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Pharmacokinetics and pharmacodynamics of prolonged oral etoposide in women with metastatic breast cancer

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Abstract The pharmacokinetics and pharmacodynamics of prolonged oral etoposide chemotherapy were investigated in 15 women with metastatic breast cancer who received oral etoposide 100 mg as a single daily dose for up to 15 days. There was considerable interpatient variability in the day 1 pharmacokinetic parameters: area under the plasma concentration time curve (AUC) (0–24 h) 1.95 ± 0.87 mg/ml per min (mean ± SD), apparent oral clearance 60.9 ± 21.7 ml/min per 1.73 m^2, peak plasma concentration 5.6 ± 2.5 μg/ml, time to peak concentration 73 ± 35 min and half-life 220 ± 83 min. However, intrapatient variability in systemic exposure to etoposide was much less with repeated doses. The intrapatient coefficient of variation (CV) of AUC for day 8 relative to day 1 was 20% and for day 15 relative to day 1 was 15%, compared to the day 1 interpatient CV of 45%. Neutropenia was the principal toxicity. Day 1 pharmacokinetic parameters were related to the percentage decrease in absolute neutrophil count using the sigmoidal E_{max} equation. A good fit was found between day 1 AUC and neutrophil toxicity ($R^2 = 0.77$). All patients who had a day 1 AUC >2.0 mg/ml per min had WHO grade III or IV neutropenia. The predictive performance of the models for neutrophil toxicity was better for AUC (percentage mean predictive error 5%, percentage root mean square error 18.1%) than apparent oral clearance, peak plasma concentration, or daily dose (mg/m^2). A limited sampling strategy was developed to predict AUC using a linear regression model incorporating a patient effect. Data sets were divided into training and test sets. The AUC could be estimated using a model utilizing plasma etoposide concentration at only two time points, 4 h and 6 h after oral dosing ($R^2 = 98.9\%$). The equation $AUC_{pr} = -0.376 + 0.631 \times C_{4h} + 0.336 \times C_{6h}$ was validated on the test set with a relative mean predictive error of −0.88% and relative root mean square error of 6.4%. These results suggest monitoring of AUC to predict subsequent myelosuppression as a strategy for future trials with oral etoposide.

Key words Etoposide · Pharmacology · Breast cancer

Introduction

Etoposide (VePesid, Bristol Myers Squibb Co, Princeton, N.J.) is a semisynthetic glycoside of podophyllotoxin with a broad spectrum of antitumor activity. It has an established role in the management of metastatic testicular tumors, small-cell lung cancer, lymphomas, leukemias and some other malignancies [16, 19]. However etoposide is generally considered an inactive drug against breast cancer. In early phase II trials, intravenous etoposide had a response rate averaging 8% in over 300 patients with advanced breast cancer [27]. Most of these patients had daily infusions for 3 days every 3–4 weeks and almost all patients had previously received other chemotherapy. One trial in 20 previously untreated patients who received intravenous etoposide at a dose of 230 mg/m^2 daily for 3 days every 4 weeks had a response rate of 15% [26].

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In an early trial no responses were seen in breast cancer with oral etoposide given for up to 5 days every 2–3 weeks [4].

The molecular mechanism of action of etoposide involves inhibition of the enzyme topoisomerase II, the activity of which is maximal in the late G2 and S phases of the cell cycle. Therefore the antitumor activity of etoposide is schedule-dependent in vitro [10]. This has been confirmed clinically in small-cell lung cancer where daily infusions of etoposide for 5 days gave a significantly higher response rate than the same total dose given over 24 hours [24]. The use of oral etoposide over more protracted periods of time is a convenient way to exploit potential schedule dependency and using this approach promising results have been achieved in refractory lymphomas, testicular tumors, small-cell lung cancer and ovarian cancer [2, 7, 13, 15, 20, 21], including responses in patients who had previously received intravenous etoposide [13, 15]. We therefore examined the activity of prolonged oral etoposide in advanced breast cancer patients, and as part of the trial, pharmacokinetic and pharmacodynamic studies were performed in 15 patients. We particularly wished to determine the variability in systemic exposure to etoposide when given by fixed dose repeated daily oral administration and hence the possibility that therapeutic drug monitoring might be necessary for oral etoposide. Clinical results and a preliminary pharmacokinetic analysis have been reported separately [1].

