Clinical Pharmacology of Chronic Oral Etoposide in Patients with Small Cell and Non-Small Cell Lung Cancer


Department of Oncology, Mario Negri Institute for Pharmacological Research, 20157 Milan, Italy [M. Z., V. T., M. D., M. D. F., D. G., A. T.], and Division of Oncology, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland [O. P., C. S., J. d. J., G. M., F. C.]

ABSTRACT

We aimed to evaluate the pharmacokinetics and pharmacodynamics of etoposide given chronically by the p.o. route to patients with small cell and non-small cell lung cancer.

Single daily p.o. doses of 100 mg etoposide were given for 21 consecutive days every 4 weeks to 39 previously untreated patients with small cell lung cancer and 10 patients with non-small cell lung cancer. Bioavailability was studied after one i.v. and one p.o. dose of 100 mg etoposide given 48 h before and on day 1 of treatment, respectively. Etoposide plasma levels were measured using the HPLC method. Inter- and intrapatient variability of the area under the curve of the concentration versus time (AUC) during the first cycle was evaluated using a limited sampling model; the variability of etoposide plasma concentrations (Ecs) during the first cycle was assessed by weekly blood samples taken 24 h after dosing.

The overall bioavailability of etoposide (mean ± SD) was 67% ± 22% and was not affected by fasting. A much higher inter- than intrapatient variability of both the AUC and 24-h Ec determined on days 8, 15, and 22 was found. Neutropenia was dose limiting and of varying degrees (mean ± SD of absolute neutrophil count nadir at the first cycle: 1.5 ± 1.2 × 10^3/μl). Neutropenia WHO grade ≥3 occurred in 38% of the patients after the first cycle. Pharmacodynamic analyses showed a significant relationship between the mean 24-h Ec and neutropenia, expressed as log of absolute neutrophil count nadir or as a relative decrease of neutrophils. A correlation between a critical value of mean 24-h Ec (0.34 μg/ml) and a high probability of achieving a greater than 80% decrease in absolute neutrophil count was found. Two pharmacodynamic models (one previously described and one developed in this study) were used to evaluate the possibility of predicting neutropenia on the basis of individual etoposide pharmacokinetics and baseline absolute neutrophil count.

Pharmacokinetic studies have shown a high interpatient variability and a relatively low intrapatient variability of AUC and 24-h Ec. The application of the pharmacodynamic models and mean 24-h Ec cutoff values has proven statistically valid to predict the occurrence of severe neutropenia. However, it remains to be demonstrated in a prospective manner whether the application of pharmacokinetic/pharmacodynamic knowledge can improve the overall therapeutic outcome of chronic p.o. treatment with etoposide.

INTRODUCTION

Etoposide, clinically used for the therapy of a variety of hematological and solid human malignancies (1), is one of the most effective anticancer agents. Data from in vitro and in vivo preclinical studies (2, 3) and more recently from clinical trials (4, 5) suggest that the etoposide activity is schedule dependent. Therefore, several investigations have been undertaken in which etoposide is administered in repeated daily doses. A regimen of chronic p.o. doses of etoposide given for 2 to 3 weeks has been reported to have an activity at least comparable to that observed with conventional i.v. schedules (6, 7). In addition, its ease of outpatient administration and apparent good tolerability have prompted the use of chronic p.o. etoposide in elderly and/or debilitated patients (8).

The main disadvantage of the p.o. administration of etoposide is the interpatient variability of its absorption. Several studies in fact have shown mean bioavailability (F) values ranging from 38 to 76% of the administered dose (9, 10). As a consequence of this variability, the same dose could be toxic in patients with high bioavailability and well tolerated but possibly ineffective in patients with low bioavailability. To minimize this variability it may be theoretically advisable to monitor the drug plasma levels and to consequently adjust the dose in each patient.

The assumption behind any attempt of a pharmacokinetically guided dose adjustment is that toxicity is related to drug plasma levels. However, it is still unclear whether the toxicity is more closely related to the length of time during which a drug concentration higher than a given threshold value is maintained or rather to the AUC^1 value.

