Cancer Chemother Pharmacol (1994) 34 (Suppl): S 69–S 75

Cancer Chemotherapy and Pharmacology

Etoposide dosage and pharmacodynamics

Simon P. Joel, Rita Shah, Maurice L. Slevin

Department of Medical Oncology, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK

Abstract. Etoposide is a schedule-dependent cytotoxic drug with high single agent activity in small-cell lung cancer and lymphoma. Despite its clear dose-dependent myelosuppressive activity, dose-dependent evidence of its anti-tumour activity is harder to demonstrate. A number of reports have correlated haematological toxicity with pharmacokinetic and physiological parameters, which explains some of the variability in dynamic effects that exists between patients. Recent reports have also suggested that anti-tumour response may be related to plasma etoposide concentration. In our own studies we have investigated factors that influence the pharmacodynamic effects of etoposide, principally with regard to haematological toxicity, and these studies have highlighted a number of patient groups who are at risk. Impaired renal function causes a reduction in clearance of etoposide, resulting in increased systemic exposure and more profound myelotoxicity. A 30% dose reduction in this group is recommended to normalise the area under the plasma concentration-time curve (AUC). Patients with low serum albumin concentrations (<35 g/l) also showed significantly worse haematological toxicity, but with no apparent change in total drug pharmacokinetics. There was, however, an increase in the free drug fraction in this group due to decreased protein binding, such that the free drug AUC was similar to that found in patients with renal dysfunction. This would also indicate that a dose reduction of around 30%–40% is required in this patient group. Patients with normal albumin levels but liver enzyme values (aspartate transaminase or gamma-glutamyl transpeptidase) more than 3 times the upper limit of normal also had a less marked but significant increase in neutropenia. In patients with normal organ function, age was the only significant factor in predicting the degree of leukopenia/neutropenia, and increasing age was also associated with decreasing drug clearance and an increase in drug AUC. A small dose reduction and/or careful monitoring is required in this patient group. Further studies are required to elucidate further the relationship between the pharmacokinetics of etoposide and its pharmacodyamics, particularly with regard to anti-tumour activity, and to determine the role of individualised therapy, based on a pharmacokinetic parameter, in reducing the dynamic variability and optimising the use of this drug.

Key words: Etoposide dosage – Pharmacodynamics

Introduction

Etoposide is a cytotoxic drug with action against a range of malignancies that has high single-agent activity in small-cell lung cancer and testicular teratoma. The intracellular target of etoposide is topoisomerase II, a nuclear enzyme that catalyses the passage of DNA across adjacent strands during cell division. This enzyme is most active during the late S and G2 phases of the cell cycle where the stabilisation of the enzyme-DNA complex induced by etoposide causes double- and single-strand breaks in DNA, with resultant cell-cycle arrest.

The dose-dependent myelosuppresion of etoposide is well documented, but evidence of an anti-tumour dose response is much less clear-cut. This is largely because phase I, and a number of phase II, studies have typically been performed in relapsed or refractory patients who are less responsive to cytotoxics but in whom dose-dependent toxicity is nonetheless apparent. Recent studies have demonstrated that the activity of etoposide is schedule-dependent, being higher when the drug is given over several days than when the same dose is given on a single day [1]. Further studies have described the activity of prolonged oral dosing of etoposide and demonstrated activity in tumour types previously unresponsive to etoposide [2].

Paper presented at the Topoisomerase Inhibitors Conference, University of Maryland Cancer Center, 27–30 October 1993, Monterey, California, USA. Supported in part by Bristol Myers Oncology Division

Correspondence to: S. P. Joel

Other reports have documented the large variability in all dynamic effects that result from standard dosing of etoposide and several have identified parameters that influence the drug's activity [3–6], including both pharmacokinetic and physiological variables. This has made it possible to optimise dosing in individual patients with more predictable dynamic effects [4].