Materials and methods

Patients were enrolled on a trial of prolonged oral etoposide chemotherapy in metastatic breast cancer [1]. Selected patients were invited to participate in the pharmacokinetic study. These patients had adequate venous access with no upper limb lymphedema, and geographical accessibility. Written informed consent was obtained and the protocol approved by the Institutional Ethics Committee.

Patients received oral etoposide 100 mg as a single daily dose taken in the morning. The duration of therapy was planned to be 15 days in 12 patients and 8 days in 3 patients. The 3 patients in whom 8 days of treatment was planned had been previously treated with chemotherapy and were considered to be at greater risk of toxicity. Three patients did not complete 15 days because of the development of toxicity between days 10 and 12. Cycles were repeated if clinically indicated every 4 weeks. Full blood counts were performed prior to treatment and on days 8 and 15 and weekly in the drug-free period.

Pharmacokinetic studies

Plasma sampling for pharmacokinetic investigation was performed in the first cycle of therapy. Blood samples (5 ml) were withdrawn using an indwelling cannula prior to drug administration and at 15 min, 30 min, 45 min, 60 min, 90 min, 2 h, 2.5 h, 3 h, 4 h, 6 h, 8 h, 12 h, and 24 h post-ingestion. Following collection, blood samples were centrifuged at 4°C and the plasma supernatant stored at −20°C until analysis. A 0–24 h urine collection was performed and a 10-ml aliquot frozen at −20°C. Pharmacokinetic sampling was performed at weekly intervals (days 1, 8 and 15) where possible. Patients were not fasted or given any specific dietary instructions on the days pharmacokinetic studies were performed.

Plasma and urine etoposide levels were determined by a reverse-phase HPLC assay using UV detection. Etoposide was extracted from 0.5-ml samples of plasma or urine by rotary mixing with 2.5 ml dichloromethane in glass test-tubes. The layers were clarified by centrifugation and 2 ml of the organic layer removed and evaporated to dryness under nitrogen at 30–40°C. The concentrated residue was reconstituted in 200 µl HPLC mobile phase and 100 µl analysed. Separations were carried out on a Waters 510 chromatograph (Millipore, Harrow, UK) fitted with a Spherisorb phenyl 5 µm 4.6 × 150 mm column (Jones Chromatography, Glamorgan, UK). Etoposide was eluted isocratically with 32.5% methanol in water (v/v) containing 0.2 *M* sodium acetate, pH 4.4, at a flow rate of 1.5 ml/min, and detected by UV absorbance at 237 nm. Quantitation was carried out by external standardization using a seven-point standard curve prepared for each analytical run. The assay was linear over the range 0.2–20 µg/ml, the Pearson correlation coefficient (r) being > 0.995. The intra- and interassay coefficients of variation were $< 10\%$ for quality assurance standards at 5 µg/ml. The analytical samples of etoposide used in these assays were obtained from Bristol Myers Squibb Laboratories (East Syracuse, N.Y.).

The etoposide area under the plasma concentration versus time curve (AUC) was calculated from time 0 to 24 h by the trapezoidal method. The apparent oral clearance (Cl) was calculated by the formula Cl = Dose/AUC as defined by Hande et al [8]. Apparent half-life was calculated using unweighted non-linear least-squares regression analysis fitted to a one-compartment model. Response and toxicity were evaluated using standard WHO criteria.

Pharmacodynamics

Hematological toxicity was expressed as the percentage decrease in absolute neutrophil count (ANC) from pretreatment to nadir. Non-linear least-squares regression analyses were performed to relate the day 1 pharmacokinetic parameters AUC (mg/ml min), Cl (ml/min per 1.73m^2), peak plasma concentration (µg/ml) and the daily dose (mg/m^2) to the hematological toxicity using the sigmoidal E_{max} equation:

$$\%\text{Decrease} = \frac{E_{max} \times X^H}{X^H + X_{50}^H}$$

where E_{max} is fixed at 100%, X is the pharmacokinetic parameter of interest, X_{50} is the value producing half of the maximal effect, and H (Hill coefficient) is a parameter affecting the shape of the curve. Both X_{50} and H were estimated in the regression analyses for each pharmacokinetic parameter.