The present study was designed to investigate the pharmacokinetic and pharmacodynamic properties of etoposide given

---

1 The abbreviations used are: AUC, area under the curve of concentration versus time; PS, performance status; Ec, etoposide plasma concentration; AUC_{exp}, experimental AUC; AUC_{pred}, predicted AUC; LSM, limited sampling model; ANC, absolute neutrophil count nadir; ANC_{pre}, pretreatment ANC; Clp, plasma clearance; VdB, volume of distribution; CV, coefficient of variation; SCLC, small cell lung cancer; C_{max}, peak concentration; t_{1/2p}, elimination half-life.

---

Received 4/7/95; revised 8/2/95; accepted 8/7/95.

1 Supported by the Italian Association for Cancer Research (Milan, Italy) and the Fondazione Ticinese per la Ricerca sul Cancro.

2 To whom requests for reprints should be addressed. Phone: 41-91-8260393; Fax: 41-91-826044.
Table 1 Characteristics of patients (n = 55)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>41/14</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>67.5</td>
</tr>
<tr>
<td>Range</td>
<td>49–84</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
</tr>
<tr>
<td>SCLC (limited)</td>
<td>40 (16)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>15</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group</td>
<td>2055</td>
</tr>
<tr>
<td>performance status</td>
<td>32</td>
</tr>
</tbody>
</table>

Pharmacokinetic and Pharmacodynamic Studies.

The disappearance of etoposide from the plasma after the first dose was studied in 22 patients, with evaluation of bioavailability in 18 of them (Table 1). The interpatient variability of the AUC on days 1 and 15 of the first cycle was studied in 35 patients; 18 of them were fasting from midnight until at least 4 h after drug consumption. The intrapatient variability of AUC was evaluated in nine patients who were also sampled on days 2 and 3.

Twenty-four h after dosing (before the subsequent daily dose) Ecs were determined weekly during the first cycle. In 46 patients only one determination (day 8) was available, whereas for 41 patients two (days 8 and 15) and for 39 patients three (days 8, 15, and 22) determinations were available. For the purpose of analysis, weekly 24-h Ecs indicated the 24-h Ecs on days 1, 8, and 15, while the mean 24-h Ec indicated the mean of the three available values (days 8, 15, and 22) of the 24-h Ecs in the same patient.

The existence of a pharmacodynamic relationship between neutropenia and some pharmacokinetic parameters determined on day 1 (AUC_{exp} C_{max} t_{1/2P}) was evaluated in 22 patients. The existence of the same relationship with the AUC_{exp} calculated by using a LSM (12) on days 1 and 15, was studied in 25 patients. The relationship between neutropenia expressed as ANC_0 and relative decrease of ANC (see below) and the mean 24-h Ec were evaluated in 39 patients. The mean 24-h Ec data were fitted versus ANC_0 and relative decrease of ANC using a linear model, a log linear model, and a maximum effect model (12). In addition, the validation of the model recently proposed by Miller et al. (13) to predict ANC_0 and described by the equation

\[ \text{ANC}_0 = 0.32 (1 + \text{ANC}_{p} \times e^{-2.47 \times \text{Ec}}) \]

was performed. The model was based both on the mean 24-h Ec and on the ANC_{p} value.

The relative decrease of ANC was calculated as:

\[ \left( \frac{\text{ANC}_0 - \text{ANC}_p}{\text{ANC}_0} \right) \times 100 \]

**Blood Sampling.** Weekly blood samples were taken on days 8, 15, and 22. Blood samples were drawn in the morning before the subsequent daily p.o. dose, the patients having been requested to take the drug always in the morning at a fixed time. To study the disappearance of etoposide from the plasma after the first p.o. administration, the AUC_{exp} was evaluated on day 1 of the first cycle. Plasma samples were taken at time 0 (before drug assumption) and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after treatment. To evaluate the bioavailability, the AUC_{exp} after the i.v. administration of 100 mg etoposide given as a 30-min infusion, was determined 48 h before the start of the p.o. therapy. Sampling times were the same as after p.o. administration, with one additional sample at the end of the infusion.

