse. Untreated patients and those previously treated with chemotherapy, radiotherapy, or both, were eligible. Patients with small cell lung cancer were eligible if they were refractory to, or could not tolerate, the standard treatment. This study was approved by the ethical committee of the Japanese Red Cross Nagoya First Hospital, and informed consent was obtained in writing from all patients.

Pretreatment evaluation included the following studies: history; physical examination; blood analyses, including a complete blood count, platelets, differential smear, serum electrolytes, total protein, albumin, total bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, creatinine, and urea nitrogen; creatinine clearance measured from 24-h urine collections; electrocardiogram; urinalysis; stool sampling for occult blood; chest radiographs and computed tomography (CT); abdominal CT and/or ultrasonography; radionuclide bone scan; and enhanced brain CT. Follow-up assessment was as follows: a complete blood count, platelets and differential smear at least twice a week; serum electrolytes, total protein, albumin, total bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen; and chest radiograph once a week. Follow-up chest CT scans were performed at 4 and/or 8 weeks, and other examinations were repeated as necessary when disease progression was suspected.

Measurable disease was not required, but was measured weekly when present. Patients who received at least one course of chemotherapy were assessed for toxicity and response using standard World Health Organization (WHO) criteria.[18]

Administration of etoposide All patients were treated as inpatients at the first course. At following courses, the patients were treated as outpatients when their drug intake was confirmed. A pill count was conducted at every follow-up. Otherwise, the patients were treated as inpatients throughout the courses. Etoposide, in 25-mg soft gelatin capsule form, was administered orally for 21 consecutive days. During the first 4 days, one capsule was taken three times daily at 7:00, 13:00, and 19:00. On day 5, the number of etoposide capsules was modified to the individualized dose (2, 3, or 4 capsules daily), depending on the mean etoposide concentration (C_{mean}) on days 3 and 4, to achieve a target concentration range of 1.0 to 1.5 μg/ml. Antiemetics were not used routinely. Colony-stimulating factors (CSF) were administered along with antibiotics when a patient experienced grade 4 leukopenia or neutropenia with infectious complications. Chemotherapy was repeated every 4 weeks until disease progression or patient refusal. The chemotherapy was discontinued before 21 days elapsed if there was grade 4 hematologic toxicity, or grade 3 or greater non-hematologic toxicity other than alopecia or emesis. The following course was delayed one week until leukocyte and platelet counts recovered to $\geq 3000/\mu l$ and $\geq 100000/\mu l$, respectively.

Dose modification To decrease the number of blood samplings, a limited sampling model (LSM) that we constructed previously for the estimation of C_{mean} was used.[17] With this model, the C_{mean} values on days 3 and 4 were calculated from concentrations measured at 13:00 and 15:00. Based on the average C_{mean} on days 3 and 4 (C_{before}), the dose was modified on day 5 to achieve the concentration of 1.0 to 1.5 μg/ml according to Table I. In this diagram, the target concentration was calculated as follows: target concentration $= C_{before} \times$ (number of capsules after dose modification)/3. For example, when the C_{before} was 0.9 μg/ml and the etoposide dose was increased to 4 capsules per day, the target concentration was 1.2 μg/ml. When the C_{before} was 1.7 μg/ml, it was decreased to 2 capsules to achieve the target concentration of 1.1 μg/ml. The target concentration range for the dose adjustment was set at 1.0 to 1.5 μg/ml. When a patient had greater than grade 1 nausea/emesis induced by etoposide, the decision as to dose modification was left to the assigned physicians. In successive courses, the starting etoposide dose was again 75 mg/body/day, and the dose modification was done in the same way as in the first course.

Table I. Diagram of Dose Modification

C_{before} [a]	Modified daily dose		Target	Time schedule of administration
	mg/body	Capsules		
–1.0	100	4	–1.3	7:00, 12:00, 17:00, 22:00
1.1–1.4	75	3	1.1–1.4	7:00, 13:00, 19:00
1.5–	50	2	1.0–	7:00, 19:00

a) Average mean concentration on days 3 and 4.

