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# Therapeutic Drug Monitoring of Etoposide in a 14-Day Infusion for Non-small-cell Lung Cancer

Yuichi Ando,[1,2] Hironobu Minami,[1] Hideo Saka,[1] Masahiko Ando,[2] Shuzo Sakai[2] and Kaoru Shimokata[1,3]

*[1]First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai, Showa-ku, Nagoya 466 and [2]Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita, Nakamura-ku, Nagoya 453*

**We investigated whether a constant plasma concentration could be obtained by the individualized administration of low-dose, prolonged-infusional etoposide. Etoposide was infused for 14 days at 40 mg/m$^2$/day initially in patients with inoperable non-small-cell lung cancer. The infusion rate was modified based upon the etoposide concentration at 24 h following the initiation of the infusion ($C_{24}$) to achieve a target concentration of 1.5 $\mu$g/ml. We postulated that severe toxicities could be avoided by maintaining the steady-state concentration at less than 2 $\mu$g/ml, while antitumor activity could be expected if the steady-state concentration was maintained at more than 1 $\mu$g/ml. In a total of 21 courses in 12 patients, the mean etoposide dose was 35±6 mg/m$^2$ daily. The $C_{24}$ was 1.8±0.4 $\mu$g/ml and ranged from 1.1 to 2.9 $\mu$g/ml. Following dose modification, the mean concentration from 96 to 336 h ($C_{mean}$) was 1.6±0.2 $\mu$g/ml and ranged from 1.2 to 2.0 $\mu$g/ml. The toxicities were well-tolerated except for one patient with WHO grade 4 leukopenia and neutropenia who developed infectious complications. There were no treatment-related deaths. Following dose modification, the inter-patient variability was decreased successfully. Although this pharmacologically-guided method needs to be validated using more patients, it could be used for therapeutic drug monitoring.**

Key words: Etoposide — Low dose — Drug monitoring — Pharmacokinetics — Non-small-cell lung cancer

Etoposide is a semi-synthetic derivative of podophyllotoxin, and is efficacious against small-cell lung cancer, testicular cancer, malignant lymphoma and leukemia, and probably against non-small-cell lung cancer.[1-3] Etoposide works through a reversible interaction with topoisomerase II,[4,5] and its efficacy has been shown to be cell cycle-dependent[6] and related to the duration of drug exposure *in vitro*.[7-9] Furthermore, clinical studies have demonstrated that etoposide has a schedule-dependent effect.[10-12] Prolonged exposure to low concentrations of the drug is important for its antitumor efficacy and, for the same total dose of etoposide, the administration of divided doses is more effective than a single dose. However, the most appropriate administration schedule is still unclear in the clinical setting.

Because continuous infusion can be used to maintain low concentrations for a prolonged period[13,14] and is helpful for determining the relationship between the pharmacokinetic parameters and the clinical effects, we have conducted a phase I study of 14-day infusional etoposide.[15] The results indicated that the optimal dose was 600 mg/m$^2$ over 14 days. In addition, patients who had responses achieved a steady-state concentration of 1.2 to 1.8 $\mu$g/ml. On the other hand, severe toxicities were observed in the patients whose steady-state concentrations were greater than 2.0 $\mu$g/ml. These observations on the pharmacodynamics are consistent with the results of prior studies suggesting that the duration of exposure to low concentrations (1 $\mu$g/ml) is important for antitumor effect, while the hematologic toxicity is dependent upon exposure to higher concentrations (2 to 3 $\mu$g/ml).[12,16-18]

However, because there is considerable inter-patient variability in etoposide pharmacokinetics,[2,19] it is difficult to achieve the same concentration in different patients with a uniform dose based on the body surface area (BSA). Slevin *et al.*[20] conducted a dose escalation study of a 5-day etoposide infusion guided by the concentration in untreated small-cell lung cancer patients. The results showed that the marked variability of the steady-state etoposide concentration was reduced following the dose modification. They suggested that the etoposide concentration could not be predicted following dosing based upon the BSA, and that therapeutic monitoring with early modification is needed to obtain reproducible concentrations.

Based on these suggestions, we intended to maintain a steady-state concentration of 1.5 $\mu$g/ml over a 14-day infusion of etoposide for chemo-naive patients with non-small-cell lung cancer[17,21] using therapeutic drug monitoring (TDM). We postulated that severe toxicities might be avoided by modifying the infusion rate to obtain a concentration of less than 2 $\mu$g/ml, and that

[3] To whom requests for reprints should be addressed.

antitumor activity could be expected by maintaining the concentration above 1 $\mu$g/ml. The objective of this study was to investigate the possible improvement of the therapeutic index by dose modification based upon the steady-state concentration of etoposide delivered by low-dose, prolonged infusion.