To assess the interpatient and intrapatient variability of the absorption, AUC_{exp} values were estimated by LSM (14) on different days during the p.o. therapy, with blood samples taken before, 1 h after, and 4 h after drug consumption.

Etoposide concentrations were determined in plasma using the HPLC method after solvent extraction, as previously described by Evans et al. (15). In our hands the detection limit of the method was 0.1 µg/ml. The linearity was quite good, with a coefficient of correlation r between the added concentration and the peak responses always ≥0.995 over the range of the calibration curve.

**Pharmacokinetic Calculations.** The AUC_{exp} was calculated using the trapezoidal rule from 0 to 24 h. and t_{1/2P}, bioavailability (F), Clp, and the Vdβ were calculated using these formulas:
where β is the elimination rate constant indicating the slope of the plasma concentration versus time curve calculated using a general nonlinear fitting program (16) and $AUC_{0\rightarrow\infty}$ is the $AUC_{exp}$ obtained after i.v. administration extrapolated to infinite.

$AUC_{pr}$ was determined by using the already reported and validated LSM (14). The model predicting the 24-h AUC is described using Eq. A:

$$AUC_{pr}(\mu g/ml h) = 5.190(\mu g/ml h) + 1.193(h) \times C_{1}(\mu g/ml) + 8.439(h) \times C_{4}(\mu g/ml) \quad (A)$$

where $C_{1}$ and $C_{4}$ are the values of the etoposide concentration determined at 1 and 4 h after p.o. administration.

**Statistical Analysis.** Pharmacokinetic parameters were compared between groups by using Duncan’s test; interpatient and intrapatient variability of the drug concentrations and AUC were also expressed as CV percentage.

For hematological toxicity analysis, the ANC and the relative percentage of decrease of ANC were expressed as function of the patient’s characteristics (age, PS), biochemical values (bilirubin, albumin, and creatinine), and pharmacokinetic parameters ($C_{max}$, $t_{1/2}$, weekly 24-h Ecs, mean 24-h Ec, and $AUC$) in univariate and multivariate regression analyses performed using Statistical Application Software (6.07 release; SAS, Cary, NC). Display for the best cutoff point of association between the mean 24-h Ec on days 8, 15, and 22 and neutropenia was defined by analyzing the receiver-operating characteristics curve (17). Ecs in patients who responded and in those who did not respond to treatment were compared using Duncan’s test.

**RESULTS**

**Pharmacokinetic Studies.** Etoposide plasma levels (mean ± SD), normalized to the dose of 100 mg/m², determined after p.o. and i.v. administration of 100 mg in 12 previously untreated patients are reported in Fig. 1. Table 2 reports the pharmacokinetic parameters (mean ± SD) of etoposide after the first dose in 22 patients without previous chemotherapy and in 6 patients pretreated with chemotherapy and/or radiotherapy. The weekly 24-h Ecs (normalized to 100 mg/m²) on days 8, 15, and 22 revealed a high interpatient variability (CV ≥ 50%) during the treatment (Table 3). The interpatient variability of 24-h Ecs was not related to a difference in the etoposide dose expressed in mg/m². In the same group of patients, the intrapatient variability, determined in 39 patients who were sampled on at least three occasions, was lower with a median CV of 29%.

The interpatient variability of the AUC determined by using LSM was evaluated in 35 patients on different days of the first cycle. Fig. 2 reports the mean ± SD and CV values of the $AUC_{pr}$ (normalized to 100 mg/m²) of days 1 and 15 in two groups of patients, one of them fasting and the other nonfasting. No statistical difference was found between the two groups. The variability of AUC was similar in the two groups, with values ranging from 35 to 58%.

After two p.o. administrations, the maximum intrapatient variability of AUC was 32%. The intrapatient variability of the AUC over 3 days, evaluated in nine patients, was relatively low, with a median CV value of 17% (range, 1–30%; Fig. 3).