Etoposide dose response

Pre-clinical studies

The relationship between dose and cytotoxic activity has been demonstrated in several pre-clinical systems. Studies carried out by Dombernowsky et al. [7] demonstrated that etoposide exerted a dose-dependent effect against L1210 leukaemia in mice and, perhaps more importantly, showed the drug to be highly schedule-dependent in this system, with administration every 3 h repeated for 24 h on days 1 and 5 (a schedule that simulated continuous infusions with adequate time for marrow recovery) proving the most effective with 100% "cures", defined as an increase in survival of >60 days in all mice. Hill and colleagues [8] investigated the activity of a number of cytotoxic drugs against murine neuroblastoma cells in vitro. Etoposide showed a clear decrease in the number of surviving cells with increasing drug concentration following a 24-h exposure to the drug, but there was no further increase in activity beyond 1 μg/ml. The shape of this dose-response curve was characteristic of those drugs that are phase-specific, with non-phase-specific drugs showing a continued exponential decrease in the surviving cell fraction with increasing dose.

Clinical studies

A number of phase I clinical trials conducted in the 1970s showed that myelosuppression, principally leukopenia, was the dose-limiting toxicity with etoposide. Information as to the optimal dose is difficult to obtain from these studies as a number of different schedules were used, as were two different oral formulations, both of which were shown to have variable bioavailability. Similarly, early phase II studies were conducted using a range of doses and schedules, again with different routes of administration. This topic has been well reviewed by Cavalli [9].

More recent phase II studies have also largely failed to demonstrate a clear dose effect with regard to anti-tumour activity. Patients entered into these studies were typically heavily pre-treated and, thus, likely to be much less sensitive to the drug, although a myelosuppressive dose-response was seen. The study of Wolff et al. [10] in patients with recurrent small-cell lung cancer (SCLC) utilising i.v. doses of 100–300 mg/m^2 on days 1–3 (total dose, 300–900 mg/m^2) reported marked increases in haematological toxicity at the three dose levels (incidence of grade IV neutropenia, 0%, 54% and 86%, respectively, at each dose) but response rates of only 1/26, 2/27 and 1/26, a clear absence of an anti-tumour dose effect.

More recently Niederle et al. [11] reported the effect of dose in previously untreated non-small-cell lung cancer at doses of 600–1110 mg/m^2 given over 3 days as 2-h infusions. There was an increase in myelotoxicity with increasing dose, but also 6 of the 26 patients entered showed a tumour response, with all 6 responders receiving doses of 990 mg/m^2 or more. There was no response at doses of 600 and 810 mg/m^2.

Bennett and colleagues [3] reported the activity of 72-h continuous infusions of etoposide in a phase I study, with a typical dose-dependent increase in myelotoxicity and dose-limiting leukopenia/granulocytopenia occurring at a dose of 150 mg/m^2 given daily for 3 days. This study also involved pharmacokinetic investigations at each dose level, which revealed marked variability in the steady-state plasma concentration at each dose. There was also good correlation between the steady-state plasma concentration and the surviving white cell fraction, with the steady-state etoposide concentration being significantly higher in patients with granulocyte nadirs of $<1\times10^9$/l and/or platelet counts of $<100\times10^9$/l than in patients with nadir counts greater than those levels (4.7 vs 2.7 μg/ml, $P<0.05$), suggesting a pharmacokinetic parameter that may predict for the degree of myelosuppression. Age also correlated highly with drug clearance, which the authors attribute to declining renal function and, hence, renal clearance with advancing age.

The studies of Slevin et al. [1] in previously untreated SCLC convincingly demonstrate the effect of schedule on etoposide activity. In the first of these studies, patients were randomised to receive 500 mg/m^2 either as a single 24-h infusion or as five daily 2-h infusions of 100 mg/m^2. Response rates were markedly different, with a 10% overall response being noted in the 24-h arm compared to a 90% overall response in the 5-day arm. Pharmacokinetic studies in these patients showed that the total area under the plasma concentration-time curve (AUC) per course of treatment was identical in the two arms but the duration of exposure to low concentrations of drug (>1 μg/ml) was doubled in the 5-day arm, suggesting that anti-tumour activity may be related to prolonged exposure to low levels of the drug. Myelosuppression was similar in the two arms, as was the duration of exposure to higher drug concentrations (>5 μg/ml), indicating that prolonged exposure to low concentrations of the drug may lead to less haematological toxicity.