## PATIENTS AND METHODS

**Patient eligibility** Patients had to fulfill all of the following criteria: histologic or cytologic proof of non-small-cell lung cancer; stage IIIB or stage IV disease; no prior chemotherapy; no other serious disease, including uncontrollable pleural or pericardial effusion, heart failure, or severe infection; age $\leq$75 years; estimated life expectancy $\geq$6 weeks; a performance status between 0 and 2 on the Eastern Cooperative Oncology Group (ECOG) scale; a leukocyte count $\geq$3,500/$\mu$l; platelets $\geq$100,000/$\mu$l; a serum creatinine $\leq$2.0 mg/dl; transaminases $\leq 2 \times$ the upper limit of normal; a total bilirubin $\leq$2.0 mg/dl; and albumin $\geq$3.0 g/dl. Patients with a postoperative relapse and those who had previously received radiotherapy were eligible, but a recovery period of 4 weeks was required prior to entry into the study. Because response to chemotherapy was not a primary endpoint of this study, patients without measurable lesions were eligible. All patients gave their informed consent prior to commencing the study.

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 and direct bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, creatinine, and urea nitrogen; a creatinine clearance measured from 24-h urine; 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. If one of these tests was abnormal, further evaluations were performed. 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; chest radiograph; and urinalysis once a week. Additional studies were repeated in patients with measurable disease. Follow-up chest CT scans were performed at 4 and/or 8 weeks, and other examinations were repeated when disease progression was suspected clinically.

**Etoposide dose and administration** All patients were treated as inpatients. The method of etoposide administration was identical to that in our prior study.[15] Etoposide was diluted in a 5% glucose solution and was infused continuously for 14 days via a central venous line using a drip pump (IVAC 530, IVAC Corporation, San Diego, CA). To keep the steady-state concentration at 1.5 $\mu$g/ml, we empirically determined that a starting dose of 40 mg/m$^2$/day of etoposide was optimal. Antiemetics were not used routinely. Colony-stimulating factors were administered along with antibiotics when patients developed a neutropenic fever. Chemotherapy was repeated every 4 weeks until disease progression or refusal by the patient. The etoposide infusion was discontinued before 14 days had elapsed following the initiation of the infusion if the platelet count fell below 25,000/$\mu$l for more than 3 days, or there was a World Health Organization (WHO) grade 3 or greater nonhematologic toxicity other than alopecia or emesis.[22]

**Sampling** Heparinized blood samples were obtained at 24, 96, 192, 288 and 336 h following the initiation of the infusion, and at 1, 3 and 6 h following the termination of the infusion. The sampling 336 h following the initiation of the infusion was performed just prior to the termination of the infusion. The plasma was immediately separated by centrifugation. The samples were stored at $-20$°C until analysis.

**Dose modification** The etoposide concentration of the sample 24 h following the initiation of the infusion ($C_{24}$) was determined immediately. The infusion rate was modified by 30 h following the initiation of the infusion based on the $C_{24}$. We considered the $C_{24}$ as a steady-state concentration because, in our phase I study, the steady-state concentration of etoposide was achieved 24 h after the start of chemotherapy and it was significantly correlated with hematologic toxicities.[15, 23, 24] We hypothesized that the etoposide concentration correlated linearly with the infusion rate after reaching this state. Therefore, the infusion rate was modified using the following formula: modified infusion rate = current infusion rate $\times$ (1.5/$C_{24}$). The etoposide concentration in a glucose solution was changed so that the total infusion volume ranged from 700 to 1,500 ml/day. Otherwise, the etoposide concentration in the glucose solution was not changed throughout the 14-day infusion. For successive courses, the starting infusion rate was the same as the modified one in the previous course, and it was modified again based on the $C_{24}$.

**Etoposide plasma concentration** The etoposide concentration was determined by high-performance liquid chromatography (HPLC pump, Waters 510, Waters Division of Millipore, Milford, MA) with an ultraviolet detector (Absorbance Detector Model 441, Waters Associates, Milford, MA) set at 280 nm. After the addition of ethyl *p*-hydroxybenzoate as an internal standard, 1 ml of plasma was extracted with 8 ml of chloroform. After centrifugation, the organic phase was dried at 40°C, and the residue was dissolved in 200 ml of N,N-dimethylformamide.