**Toxicity and Tumor Response.** Forty-five patients were evaluable for toxicity after the first cycle of treatment, with seven of them requiring a treatment interruption because of neutropenia. Neutropenia proved to be highly variable among patients, with an ANC (mean ± SD) of 1.5 ± 1.2 × 10³/μl (range, 0.1–5.5) and a relative decrease of ANC (mean ± SD) of 70 ± 23% (range, 20–99) after the first cycle. After the first cycle, neutropenia WHO grade ≥3 was observed in 38% of patients but neutropenic fever occurred in only 11%, complicated by septic death in one patient with progressive extensive SCLC. The ANC occurred at the end of the 3 weeks of therapy in the majority of patients, with recovery to normal values in the following week. Severe thrombocytopenia was never observed. The multivariate analysis was performed by examining as risk factors for hematological toxicity age, PS, creatinine value, albumin value, weekly 24-h Ecs (determined either on day 8 or 15), mean 24-h Ec, and AUC. Only the baseline creatinine value (P = 0.010) and mean 24-h Ec (P = 0.011) were correlated with the relative decrease of ANC.

Among 14 evaluable patients with limited disease SCLC, complete and partial responses were achieved in 3 and 6 patients, respectively, for an overall response rate of 64% (95% confidence intervals, 35–87%). Only partial responses were observed in 10 of 19 evaluable patients with extensive SCLC, with an overall response rate of 53% (95% confidence intervals,
Table 2 Mean (±SD) pharmacokinetic parameters after 100 mg of p.o. and i.v. etoposide

<table>
<thead>
<tr>
<th>Previous treatment</th>
<th>No. of patients</th>
<th>t_{max} \text{a} (h)</th>
<th>C_{max} (µg/ml)</th>
<th>t_{1/2β} (h)</th>
<th>AUC_{exp} (µg/ml h)</th>
<th>Clp (ml/min/m²)</th>
<th>Vdβ (liter/m²)</th>
<th>F (%)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.o.</td>
<td>22</td>
<td>1.25b</td>
<td>7.8 ± 3.2</td>
<td>6.0 ± 1.5</td>
<td>56.9 ± 22.0</td>
<td>69 ± 27</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>12</td>
<td></td>
<td>22.3 ± 5.7</td>
<td>6.4 ± 0.9</td>
<td>92.4 ± 26.1</td>
<td>10.1 ± 2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.o.</td>
<td>6</td>
<td>1.25b</td>
<td>10.3 ± 3.7</td>
<td>5.0 ± 1.1</td>
<td>55.0 ± 20.4</td>
<td>62 ± 9.0</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>6</td>
<td></td>
<td>21.0 ± 4.3</td>
<td>6.4 ± 1.7</td>
<td>89.4 ± 29.9</td>
<td>10.1 ± 2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.o.</td>
<td>28</td>
<td>1.25b</td>
<td>8.3 ± 3.4</td>
<td>5.6 ± 1.5</td>
<td>56.5 ± 21.3</td>
<td>67 ± 22</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>18</td>
<td></td>
<td>21.9 ± 5.2</td>
<td>6.4 ± 1.2</td>
<td>91.4 ± 26.6</td>
<td>10.1 ± 2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\text{a} t_{max}, \text{time to C}_{max}.

\text{b} Median.

Table 3 Twenty-four-h plasma concentrations of etoposide (mean ± SD) determined weekly during the first cycle

<table>
<thead>
<tr>
<th>Day 8 (n = 46)</th>
<th>Day 15 (n = 41)</th>
<th>Day 22 (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/ml'</td>
<td>0.493 ± 0.310</td>
<td>0.497 ± 0.250</td>
</tr>
<tr>
<td>CV (%)</td>
<td>63</td>
<td>50</td>
</tr>
</tbody>
</table>

\text{a} Plasma levels normalized to the dose of 100 mg/m².