To investigate the effect of the dose modification, C_{mean} values on days 10 and 20 were obtained, and C_{after} was defined as the average of the C_{mean} values on days 10 and 20. While the patients were treated with 3 capsules daily, the LSM was used to calculate the C_{mean} from concentrations measured at 13:00 and 15:00.

While the patients were treated with 2 capsules daily, samples were obtained at 7:00, 9:00, 13:00, and 19:00. The area under the concentration versus time curve (AUC) was obtained by the trapezoidal method. Then the C_{mean} was calculated by dividing the AUC by the observed time. Although the number of samplings was small, we confirmed that the C_{mean} calculated with these 4 points could predict well the mean concentration determined by 7 point samplings in another study setting [mean predictive error (MPE) $= -0.03$ μg/ml, -2.7%; root-mean-squared error (RMSE) $= 0.05$ μg/ml, 4.7%; $n=8$].

While the patients were treated with 4 etoposide capsules daily, the samples were obtained at 12:00 and 14:00, or 17 : 00 and 19 : 00, and the C_{mean} was also determined using the LSM originally developed for the 25×3 mg/day schedule. To confirm that the LSM could be used for the estimation of C_{mean} for 25×4 mg/day etoposide, blood samples were collected at 0, 0.5, 1, 2, 3, and 5 h following the drug administration in 6 patients. The trapezoidal rule was used to obtain the AUC. Because steady-state was achieved, the C_{mean} was calculated by dividing the AUC by the time (5 h), and compared to the value predicted by the LSM. The MPE and RMSE were used to evaluate the performance of the model.[19]

Etoposide plasma concentration Heparinized blood samples were obtained via a peripheral venous catheter when more than two samples per day were needed. The plasma samples were separated immediately by centrifugation. The etoposide concentration of samples on days 3 and 4 was measured immediately, and samples drawn after the dose modification were stored at -20°C for a maximum of 2 weeks until assay.

The etoposide concentration was determined by high-performance liquid chromatography (HPLC pump, Waters 510, Waters Division of Millipore, Milford, MA) as reported in our previous study.[15] Briefly, after the addition of ethyl *p*-hydroxybenzoate as an internal standard, a plasma sample was extracted with chloroform. After centrifugation, the organic phase was dried, and the residue was dissolved in *N,N*-dimethylformamide. This solution was injected into a reverse-phase C18 HPLC column (DEVELOSIL ODS-5, 4.6×250 mm, Nomura Chemical Co., Ltd., Seto) at 60°C. The detection limit was 0.05 μg/ml. The intra- and inter-assay coefficients of variation were under 5% and under 10%, respectively.

Statistical analysis The surviving fraction (SF) of blood count was calculated as follows: SF = (nadir count)/(pretreatment count). The pharmacodynamic relationships were evaluated by linear regression analysis and a value of $P<0.05$ was considered to be statistically significant.

RESULTS

Fifteen patients received a total of 26 courses of the 21-day oral etoposide therapy between July 1994 and May 1995 (Table II). The number of courses per patient was 1 to 4 with a median of 2. Compliance regarding drug intake was confirmed in all patients. Seven patients could not receive more than one course because of disease progression in two, worsened performance status in one, request to change the regimen in one, grade 4 leukopenia in one, treatment-related death in one, and early death

Table II. Characteristics of Patients

Number of eligible patients	15
Men/Women	11/4
Median age (years) (range)	56 (44–70)
Performance status	
0/1/2/3	2/4/6/3
Clinical stage	
IIIB/IV/Postoperative relapse	4/8/3
Histology	
Adenocarcinoma	9
Squamous cell	4
Small cell	2
Prior therapy	
Chemotherapy	1
Chemo-radiotherapy	1
Radiotherapy	
Chest	2
Brain	1
Surgery and chemotherapy	3
Neither	7

Table III. Toxicities by WHO Grade (All Courses)

	Grade				
	0	1	2	3	4
Leukopenia	4	3	13	4	2
Neutropenia	7	7	5	5	2
Anemia	6	7	3	8	2
Thrombocytopenia	24	0	1	1	0
Nausea/Emesis	18	1	4	3	0
Mucositis	19	4	1	2	0
Alopecia[a)]	4	14	3	0	0
Liver	23	2	1	0	0
Renal	25	1	0	0	0

a) Twenty-one of 26 courses were evaluable.

due to primary disease in one (on day 27). Two subsequent courses were delayed by 1 week due to leukopenia.