Limited sampling model

To enable measurement of the AUC with a small number of blood samples in future studies, a limited sampling strategy was developed. A multiple linear regression model incorporating a patient effect was selected for the analysis since the data contained multiple observations from the majority of the patients. The maximum likelihood method was used to estimate the parameters in the model based on a random patient effect and assuming that the observations within each patient had a multivariate normal distribution. The selection of variables into the model was carried out using a forward selection procedure so that at each step only one variable was added to the regression model which already contained all the variables selected in the previous steps. The variable added to the current model at each step was the one associated with the highest log-likelihood value after the incorporation of an extra variable in the model. The selection of further variables was carried out in a similar manner

until the coefficient of determination (R^2) reached at least 95% (i.e. at least 95% of the variation in AUC was explained by the model). All the data sets with the concentration recorded at all time points were divided into training and test sets for deriving and testing the model. Patients were selected into the training and test sets at random so that each set consisted of approximately the same number of patients with the same number of complete data sets.

The analyses were performed using the P5V module of the BMDP Statistical Package (1990 version).

Predictive performance

For each of the pharmacodynamic models and the limited sampling models developed, the predictive performance was examined by calculating the bias and precision. The bias was measured by calculating the absolute mean prediction error (MPE) and the percentage MPE (%MPE). The precision was measured by calculating the root mean square prediction error (RMSE) which was also expressed as a percentage of the mean of the observed values (%RMSE) [22]. The formulae used were:

$$\text{MPE} = \frac{\sum(\text{PRED} - \text{OBS})}{n}, \quad \%\text{MPE} = \frac{\sum(\text{PRED} - \text{OBS}) \times 100/\text{OBS})}{n},$$

$$\text{MSE} = \frac{\sum(\text{PRED} - \text{OBS})^2}{n}, \quad \text{RSME} = \sqrt{\text{MSE}},$$

$$\%\text{RMSE} = \frac{\text{RMSE} \times 100}{\text{OBS}_{\text{mean}}},$$

where PRED and OBS represent the predicted and corresponding observed values respectively, OBS_{mean} is the mean of the observed values and summation is over the n samples under study.

Results

Clinical results

The pharmacokinetic study was performed in 15 patients (Table 1). Two patients were aged > 65 years. All 15 patients had normal serum creatinine (institution normal < 140 μmol/l) and normal serum bilirubin (institution normal < 17 μmol/l). The serum albumin was normal in 14 patients and in the other patient was 33 g/l (institution lower limit normal 34 g/l). None of the patients had documented liver metastases but two had elevated serum alanine transaminase (ALT) levels (56 U/l and 208 U/l; institution normal < 40 U/l).

The principal toxicity was myelosuppression, particularly neutropenia (Table 2). One patient developed WHO grade IV neutropenia and thrombocytopenia on day 10 and died of septicemia on day 14. Two other patients discontinued oral etoposide between day 8 and day 15 because of myelosuppression (one patient) and myocardial infarction (one patient). Nausea occurred in five patients but was always ≤ grade II. Grade I diarrhea occurred in one patient. Of 12 patients assessable for response, 5 (42%) had a partial response.

Pharmacokinetics

There were 33 sets of blood samples obtained from the 15 patients. Six patients were sampled on days 1, 8 and 15, five patients on days 1 and 8, one patient on day 1 and 15, and three patients on day 1 only. Pharmacokinetic results on day 1 are listed in Table 3. The patients' body surface area ranged from 1.5 to 1.9 m^2 and the oral etoposide dose therefore was 53–67 mg/m^2. There was no significant linear relationship between dose (mg/m^2) and etoposide AUC on day 1 within this narrow dose range ($r = 0.36$, $P = 0.18$).

Table 1 Patient details ($n = 15$)

Age	
Median (years)	58
Range (years)	41–72
Performance status (ECOG)	
Zero	2
One	9
Two	2
Three	2
Previous chemotherapy	
None	8
1 regimen	6
2 regimens	1
Pretreatment serum creatinine (mean ± SD; μmol/l)	86 ± 15
Pretreatment serum bilirubin (mean ± SD; μmol/l)	7.5 ± 2.5
Pretreatment serum albumin (mean ± SD; g/l)	40 ± 3
Duration of etoposide therapy	
15 days	9
12 days	1
10 days	2
8 days	3

Table 2 Hematological toxicity following oral etoposide, first cycle ($n = 15$)

	WHO grade				
	0	1	2	3	4
Total white cells	5 (33%)	3 (20%)	6 (40%)	0	1 (7%)
Neutrophils	6 (40%)	2 (13%)	3 (20%)	2 (13%)	2 (13%)
Platelets	13 (87%)	1 (7%)	0	0	1 (7%)
Hemoglobin	7 (47%)	4 (27%)	4 (27%)	0	0