Pharmacodynamic Studies. No correlations were found among C_{max}, AUC_{exp}, weekly 24-h Ecs, and t_{1/2β} determined after the first dose of etoposide in 22 patients and neutropenia. On the contrary, statistically significant linear and log- linear correlations by univariate analysis were found between the mean 24-h Ec, determined on days 8, 15, and 22 in 39 patients, and the degree of neutropenia expressed as ANC_{n} (r = 0.47, P = 0.0033) and log- of ANC_{n} (Fig. 4A; P = 0.0011). The relative decrease of ANC was found to be correlated to the mean 24-h Ec according to a maximum effect model (Fig. 4B). The value of 0.34 µg/ml appeared to be the best cutoff point of the mean 24-h Ec for dividing patients into two groups (P < 0.01) with different risks of toxicity. In fact, the mean relative decrease of ANC was significantly higher (P < 0.01) in those patients who maintained a mean 24-h Ec during the cycle of ≥0.34 µg/ml than in those with a mean 24-h Ec of <0.34 (Fig. 5). In addition, in 14 patients who suffered from severe hematological toxicity with an ANC_{n} of <1.0 × 10^{3}/µl during the first cycle, the mean ± SD of mean 24-h Ec was 0.53 ± 0.19 µg/ml, significantly higher (P < 0.01) than the 0.20 ± 0.06 µg/ml achieved in the other patients (Fig. 6).

Using the mean 24-h Ec of the 39 patients of the present study, the validation of Miller’s (13) model and the development of a new one by elaborating the data according to Miller’s (13) procedure were performed. The resulting model was described using the equation ANC_{n} = 0.44(1 + ANC_{n} × e^{-2.54×E_{c}}). Table 4 reports the ANC_{n} values observed and predicted by both models. Fitting our data to Miller’s (13) model, we well predicted ANC_{n} in the first 14 patients who presented an ANC of <1.0 × 10^{3}/µl; the sensitivity of the model was 79%, and the positive predictive value for WHO grades 3–4 neutropenia was 65%. With our model, the predictive values were not statistically different from those observed (paired t test, P = 0.79–76%). One partial response was reported among seven evaluable patients with non-small cell lung cancer (14%).

Fig. 2 Intropatient variability of the AUC (mean ± SD) of etoposide on days 1 and 15 in nonfasting (□; n = 17) and fasting (●; n = 18) patients.

Fig. 3 Intrapatient variability of the AUC of etoposide on days 1–3 (n = 9).
0.958), but the model overestimated the ANC. For ANC values <1.0 x 10^3/µL, the sensitivity of the model was 36%.

No correlations were found in the 25 patients for whom AUCpr and weekly neutrophil counts were available, with either ANCn (r = 0.32, P > 0.1) or the relative decrease of ANC (r = 0.38, 0.05 < P < 0.1). However, in 8 patients who achieved an ANCn of <1.0 x 10^3/µL, the mean ± SD of AUCpr was 39.0 ± 14.7 µg/ml h, higher (P < 0.05) than the 27.8 ± 6.5 µg/ml h found in the remaining 17 patients (Fig. 6).

Of 33 patients with SCLC evaluable for tumor response, 26 had been sampled at weekly intervals to determine their 24-h Ecs. The mean ± SD of 24-h Ecs achieved in the group of 16 responders was 0.37 ± 0.21 µg/ml, higher than the value of 0.21 ± 0.09 µg/ml reported in the group of 10 nonresponding patients (P = 0.017).

DISCUSSION

The main problem with the chronic administration of p.o. etoposide is the high interpatient variability with regard to neutropenia, with the occurrence of febrile neutropenia in up to 30% of the patients in the different series (18, 19). Old age and low PS seem to be the most important clinical risk factors predicting for severe myelotoxicity, even though their significance is difficult to prove because of the variable bioavailability of the drug (see below) and of the limited number of patients reported so far. In the present study, where a 21-day course has been preceded by a single i.v. dose, myelotoxicity has been the main toxic effect of chronic oral p.o. etoposide, with neutropenia WHO grade ≥3 in 38% of patients after the first cycle and one neutropenia-related toxic death in an elderly patient with progressive extensive SCLC.

It appears, however, that neutropenia is variable also after daily i.v. treatment with etoposide even though its degree is
difficult to evaluate because weekly blood counts have not been performed regularly (5, 20), and neutrophil counts were reported only as mean (5) or median (20), without SD values.