Forty microliters of this solution was injected into the HPLC using an automatic injector (WISP 710B, Waters Associates). The mobile phase was composed of 1396:14:560 (vol:vol:vol) 0.02 *M* sodium sulfate:acetic acid:acetonitrile, and the HPLC separations were achieved at a flow rate of 1.2 ml/min at a temperature of 60°C using a reverse-phase C18 column (DEVELOSIL ODS-5, 4.6× 250 mm, Nomura Chemical Co., Ltd., Seto). The detection limit was 0.05 $\mu$g/ml. The intra- and inter-assay coefficients of variation (CV) were under 5% and 10%, respectively.

**Treatment evaluation** Patients who received at least one course of chemotherapy were assessed for toxicity and response using standard WHO criteria.[22]

**Pharmacokinetic studies** The mean concentration ($C_{mean}$) was calculated using the arithmetic mean of concentrations at 96, 192, 288 and 336 h following the initiation of the infusion. Using the computer program MULTI,[25] the elimination half-life ($T_{1/2}$) was calculated from the equation: $T_{1/2}=\ln 2/k$, where $k$ is the elimination rate constant given by the slope of the natural logarithm of the concentration versus time. Other parameters were calculated as follows: systemic clearance ($Cl_s$) =infusion rate following the modification/$C_{mean}$; distribution volume at steady-state ($V_{ss}$)=$Cl_s/k$.

**Statistical analysis** All data other than $T_{1/2}$ were reported as the arithmetic mean±standard deviation (SD), and the $T_{1/2}$ as the harmonic mean±pseudo standard deviation.[26] The coefficient of variation (CV) was defined as follows: CV=SD/mean×100. Survival was calculated from the date of starting chemotherapy to the last follow-up exam or death. Differences were evaluated by using the Wilcoxon signed-rank test. The *P* values were two-sided. Differences of variances were evaluated by the F test, and the *P* values were one-sided. A value of $P<0.05$ was considered to be statistically significant.

## RESULTS

**Patient population** Twelve patients, nine men and three women, received a total of 21 courses of the 14-day infusion of etoposide between July 1993 and June 1994 (Table I). Their median age was 64.5 years (range, 56 to 71 years). Two patients with stage IIIB had malignant pleural effusion and pericardial effusion, respectively. Among the eight patients with stage IV disease, the number of metastatic sites ranged from 1 to 4 (median 1.5). One patient had received prior radiotherapy to his thoracic spine with a total dose of 38 Gy. The creatinine clearance of the patients ranged from 33 to 93 ml/min with a median of 63 ml/min.

**Treatment** The etoposide infusions were completed in every cycle. The number of etoposide infusions was 1 in six patients, 2 in three, and 3 in three. The total etoposide dose actually administered in each cycle was 493±82 mg/m$^2$, which was 99% of the intended dose (498±92 mg/m$^2$), assuming that the infusion rate of etoposide was modified only at 30 h following the initiation of the infusion. Eventually, the mean dose of etoposide was 35 ±6 mg/m$^2$ daily.

The actual dose of etoposide administered in the first and subsequent courses was 522±84 mg/m$^2$ (n=12) and 454±65 mg/m$^2$ (n=9), respectively.

Table I. Characteristics of Patients

| | |
|---|---|
| Number of eligible patients | 12 |
| Men/Women | 9/3 |
| Age (years) | |
| Median | 64.5 |
| Range | 56–71 |
| ECOG performance status | |
| 0/1/2 | 3/4/5 |
| Clinical stage | |
| IIIB/IV/postoperative relapse | 2/8/2 |
| Histology | |
| Adenocarcinoma | 9 |
| Squamous cell | 2 |
| Large cell | 1 |
| Prior therapy | |
| Radiotherapy | 1 |
| Surgery | 2 |
| Neither | 9 |

Table II. Hematologic Toxicities

| | Grade | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| First course (Total=12) | | | | | |
| Leukocyte | 0 | 4 | 4 | 3 | 1 |
| Neutrophil | 0 | 1 | 4 | 3 | 4 |
| Hemoglobin | 2 | 4 | 4 | 2 | 0 |
| Platelets | 11 | 0 | 0 | 1 | 0 |
| All courses (Total=21) | | | | | |
| Leukocyte | 1 | 9 | 7 | 3 | 1 |
| Neutrophil | 2 | 3 | 7 | 4 | 5 |
| Hemoglobin | 3 | 6 | 8 | 4 | 0 |
| Platelets | 18 | 1 | 0 | 2 | 0 |