Table 3 Pharmacokinetic parameters following oral etoposide on day 1 ($n = 15$)

	Mean ± SD	Range
AUC (0–24 h) (mg/ml min)	1.95 ± 0.87	0.88–4.38
Apparent oral clearance (ml/min/1.73m^2)	60.9 ± 21.7	25–110
Peak plasma concentration (μg/ml)	5.6 ± 2.5	2.0–10.4
Time to peak concentration (min)	73 ± 35	30–152
Half-life (min)	220 ± 83	137–396

Table 4 Patient pharmacokinetic variability following oral etoposide (*CV* coefficient of variation

	Day 1 mean ± SD	CV	Day 8 mean ± SD	CV	Day 15 mean ± SD	CV
AUC (mg/ml min)						
Interpatient	1.95 ± 0.87	45%	2.31 ± 1.11	48%	1.79 ± 0.42	23%
Intrapatient[a]	100%	–	122% ± 25%	20%	120% ± 18%	15%
Apparent oral clearance (ml/min/1.73m^2)						
Interpatient	61 ± 22	36%	53 ± 21	40%	61 ± 21	34%
Intrapatient[a]	100%	–	84% ± 13%	15%	85% ± 12%	14%
Peak concentration (μg/ml)						
Interpatient	5.6 ± 2.5	45%	5.7 ± 2.7	47%	4.7 ± 1.9	40%
Intrapatient[a]	100%	–	107% ± 32%	30%	113% ± 21%	19%

[a] % of day 1 value

Similarly, there was no significant linear relationship between dose (mg/m^2) and the day 1 peak plasma concentration ($r = 0.35$, $P = 0.2$), the time to peak plasma concentration being 73 ± 35 min. The interpatient coefficients of variation on day 1 were 45% for AUC, 36% for Cl, 45% for peak plasma concentration and 38% for half-life. The urine recovery of etoposide over the 24 h period was assessed in nine patients and was 18% ± 6% (mean ± SD; range 11–31%) of the oral dose.

Patient pharmacokinetic variability is summarized in Table 4. In comparison with interpatient variability, less variability was seen on repeated dosing in the same patient. The intrapatient coefficient of variation for day 8 relative to day 1 was 20% for AUC, 15% for Cl, and 30% for peak plasma concentration. For day 15 relative to day 1 the intrapatient coefficients of variation were 15% for AUC, 14% for Cl, and 19% for peak plasma concentration.

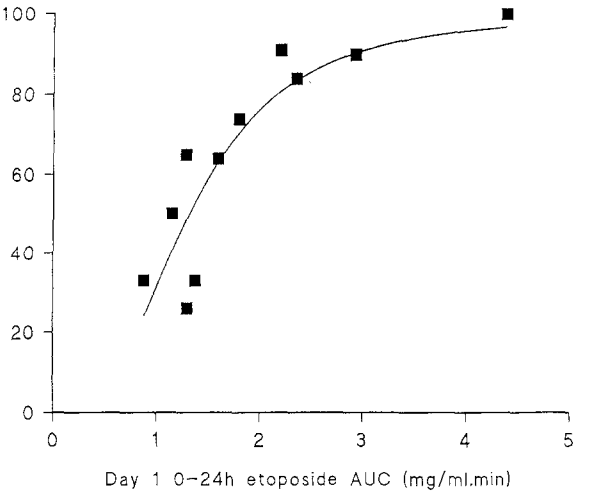

Fig. 1 Relationship between percentage decrease in absolute neutrophil count and day 1 AUC. The estimated parameters are: $H = 2.82$ $AUC_{50} = 1.32$ ($R^2 = 0.77$) where H is the Hill coefficient affecting the shape of the curve and AUC_{50} is the value of AUC resulting in 50% decrease of the absolute neutrophil count.

Pharmacodynamics

Pharmacodynamic relationships were modelled using data from the 11 patients who had 15 days of oral etoposide or in whom 15 days was planned but who stopped early because of the development of hematological toxicity. The model to predict the neutrophil toxicity using the day 1 AUC provided a good fit to the data ($R^2 = 0.77$; Fig. 1). A good fit was also obtained using day 1 Cl (ml/min per 1.73m^2) as the predictor ($R^2 = 0.68$). The models using daily dose (mg/m^2) and peak plasma concentration did not provide such a good fit to the data ($R^2 = 0.37$ and 0.35 respectively). Table 5 lists the MPE and RMSE for the models established. There was no evidence of bias in any of the models. The model based on the day 1 AUC had the lowest RMSE. This suggests that the day 1 AUC may be the best predictor of neutrophil toxicity.