In many of the studies performed so far with chronic p.o. etoposide, drug plasma monitoring has been performed to evaluate: (a) the pharmacokinetic profile and the inter- and intrapatient variability of the kinetic parameters of etoposide and (b) the existence of a pharmacodynamic relationship between pharmacokinetic parameters and the biological effects of the drug such as toxicity or antitumor activity.

In the present study, in a group of 12 patients without previous chemotherapy, receiving single daily doses of etoposide ranging from 44 to 79 mg/m², the mean ± SD bioavailability of etoposide was 69% ± 27%, in agreement with that of 76% ± 22% recently reported by Hande et al. (10) in 11 patients receiving 100 mg. Both values are significantly greater than those previously achieved after etoposide doses of >150 mg/m² (10, 21, 22). Previous exposure to chemotherapy did not seem to affect bioavailability, since in a group of six pretreated patients we found a bioavailability value of 62% ± 9.0%, similar to those observed in previously untreated patients and to the 75% ± 21% reported by Marzola et al. (23). In the group of 22 untreated patients analyzed in the present study, the variability of experimental AUC values expressed as CV was 39%. The interpatient variability did not appear to be related to food ingestion, as shown by the comparison of the AUC values achieved in fasting and nonfasting patients, respectively.

The available information about intrapatient variability after repeated daily p.o. doses is scant. Calvert et al. (24) reported that the AUC values after two p.o. doses, determined in 7 patients on days 1 and 8, varied by approximately 30%. In the present study, which is the only one evaluating AUC after three repeated p.o. doses in nine patients, the variability of AUC, expressed as a median CV value, is 17%. The interpatient variability of 24-h EcS was relatively low (median CV, 29%) as compared to the interpatient one, which was higher than 50%.

Recently, several authors have reported interesting pharmacodynamic relationships between etoposide plasma levels, response, and hematological toxicity. Slevin et al. (5) suggested a correlation of the time of exposure to levels above 1 µg/ml with the response in patients with SCLC treated with i.v. administration of etoposide. Clark et al. (20) found in responsive patients a significantly prolonged exposure to EcS greater than 0.5, 1, 1.5, 2, 3, and 4 µg/ml over that in nonresponders. On the other hand, differences in exposure times to etoposide concentrations of 5 µg/ml or higher in responders and nonresponders were not significant. On the basis of the results achieved in the study in which the 5- and the 8-consecutive-daily infusion regimens were compared, Clark et al. (20) have suggested that duration of exposure to etoposide levels between 1 and 2 µg/ml may be most important in terms of antitumor efficacy, while myelotoxicity may be dependent on exposure to higher concentrations of between 2 and 3 µg/ml. Our results provide no insight into this question since lower concentrations were maintained. In fact, the mean 24-h Ec was always <1 µg/ml. However, since severe neutropenia was nevertheless observed in our study, it seems that myelotoxicity may also be caused by exposure to concentrations lower than 1 µg/ml, provided they are maintained for more than 8 days. Myelotoxicity was found to be related to baseline creatinine values (P = 0.010), a finding in agreement with the previously published evidence of a relationship between renal function and etoposide clearance (25).

With regard to the relationship with antitumor efficacy, we found higher etoposide levels in responders than in nonresponders (P = 0.017). Although statistically significant, this difference should be taken with caution due to the relatively low number of cases investigated.

The use of daily fractionated doses of etoposide has been shown to decrease the fluctuation in blood levels observed after single dosing (26). The administration of 25 mg three times daily resulted in a mean etoposide concentration, calculated over a period of 6 h, of 1.1 ± 0.3 µg/ml, with peak concentrations ranging from 0.6 to 2.5 µg/ml. These results suggest that split doses could simulate a continuous i.v. infusion of etoposide. They also suggest that the pharmacokinetic results of studies with different schedules of etoposide administration cannot be
compared and that a great caution should be taken when the conclusions drawn in one study on possible pharmacodynamic relationships are applied in another.