**Hematologic toxicity** The hematologic toxicities were well-tolerated. There were no treatment-related deaths. The most common hematologic toxicity was neutropenia (Table II). Only one patient had WHO grade 4 leukopenia (8% of the first course, and 5% of all the courses). The median leukocyte nadir was 2,500/$\mu$l (range, 100 to 3,800/$\mu$l) for the first course, and 2,900/$\mu$l (range, 100 to 4,700/$\mu$l) for all of the courses. Grade 4 neutropenia was observed in five courses in four patients. Grade 3 anemia was observed in four courses in two patients, and grade 3

Table III. Pharmacokinetic Parameters

| | $T_{1/2}$ (h) | $Cl_s$ (ml/min/m$^2$) | $V_{ss}$ (liter/m$^2$) | $C_{24}$ ($\mu$g/ml) | $C_{mean}$[a] ($\mu$g/ml) |
|---|---|---|---|---|---|
| All courses (Total=21) | | | | | |
| Mean±SD | 6.0±1.9 | 15.1±2.5 | 8.8±3.5 | 1.8±0.4 | 1.6±0.2 |
| Range | 3.9–19.8 | 11.1–19.6 | 5.6–19.9 | 1.1–2.9 | 1.2–2.0 |
| First course (Total=12) | | | | | |
| Mean±SD | 5.4±1.4 | 15.8±2.2 | 7.7±2.0 | 1.7±0.3 | 1.6±0.2 |
| Range | 3.9–9.8 | 12.4–19.6 | 5.6–11.5 | 1.1–2.1 | 1.2–2.0 |

Abbreviations: $T_{1/2}$, half-life, harmonic mean and pseudo standard deviation; $Cl_s$, systemic clearance; $V_{ss}$, distribution volume at steady-state; $C_{24}$, etoposide concentration at 24 h after the initiation of the infusion; $C_{mean}$, mean concentration following dose modification.
*a*) The $C_{mean}$ was calculated using the arithmetic mean of concentrations at 96, 192, 288 and 336 h following the initiation of the infusion.

thrombocytopenia was experienced in two courses in two patients. The leukocyte nadir was observed from 9 to 26 days (median, 20) following the initiation of the infusion, and the neutrophil nadir was from 15 to 28 days (median, 22). The hemoglobin and platelet nadirs were observed from 10 to 24 days (median 17) and from 6 to 21 days (median, 17), respectively, following the initiation of the infusion. One patient experienced WHO grade 4 leukopenia and neutropenia complicated with pneumonia on day 17, when the administration of colony-stimulating factors and parenteral antibiotics was started. He recovered well by day 25.

**Nonhematologic toxicity** One patient experienced WHO grade 3 nausea, but no other WHO grade 3 or greater nonhematologic toxicities were observed. Alopecia developed in all evaluable patients. Grade 1 or 2 stomatitis occurred in seven courses in six patients. Grade 1 or 2 nausea was encountered in ten courses in seven patients.

**Pharmacokinetics** Pharmacokinetic evaluations were performed in all courses (Table III). The pharmacokinetic parameters obtained in this study were comparable with those in a previous study.[15] There was no apparent relationship between these pharmacokinetic parameters and the creatinine clearance. The $C_{24}$ of all courses was 1.8±0.4 $\mu$g/ml and ranged from 1.1 to 2.9 $\mu$g/ml. Following dose modification, the $C_{mean}$ was 1.6± 0.2 $\mu$g/ml and ranged from 1.2 to 2.0 $\mu$g/ml. Although the difference between the $C_{24}$ and $C_{mean}$ was not significant ($P$=0.296), the inter-patient CV of the etoposide concentrations was decreased from 22% to 12% by the dose modification. The values of inter-patient CV at each sampling point were 14% ($P$=0.015), 13% ($P$=0.008), 19% ($P$=0.102), and 19% ($P$=0.153) at 96, 192, 288, and 336 h following the initiation of the infusion, respectively. The inter-patient CV of concentrations from 96 to 336 h tended to become greater as the treatment time increased. During the first course in all patients, the difference between the $C_{24}$ and $C_{mean}$ was small (1.7±0.3 $\mu$g/ml versus 1.6±0.2 $\mu$g/ml, $P$=0.859), but the inter-patient CV was also decreased from 17% to 13% by the dose modification.

The intra-patient CV of the etoposide concentrations from 96 to 336 h was 11±7% and ranged from 3% to 25% with a median of 11%.