A day 1 AUC of > 2.0 mg/ml.min was followed by WHO grade III or IV neutropenia in 4/4 patients (with

Table 5 Predictive performance of the models for neutrophil toxicity

Predictor	r^a	MPE (95% CI)[b]	%MPE	RMSE	%RMSE
AUC (mg/ml. min)	0.88	−0.9 (−9.1, 7.3)	5	11.7	18.1
Apparent oral clearance (ml/min/1.73m^2)	0.84	−0.7 (−10.3, 8.9)	8	13.7	21.2
Peak concentration (μg/ml)	0.62	−0.7 (−14.4, 13.0)	14	19.5	30.2
Dose (mg/m^2)	0.60	0.7 (−13.3, 14.7)	14	19.9	30.8

[a]Correlation coefficient between actual and predicted values
[b]95% confidence interval based on a *t*-distribution

Table 6 Predictive performance of the limited sampling model

Data Set	r^a	MPE (95% CI)[b]	%MPE	RMSE	%RMSE
Training	0.99	0.00 (−0.09, 0.09)	0.95	0.13	5.5
Test	0.97	−0.01 (−0.10, 0.08)	−0.88	0.11	6.4

[a]Correlation coefficient between actual AUC and predicted AUC
[b]95% confidence interval based on a *t*-distribution

one death from sepsis) compared to 0/7 in whom the day 1 AUC was < 2.0 mg/ml. min No difference was found between the day 1 AUC of the 5 responders compared to the 7 non-responders (2.0 ± 0.7 mg/ml. min, and 1.7 ± 0.5 mg/ml. min, respectively). The calculated time of plasma concentration greater than 1μg/ml on day 1 also did not differ between the responders and nonresponders (430 ± 85 min and 410 ± 120 min, respectively).

Limited sampling model

The limited sampling model was developed from 20 data sets (samples) from 13 patients. Each data set had etoposide measured at all 14 time points. Seven of the 13 patients had two complete data sets each and each of the remaining patients had one complete data set. A training set was derived by randomly selecting four patients from the seven patients with two data sets each and three from the six patients with one data set. The remaining data sets became the test set. The training and test sets were thus based on 11 and 9 data sets, respectively. The AUC was expressed as mg/ml. min and the etoposide concentrations measured in units of μg/ml.

The variable C_{4h}, the concentration at 4 h, was selected in the first step of the forward selection procedure, R^2 being 88.2%. The addition of C_{6h}, the concentration at 6 h, in step 2 increased the $R^2 \geq 98.9\%$. Thus a model with only two time points satisfied the predetermined selection criterion $R^2 \geq 95\%$. The third variable that would have been chosen was $C_{1.5h}$, which would have increased the R^2 to 99.6%. The equation based on C_{4h} and C_{6h} was:

$$AUC_{pr} = -0.376 + 0.631 \times C_{4h} + 0.336 \times C_{6h}$$

Using this equation the AUC_{pr} was computed for the nine data sets from the six patients in the test set. Figure 2 shows the correlation between the actual AUC and the predicted AUC for the training and test sets. There is no indication of any bias in the model (Table 6).

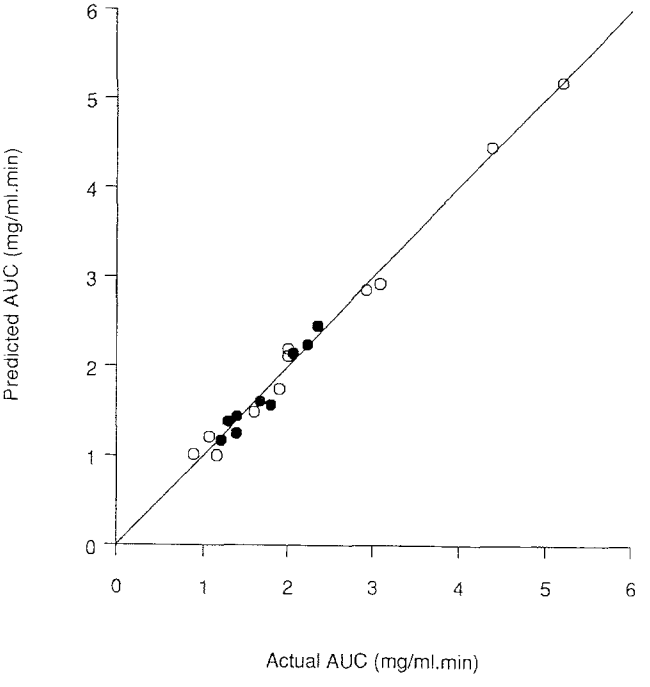

Fig. 2 Limited sampling model: correlation between actual and predicted AUC. (○ Training set, ● test set, — line of identity)