Two patients experienced grade 4 leukopenia with fever on day 15 and day 18 in the first course, respectively (Table III), when they discontinued the chemotherapy and began to receive CSF and antibiotics. One of them also developed non-paralytic ileus, grade 3 mucositis and grade 1 renal disturbance. Despite intensive treatment, he died on day 20. Two patients experienced grade 4 anemia that improved after treatments without blood transfusion. Three patients had grade 3 nausea/emesis.

Among 9 patients with measurable lesions from non-small-cell lung cancer, five displayed no change and four had progressive disease. One patient with small cell lung cancer had a partial response, but wished to change her regimen to cisplatin plus intravenous etoposide, because her performance status had improved. Another patient with small cell lung cancer died of the primary disease at day 27 though her chest discomfort had improved remarkably with the treatment.

Pharmacologic analyses When the LSM for the 25×3 mg/day schedule was validated in 6 patients receiving 4 capsules a day, the estimation of C_{mean} by the model was well correlated with the measured mean concentration ($r=0.991$, $P=0.0001$, n=6), and was considered to be unbiased (MPE=−0.01 μg/ml, −1.0%) and precise (RMSE=0.03 μg/ml, 2.8%). Therefore, this model was applicable to patients on 4 capsules a day.

The dose escalation could not be performed according to Table I due to nausea/emesis in two courses of one patient, who was therefore excluded from the pharmacokinetic analyses. In two patients whose chemotherapy was discontinued on day 15 and day 18, respectively, the C_{mean} of day 10 was substituted for the C_{after} in the former, and the C_{mean} of day 18 was substituted for that of day 20 in the latter. Accordingly, the data on 14 patients given 24 courses were used in the pharmacokinetic analyses of dose modification. There were no significant differences of C_{mean} between days 3 and 4 and between days 10 and 20.

Among the 24 courses in which the planned dose modification was performed, the mean dose administered was 75±15 mg/body/day (mean±SD), which corresponded to 49±8 mg/m²/day (range, 29 to 60 mg/m²/day). In the 5 courses of 4 patients where the dose was reduced to 50 mg/body/day, the mean concentration was decreased from 1.7±0.1 (C_{before}) to 1.3±0.2 (C_{after}) μg/ml (mean±SE). In one patient with the C_{before} of 2.0 μg/ml, the mean concentration was not decreased despite the dose reduction (Fig. 1). In the 7 courses of 6 patients with C_{before} under 1.0 μg/ml, the concentration was increased from 0.9±0.0 (C_{before}) to 1.2±0.1 (C_{after}) μg/ml after dose escalation to 100 mg/body/day. In the remaining 12 courses in 9 patients without dose modification, the C_{before} and the C_{after} were 1.2±0.0 and 1.3±0.1 μg/ml, respectively. Eventually, the C_{after} was within 1.0 to 1.5 μg/ml in 13 of 24 courses.