**Pharmacodynamics** The hematologic toxicities and $C_{mean}$ were not clearly related in this study. In the patient who experienced WHO grade 4 leukopenia, the $C_{24}$ and $C_{mean}$ were 1.7 and 1.5 $\mu$g/ml, respectively. In the five courses in four patients with WHO grade 4 neutropenia, the $C_{mean}$ was 1.7±0.1 $\mu$g/ml (range, 1.5 to 1.9). The intra-patient CV of the concentrations from 96 to 336 h also did not correlate with the observed toxicities.

One patient with a $C_{24}$ of 2.9 $\mu$g/ml experienced WHO grade 3 nausea, and his symptoms improved after the $C_{mean}$ decreased to 1.7 $\mu$g/ml following dose reduction. However, there was no apparent relationship between the nonhematologic toxicities and the $C_{mean}$.

**Treatment outcome** Eight patients had measurable lesions. One (13%; 95% confidence interval, 0% to 37%) had a partial response, and the duration of this response was 5 weeks. Five (63%) had no change, and two (25%) had progressive disease. The patients who had a partial response achieved a $C_{mean}$ of 1.9 $\mu$g/ml. Nine patients (75%) had died by October 20, 1995. The median survival of all the patients was 29 weeks (range, 6 to 100+ weeks).

## DISCUSSION

Using dose modification during the early steady-state (24 h following the initiation of the infusion), the $C_{mean}$ could be maintained in the range from 1.2 to 2.0 $\mu$g/ml, and the inter-patient CV of the etoposide concentrations was decreased from 22% to 12%. Because the initial starting dose was adequate for achieving a steady-state concentration of approximately 1.5 $\mu$g/ml, the effect of

the dose modification study became less clear. However, this dose modification protocol based on the etoposide concentration did reduce the inter-patient variability more than did normalizing the dose to the BSA. Because the intra-patient CV of the concentrations from 96 to 336 h was 11%, an inter-patient CV of 12% is likely to be the limit of the dose modification in this study. In the study by Slevin *et al.*,[20] their reduced variability in the etoposide concentration following the dose modification was equivalent to our results.

Our study did not demonstrate a clear correlation between the etoposide concentration and the toxicities. One possibility is that the range of the steady-state concentration was too narrow to show such a correlation. One patient who experienced WHO grade 4 leukopenia developed infectious complications. The $C_{mean}$ of this patient was 1.5 $\mu$g/ml, and we considered that the unbound (active) etoposide concentration was not elevated because the patient's serum albumin and bilirubin were normal.[27] There was no apparent reason for this unexpected toxicity except for the fact that this patient was the oldest in our group (71 years old). In the remaining patients, the toxicities were well-tolerated, and severe toxicities seemed to be avoided owing to the dose modification. Except for the neutrophil count, the proportion of WHO grade 4 toxicities relative to that of grade 3 seemed to be small. However, it remains unclear from this small study whether the incidence of severe toxicity was decreased by this dose modification protocol.

On the other hand, although the $C_{mean}$ were greater than 1 $\mu$g/ml in all patients, antitumor efficacy was observed in only one patient. It is important to investigate whether antitumor activity could be increased if the etoposide concentrations were maintained at a level greater than 1 $\mu$g/ml. However, the small number of patients in our study precluded us from examining this problem.

In this study, the intra-patient CV of the steady-state concentrations from 96 to 336 h was $11\pm7$%. This is similar to previous studies of infusional etoposide in which the steady-state intra-patient CV was approximately 15%.[15, 23, 24] Because the steady-state concentration of etoposide in a prolonged infusion is very low (approximately 1 $\mu$g/ml), the etoposide level can be markedly affected. This means that a single sampling point is inadequate to predict an etoposide concentration for precise dose modification.[19] For practical convenience, two or three sampling points may be adequate.

The optimal doses of antineoplastic agents have been decided by traditional phase I studies and have been normalized by measuring the body weight and height to calculate the BSA. Dose modifications have been based empirically on the patient's pretreatment characteristics or the effects of the previous treatment cycle. However, this approach has the potential risk that some patients may be undertreated or that others may be overtreated, resulting in severe toxicities. A pharmacologically guided dosing strategy is a new and promising method when there is a relationship between the pharmacokinetic parameters and the pharmacodynamics of drugs such as etoposide.[20, 23, 24] Furthermore, a prolonged administration schedule makes it possible to individualize the treatment by dose modification using TDM. We believe that the prolonged low-dose administration of etoposide would be an appropriate usage and that we can improve the therapeutic index of this drug by decreasing inter-patient variability with TDM. Further studies are needed to confirm the suggestions of this small study.

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