Discussion

Prolonged oral etoposide is a potentially important new approach to the treatment of metastatic breast cancer. In the 15 patients who participated in this pharmacokinetic study, the response rate was 42%. In all, 38 patients were treated with prolonged oral etoposide at doses of 100 mg/day or 50 mg/day at our institution and the response rate overall was 27% [1]. The response rate was dependent on prior treatment, being 45% in patients who had not previously received chemotherapy and 22% in previously treated patients [1]. The higher response rate in the pharmacokinetic study patients reflects the selection of patients with relatively good performance status and mainly without prior chemotherapy. The activity of prolonged oral etoposide in breast cancer has recently been confirmed by Palombo et al. who treated 18 patients, the majority of whom had prior chemotherapy, with oral etoposide 50 mg/m^2 for up to 21 days and obtained a response rate of 22% [17]. Although no randomized trials between conventional intravenous etoposide and prolonged oral etoposide have been done in breast cancer, these results suggest that in breast cancer the antitumor effect of etoposide is schedule-dependent.

The pharmacokinetic parameters obtained in this study are consistent with those reported by others in studies of oral etoposide at a dose of 100 mg/day [5, 6, 8, 20, 25]. As in other studies there was considerable variability between patients with the pharmacokinetic parameters varying as much as five-fold. The cause of this variability is unknown. We did not dose patients intravenously to measure bioavailability so the variability may reflect differences in absorption between patients. Poor renal function alters the pharmacokinetics of intravenous etoposide [3] but was not present in our patients. The time of plasma concentration > 1.0 μg/ml in this study is also similar to that reported following an oral etoposide dose of 100 mg [5].

The pharmacology of etoposide after oral administration is known to be dose dependent. The absorption of etoposide is saturable, with proportionately less of an oral dose absorbed when the dose exceeds 200 mg [25]. The bioavailability of oral etoposide is considered to be 50% for conversion of intravenous to oral dosing but the bioavailability of etoposide following a 100 mg dose has recently been reported to be 76% which was significantly higher than the 48% seen after a dose of 400 mg [8]. At an oral dose of 400 mg, bioavailability showed considerable intrapatient variability and intrapatient coefficients of variation were up to 53% for AUC and 45% for peak plasma levels after repeated doses [9]. Our results indicate that the variability in systemic exposure to etoposide after repeated oral doses of 100 mg is less than that after 400 mg, making dose adjustment to avoid potential toxicity a rational strategy when etoposide is given by this schedule.

The major toxicity of oral etoposide was myelosuppression. Severe myelotoxicity with resultant death from neutropenia was seen in this study, in our larger clinical experience [1], and in other trials of prolonged oral etoposide [2, 7, 13, 15, 20, 21]. It has been suggested that adverse clinical factors (age > 65 years, poor performance status) and biochemical factors (elevated serum creatinine, hypoalbuminemia) predict for toxicity following etoposide [12]. The small number of patients in this study and the lack of any with renal impairment or significant hypoalbuminemia prevented these factors being examined, but in a larger trial of oral etoposide in small-cell lung cancer patients there was no relationship between toxicity and any of these parameters [20]. Close monitoring of white cell counts has been recommended to prevent undue toxicity [20, 21], but both patients in this study who developed myelosuppression between day 8 and day 15 had normal white cell and neutrophil counts on day 8. Therefore, reliance on frequent blood counts to detect toxicity may not be adequate, and may be unnecessary if patients at low risk of toxicity could be identified early in the treatment cycle.