The pharmacodynamic analyses were performed in the first courses only (n=15). A log-transformed SF of leukocyte count tended to correlate inversely with C_{after}

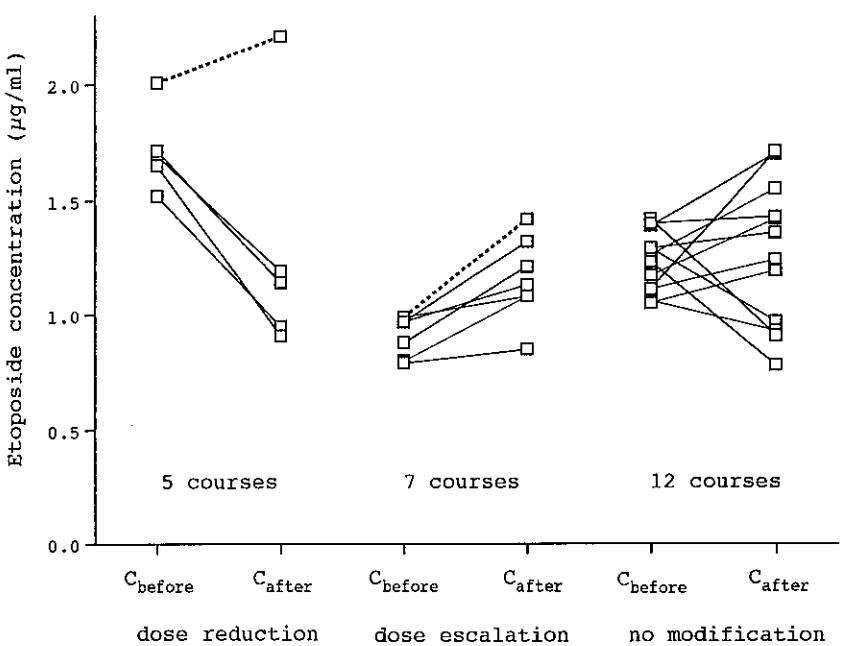

Fig. 1. Etoposide concentrations before (C_{before}) and after (C_{after}) dose modification are shown according to three modification styles. Dotted lines indicate the values of the patients who experienced grade 4 leukopenia and neutropenia.

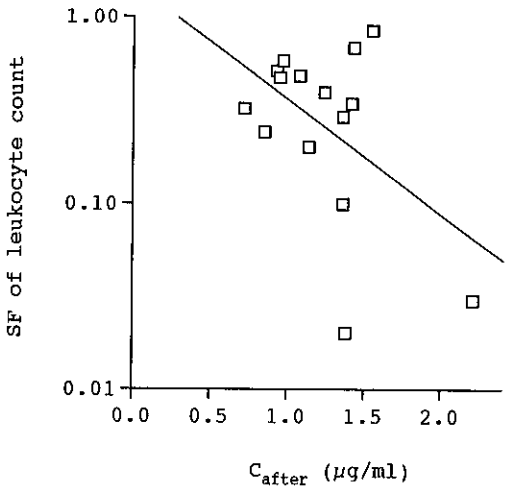

Fig. 2. Log-transformed surviving fraction (SF) of leukocyte count tends to correlate with the mean etoposide concentration after dose modification (C_{after}, $r=0.491$, $P=0.0631$).

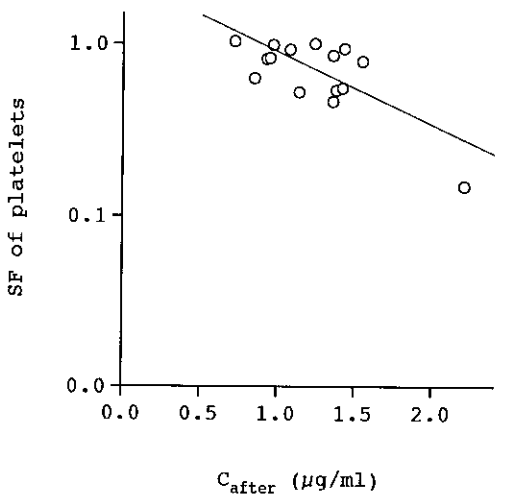

Fig. 3. Log-transformed surviving fraction (SF) of platelets correlates significantly with the mean etoposide concentration after dose modification (C_{after}, $r=0.742$, $P=0.0015$).