Mick and Ratain (27) elaborated a nonlinear model that allows the prediction of WBC nadir on the basis of the plasma steady-state drug concentration achieved during continuous infusion of etoposide. Miller et al. (13) proposed a pharmacodynamic model for chronic p.o. etoposide, given as single daily doses, to predict the hematological toxicity at the end of the cycle of therapy. The nonlinear model was based on ANCs and on the mean 24-h Ec values, calculated as the mean of the concentrations present before the subsequent daily doses, assessed at weekly intervals. We tried to validate the model proposed by Miller et al. (13) and to develop a new one based on our own data. The results obtained suggest that our model is not clinically applicable, since severe neutropenia, the occurrence of which is variable and could be associated with major complications, cannot be predicted with sufficient precision. The application of this model with a relatively low sensitivity (36%) could therefore be misleading, allowing the continuation of treatment even when the chances of developing myelotoxicity are high. Applying Miller’s (13) model to our data in the same range of ANCs values, the sensitivity turned out to be 79%, and the positive predictive value for WHO grades 3–4 neutropenia was 65%. Miller and Tolley (28), in a prospective validation of their model, have found higher sensitivity and specificity (28). In only 2 of 21 cases studied were the ANCs values not predicted with sufficient precision. It is not clear why Miller et al. (13) have found a much better sensitivity as compared to ours. We have noted, however, that the patients investigated by Miller et al. (13) have mean 24-h Ec twice that found in our study. This difference in 24-h Ec may be due to the differences in protocols and dosage schedules used in the two studies, with 100 mg/m² cisplatin on day 1, followed by a daily dose of 50 mg/m² etoposide in the Miller et al. (13) study and with single-agent etoposide given at a daily total dose of 100 mg in our study. It may also be that cisplatin, causing subclinical damage to the renal function, could delay the elimination of etoposide and consequently increase toxicity.

In a previous report (7), we observed the existence of a cutoff value (0.32 μg/ml) for mean 24-h Ec that, if maintained throughout the cycle, was associated with a high probability of achieving an 85% decrease of ANC. In the present report, we have confirmed in a group of 39 patients the existence of a comparable cutoff value. Although the difference in the risk of neutropenia in patients with mean 24-h Ec values ≥0.34 μg/ml was statistically significant (P < 0.01), it remains to be established whether these values can be prospectively used to predict which patients will suffer from severe toxicity, thus modifying the total dose of etoposide. In this respect it may be useful to consider that of 15 patients who presented severe neutropenia (ANC ≤1.0 × 10³/μl), 12 had mean 24-h Ec values ≥0.34 μg/ml (i.e., 20% false negative). Therefore, had the threshold value of 0.34 μg/ml been taken as the level at which to stop treatment, reducing the total etoposide dose, it would have been possible to avert severe neutropenia in 80% of the cases. On the other hand, of 24 patients who did not show severe neutropenia, 6 had mean 24-h Ec values ≥0.34 μg/ml. Thus, had the threshold value of 0.34 μg/ml been used to identify patients requiring dose reductions, we would unnecessarily have reduced the etoposide dose in 25% of the cases, and this might have hampered the treatment efficacy.

It is still open to question whether the therapeutic outcome of chronic p.o. etoposide treatment can be improved by applying pharmacokinetic/pharmacodynamic models or mean 24-h Ec cutoff values found associated with a high risk of neutropenia and, if so, to what extent. Prospective randomized trials are needed to determine whether pharmacokinetic/pharmacodynamic monitoring can improve the safety and therapeutic outcome of chronic p.o. etoposide treatment over those of the standard clinical monitoring of hematological toxicity.

ACKNOWLEDGMENTS

We thank Luana Crivellaro for assistance in manuscript preparation, and the nurses and the patients for their participation in the study.

REFERENCES

19. Smit, E. F., and Postmus, P. E. A phase II study of oral etoposide (OE) 100 mg/day for 21 days (D) q 5 weeks (W) in untreated elderly (E) and poor performance status (PPS) small-cell lung cancer (SCLC) patients (pts) (Abstract). Lung Cancer, 7 (Suppl.): 136, 1991.
Clinical Cancer Research


M Zucchetti, O Pagani, V Torri, et al.


Updated version Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/12/1/1517

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.