We found a good relationship using a sigmoidal E_{max} model between etoposide AUC after the day 1 dose and subsequent neutropenia. The coefficient of determination of 77% is high for a study involving patients with varying amounts of prior chemotherapy. Although the patient numbers were small, a day 1 AUC of > 2.0 mg/ml. min divided patients who developed severe neutropenia from those who did not. Cl was also predictive of neutropenia, but was slightly inferior to AUC. The relationship between peak plasma level and neutropenia was weaker. The time to peak plasma level ranged from 30 to 152 min, and in this interval six sampling times occurred so it is unlikely the measured peak plasma level was significantly different from the true peak level. Daily dose was also less accurate at predicting subsequent neutropenia than day 1 AUC. Previous studies have related toxicity following oral etoposide to trough plasma levels at 24 h post-dose. Sessa et al. [20] found only a weak correlation between neutrophil toxicity and 24-h etoposide level, but a 24-h level > 0.32 μg/ml was associated with more severe myelosuppression. Miller et al. [14] have developed a pharmacodynamic model relating white cell and neutrophil nadir to pretreatment values and the 24-h etoposide level. In their study patients also received cisplatin which contributed to myelosuppression and may also alter the pharmacokinetics of etoposide [18, 23]. Thus, their model may not be able to be extrapolated to toxicity after oral etoposide alone.

Our data suggest that neutropenia following oral etoposide can be predicted from the day 1 AUC. We could not relate AUC to response, although the numbers were too small to exclude any relationship. However, patients did not have to experience significant toxicity to achieve a response, as has also been found in another study [21]. This suggests that modifying AUC

to reduce toxicity may be possible without reducing antitumor activity. We also could not relate response to estimated time of plasma levels exceeding 1 μg/ml, which has been suggested to be related to response in small-cell lung cancer patients [24].

If day 1 AUC is to be used to predict subsequent toxicity in prospective trials in a larger patient population then a limited sampling strategy is essential. We have shown that it is possible to estimate the actual AUC with a high degree of precision by measuring the etoposide level in plasma at only two time points, 4 h and 6 h after the oral dose. A limited sampling model for AUC after oral etoposide has also been developed by Gentili et al. [6]. In both our model and these authors', the single time point that was most predictive of AUC was that at 4 h. Gentili et al. were also able to validate their model using a historical data set from a previous clinical trial, which we did not have the opportunity to do. Our model will be examined prospectively in future clinical trials with oral etoposide in other tumor types. A further limited sampling model for oral etoposide has been developed [11] but only for the AUC from 0 to 12 h.

The results from this pharmacokinetic and pharmacodynamic study indicate a possible future strategy for trials with oral etoposide. Using the limited sampling strategy a patient's AUC is calculated on day 1. If the value is > 2 mg/ml. min a dose reduction to 50 mg/day could be made to prevent serious toxicity. If the AUC is < 2 mg/ml. min the risk of serious toxicity is small and intensive monitoring is not necessary. Patients with a low AUC could be dose escalated or considered for other approaches such as a more prolonged duration of treatment or combination with a more myelotoxic drug.