($r=0.491$, $P=0.0631$, Fig. 2). There was a significant inverse correlation between log-transformed SF of platelets and C_{after}, though thrombocytopenia was not a substantial clinical problem ($r=0.742$, $P=0.0015$, Fig. 3). There was no apparent correlation between the C_{after} and other hematologic and non-hematologic toxicities, including neutropenia, anemia, nausea/emesis, mucositis, or alopecia.

DISCUSSION

The etoposide concentrations could be controlled as intended in most courses. Patients whose dose was reduced could avoid unnecessary side effects, and most patients were treated safely during their chemotherapy. On the other hand, maintaining the etoposide concentration above 1 μg/ml is believed to improve the antitumor activity of the drug, albeit no patients with non-small-cell lung cancer had a partial response in this study.[6, 7, 10, 11] Because we did not examine whether the TDM reduces the toxicities and improves the treatment results, a larger study remains necessary to confirm that the therapeutic efficacy is improved by introducing TDM rather than conventional methods.

In the patients without the dose modification, the distribution of C_{after} was scattered around the target range, whereas their C_{before} values were within the target range (Fig. 1). This fact implies that intra-patient variability lessened the benefits of the TDM on individualization of the present chemotherapy. However, we could prevent C_{after} above 1.5 μg/ml from becoming higher in most courses, and that below 1.0 μg/ml from becoming lower by means of the TDM strategy. Thus, the inter-patient variability of the etoposide concentration could be reduced. We believe that unnecessary toxicity, which might otherwise have occurred if high concentrations had been maintained, was prevented in some patients.

The etoposide concentration was not decreased by dose reduction in one patient. It is difficult to manage the drug concentration by altering the dose uniformly based on the concentration, especially when a drug is administered orally. The relationship between the dose and concentration varies depending on the patient's physiopathologic characteristics or the targeted concentration range. For more precise adaptive control, the concept of population pharmacokinetics, including these characteristics, should be useful.[20]

One patient encountered severe leukopenia and neutropenia even though the C_{after} was within the target range after the dose escalation. We could not pinpoint the reason for this unpredictable toxicity, and the dose escalation in this protocol might enhance the toxicities. This fact suggested that these toxicities can not be predicted from the plasma concentration only. Other factors, i.e., age, gender, liver and renal function, treatment history, etc., should be included in a future pharmacodynamic model. Furthermore, drug delivery to the target site and sensitivity to the drug would be important factors. The target concentration range for TDM should be individualized on the basis of such information, whenever available.

Our results suggested that TDM is applicable to prolonged oral etoposide treatment and might be effective.

However, the benefit of TDM was not obvious in this study because the distribution of the C_{before} (0.8 to 2.0 μg/ml) was relatively narrow compared with the target range (1.0 to 1.5 μg/ml). The TDM would be more effective when the patient population is more heterogeneous, i.e., in elderly patients, or when we use a drug with larger inter-patient variability in terms of its pharmacokinetics.

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REFERENCES

1) Fleming, R. A., Miller, A. A. and Stewart, C. F. Etoposide: an update. *Clin. Pharm.*, **8**, 274–293 (1989).
2) O'Dwyer, P. J., Leyland-Jones, B., Alonso, M. T., Marsoni, S. and Wittes, R. E. Etoposide (VP-16-213). Current status of an active anticancer drug. *N. Engl. J. Med.*, **312**, 692–700 (1985).
3) Radice, P. A., Bunn, P. A., Jr. and Ihde, D. C. Therapeutic trials with VP-16-213 and VM-26: active agents in small cell lung cancer, non-Hodgkin's lymphomas, and other malignancies. *Cancer Treat. Rep.*, **63**, 1231–1237 (1979).
4) Abratt, R. P., Willcox, P. A., de Groot, M., Goodman, H. T., Jansen, E. R. and Mame Salton, D. G. Prospective study of etoposide scheduling in combination chemotherapy for limited disease small cell lung carcinoma. *Eur. J. Cancer*, **27**, 28–30 (1991).
5) Cavalli, F., Sonntag, R. W., Jungi, F., Senn, H. J. and Brunner, K. W. VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosage schedules. *Cancer Treat. Rep.*, **62**, 473–475 (1978).
6) Slevin, M. L., Clark, P. I., Joel, S. P., Malik, S., Osborne, R. J., Gregory, W. M., Lowe, D. G., Reznek, R. H. and Wrigley, P. F. M. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. *J. Clin. Oncol.*, **7**, 1333–1340 (1989).
7) Greco, F. A. Chronic etoposide administration: overview of clinical experience. *Cancer Treat. Rev.*, **19** (Suppl. c), 35–45 (1993).
8) Johnson, D. H., Greco, F. A., Strupp, J., Hande, K. R. and Hainsworth, J. D. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J. Clin. Oncol.*, **8**, 1613–1617 (1990).
9) Waits, T. M., Johnson, D. H., Hainsworth, J. D., Hande, K. R., Thomas, M. and Greco, F. A. Prolonged administration of oral etoposide in non-small-cell lung cancer: a phase II trial. *J. Clin. Oncol.*, **10**, 292–296 (1992).
10) Minami, H., Shimokata, K., Saka, H., Saito, H., Ando, Y., Senda, K., Nomura, F. and Sakai, S. Phase I clinical and pharmacokinetic study of a 14-day infusion of etoposide in patients with lung cancer. *J. Clin. Oncol.*, **11**, 1602–1608 (1993).
11) Clark, P. I., Slevin, M. L., Joel, S. P., Osborne, R. J., Talbot, D. I., Johnson, P. W. M., Reznek, R., Masud, T., Gregory, W. and Wrigley, P. F. M. A randomized trial of two etoposide schedules in small-cell lung cancer: the influence of pharmacokinetics on efficacy and toxicity. *J. Clin. Oncol.*, **12**, 1427–1435 (1994).
12) Miller, A. A., Tolley, E. A., Niell, H. B., Griffin, J. P. and Mauer, A. M. Pharmacodynamics of prolonged oral etoposide in patients with advanced non-small-cell lung cancer. *J. Clin. Oncol.*, **11**, 1179–1188 (1993).
13) Harvey, V. J., Slevin, M. L., Joel, S. P., Smythe, M. M., Johnston, A. and Wrigley, P. F. M. Variable bioavailability following repeated oral doses of etoposide. *Eur. J. Cancer Clin. Oncol.*, **21**, 1315–1319 (1985).
14) Slevin, M. L., Joel, S. P., Papamichael, D., Smith, I., Ellis, P., Nicolson, M., Woodhull, J. and Talbot, D. C. Therapeutic monitoring of infusional etoposide in previously untreated small cell lung cancer (SCLC). *Proc. Am. Soc. Clin. Oncol.*, **13**, 133 (1994).
15) Ando, Y., Minami, H., Saka, H., Ando, M., Sakai, S. and Shimokata, K. Therapeutic drug monitoring of etoposide in a 14-day infusion for non-small-cell lung cancer. *Jpn. J. Cancer Res.*, **87**, 200–205 (1996).
16) Hande, K. R., Krozely, M. G., Greco, F. A., Hainsworth, J. D. and Johnson, D. H. Bioavailability of low-dose oral etoposide. *J. Clin. Oncol.*, **11**, 374–377 (1993).
17) Minami, H., Ando, Y., Sakai, S. and Shimokata, K. Clinical and pharmacologic analysis of hyperfractionated daily oral etoposide. *J. Clin. Oncol.*, **13**, 191–199 (1995).
18) "WHO Handbook for Reporting Results of Cancer Treatment," Offset publication 48 (1979). World Health Organization, Geneva.
19) Sheiner, L. B. and Beal, S. L. Some suggestions for measuring predictive performance. *J. Pharmacokinet. Biopharm.*, **9**, 503–512 (1981).
20) Beal, S. L. and Sheiner, L. B. Methodology of population pharmacokinetics. *In* "Drug Fate and Metabolism, vol. 5," ed. E. R. Garrett and J. Hirtz, pp. 135–183 (1985). Marcel Dekker, New York.