References

1. Calvert AH, Lind MJ, Millward MJ, Cantwell BMJ, Gumbrell L, Proctor M, Simmons D, Chapman F, Robinson A, Charlton C, Balmanno K, Newell D (1993) Long-term oral etoposide in metastatic breast cancer: clinical and pharmacokinetic results. Cancer Treat Rev 19 [Suppl C]: 27
2. Clark PI, Cottier B (1992) The activity of 10-, 14-, and 21-day schedules of single-agent etoposide in previously untreated patients with extensive small cell lung cancer. Semin Oncol 19 [Suppl 14]: 36
3. D'Incalci M, Rossi C, Zucchetti M, Urso R, Cavalli F, Mangioni C, Willems Y, Sessa C (1986) Pharmacokinetics of etoposide in patients with abnormal renal and hepatic function. Cancer Res 46: 2566
4. Falkson G, Dyk J van, Eden EB van, Merwe AM van der, Burgh JA van den, Falkson HC (1975) A clinical trial of oral form of 4-demethyl-epipodophyllotoxin-B-dethylidine glucoside (NSC 141540) VP16-213 Cancer 35: 1141
5. Gaast A van der, Vlastuin M, Kok TC, Splinter TAW (1992) What is the optimal dose and duration of treatment with etoposide? II. Comparative pharmacokinetic study of three schedules: 1×100 mg, 2×50 mg, and 4×25 mg of oral etoposide daily for 21 days. Semin Oncol 19 [suppl 14]: 8
6. Gentili D, Zucchetti M, Torri V, Sessa C, Jong J de, Cavalli F, D'Incalci M (1993) A limited sampling model for the pharmacokinetics of etoposide given orally. Cancer Chemother Pharmacol 32: 482
7. Hainsworth JD, Johnson DH, Frazier SR, Greco FA (1990) Chronic daily administration of oral etoposide in refractory lymphoma. Eur J Cancer 26: 818
8. Hande KR, Krozely MG, Greco FA, Hainsworth JD, Johnson DH (1993) Bioavailability of low-dose oral etoposide. J Clin Oncol 11: 374
9. Harvey VJ, Slevin ML, Joel SP, Smythe MM, Johnston A, Wrigley PFM (1985) Variable bioavailability following repeated oral doses of etoposide. Eur J Cancer Clin Oncol 21: 1315
10. Hill BT, Whelan RDH, Rupniak HT, Dennis DY, Rosholt MA. (1981) A comparative assessment of the in vitro effect of drugs on cells by means of colony assays or flow microfluorimetry. Cancer Chemother Pharmacol 7: 21
11. Joel SP, Dolega-Ossowski E, Jones K, Clark PI, Johnson P, Slevin ML (1991) The bioavailability of oral etoposide during prolonged administration and the development of a limited sampling strategy for the estimation of AUC after an oral dose. Proc Am Assoc Cancer Res 32: 178
12. Joel SP, Clark PI, Slevin ML (1992) Risk factors which predict for haematological toxicity with etoposide. Br J Cancer 65 [Suppl 1]: 11
13. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer. A phase II trial. J Clin Oncol 8: 1613
14. Miller AA, Tolley EA, Niell HB, Griffin JP, Mauer AM (1993) Pharmacodynamics of prolonged oral etoposide in patients with advanced non-small-cell lung cancer. J Clin Oncol 11: 1179
15. Miller JC, Einhorn LH (1990) Phase II study of daily oral etoposide in refractory germ cell tumors. Semin Oncol 17 [Suppl 2]: 36
16. O'Dwyer PJ, Leyland-Jones B, Alonso MT, Marsoni S, Wittes RE (1985) Etoposide (VP-16–213): Current status of an active anticancer drug. N Engl J Med 312: 692
17. Palombo H, Estape J, Vinolas N, Grau JJ, Mane JM, Danielas M, Mellado B (1994) Chronic oral etoposide in advanced breast cancer. Cancer Chemother Pharmacol 33: 527
18. Pfluger K-H, Schmidt L, Mertal M, Jungclas H, Havemann K (1987) Drug monitoring of etoposide (VP16-213): correlation of pharmacokinetic parameters to clinical and biochemical data from patients receiving etoposide. Cancer Chemother Pharmacol 29: 59
19. Rowinsky EK, Donehower RC (1992) Vinca alkaloids and podophyllotoxins. In: Perry MC (ed) The chemotherapy source book. Williams & Wilkins, Baltimore, p 359
20. Sessa C, Zuchetti M, Torri V, Pagani O, D'Incalci M, Gentili D, Martinelli G, deJong J, Alerci M, Cavalli F (1993) Chronic oral etoposide in small-cell lung cancer: clinical and pharmacokinetic results. Ann Oncol 4: 553
21. Seymour MT, Mansi JL, Gallagher CJ, Gore ME, Harper PG, Evans TRJ, Edmonds PM, Slevin ML (1994) Protracted oral etoposide in epithelial ovarian cancer: a phase II study in patients with relapsed or platinum-resistant disease. Br J Cancer 69: 191
22. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9: 503
23. Sinkule JA, Hutson P, Hayes FA, Etcubanas E, Evans W (1984) Pharmacokinetics of etoposide in children and adolescents with refractory solid tumours. Cancer Res 44: 3109
24. Slevin ML, Clark PI, Joel SP, Malik S, Osborne RJ, Gregory WM, Lowe DG, Reznek RH, Wrigley PFM (1989) A randomized trial to examine the effect of schedule on the activity of etoposide in small cell lung cancer. J Clin Oncol 7: 133
25. Slevin ML, Joel SP, Whomsley R, Devenport K, Harvey VJ, Osborne RJ, Wrigley PFM (1989) The effect of dose on the bioavailability of etoposide: confirmation of a clinically relevant observation. Cancer Chemother Pharmacol 24: 329
26. Wander HE, Rauschning W, Meyer D, Achterrath W, Nagel G-A (1989) Phase II study with etoposide in previously untreated advanced breast cancer. Cancer Chemother Pharmacol 24: 261
27. Wittes RE (1985) Compilation of phase II results with single antineoplastic agents. Cancer Treat Symposia 4: 1