A number of studies conducted over the last 3–4 years have investigated prolonged dosing, typically involving oral administration over 10–21 days. The maximum tolerated dose (MTD) in these studies is typically around 50 mg/m^2 over 21 days [2], which, assuming a bioavailability of 60% at that dose level [12], equates to a received systemic dose of around 630 mg/m^2, higher than that achieved with typical dosing over 3–5 days, suggesting that myelosuppression may be reduced with prolonged exposure. (Recent data from Hande et al. [13] report an even higher bioavailability at this dose level; thus, the systemic dose may be even higher than this figure.) Of particular interest from the phase I study with prolonged oral administration of etoposide is the observation that responses were seen in patients who had previously been unresponsive [2]. However, the marked variability in bioavailability that occurs with oral dosing [12] means that

studies aiming to optimise dosing by targeting a particular AUC or plasma level measured on a single day will be difficult to conduct using oral administration.

A number of investigators have thus more recently moved to prolonged infusion of etoposide over 14 days. The decreased myelotoxicity of this schedule has been described by Minami et al. [14], who reported an MTD of 600 mg/m^2, with only one of six patients experiencing grade III/IV leukopenia at that dose level. However, at the next dose level (which achieved a median steady-state concentration of 2.2 μg/ml as compared with 1.7 μg/ml at 600 mg/m^2), all four patients treated experienced grade IV leukopenia.

Kunitoh and Watanabe [15] combined a prolonged infusion of etoposide with cisplatin in a study of 30 patients with advanced non-small-cell lung cancer. There was an expected increase in myelosuppression at the higher dose as compared with the lower doses (grade IV leukopenia in 2/19 patients treated at 20 and 25 mg/m^2 daily and 5/10 patients treated at 30 mg/m^2). Responses were seen at all dose levels (3/10 at 20 mg/m^2, 1/10 at 25 mg/m^2 and 4/10 at 30 mg/m^2). There was, however, marked variability in the steady-state plasma concentration, and when patients were grouped according to this parameter a concentration-dependent dose response, although involving small numbers, was suggested. Among 10 patients with steady-state concentrations of <0.99 μg/ml there was only 1 response, whereas among 11 patients with steady-state concentrations of >1.2 μg/ml there were 5 responses. This highlights the importance of inter-individual drug handling in determining the treatment outcome and suggests that pharmacodynamic variability may be reduced by standardising a kinetic parameter such as AUC or steady-state plasma concentration rather than dose.

Optimised dosing studies

Very few studies have attempted individual dose optimisation in patients using etoposide. Ratain and colleagues [4] have continued with 3-day infusions of etoposide as described by Bennett et al. [3] and have further demonstrated the marked variability in both steady-state plasma concentration and dynamic effect as measured by the degree of leukopenia. The surviving WBC fraction was dependent on a number of factors: the etoposide concentration at 24 h, serum albumin level, performance status and transfusion history. Using these parameters, doses were derived in individual patients that were predicted to achieve a nadir WBC of 1.7×10^9/l. This resulted in a shift in the distribution of leukopenia, with 50% of the individually dosed group achieving the predicted grade III leukopenia. More importantly, this resulted in a 22% dose increase in the individualised arm (459 mg/m^2 as compared with 375 mg/m^2 with standard dosing), albeit with a very large dose range (225–750 mg/m^2). This approach permits dose intensification with more predictable results in individual patients as compared with the largely unpredictable and very variable dynamic effects seen with standard dosing schemes.

Table 1. Infusional etoposide in previously untreated small-cell lung cancer at two plasma concentrations (*CI* Continuous infusion)

	2-μg/ml CI for 5 days	3-μg/ml CI for 5 days
Number of patients	20	20
Nadir WBC ($\times 10^9$/l)	4.2	3.0*
Nadir neutrophils ($\times 10^9$/l)	2.3	0.9*
Grade III/IV neutropenia	4/20	11/20**
Median dose (mg)	457	748

* $P < 0.05$ (Mann-Whitney *U*-test) vs 2-μg/ml CI
** $P < 0.05$ (Fischer's exact test, two-tailed) vs 2-μg/ml CI

At St. Bartholomew's Hospital we have been collaborating with colleagues at the Royal Marsden Hospital, Surrey, and the Churchill Hospital, Oxford, to determine the activity of single-agent etoposide in previously untreated SCLC, but targeting specific plasma concentrations achieved with 5-day infusions, of etoposide at levels of 2 and 3 μg/ml in sequential cohorts of patients. The results obtained in this study to date are shown in Table 1. On day 1 all patients received a loading dose and infusional dose based on population pharmacokinetic parameters, and after 24 h the dose was modified on the basis of the 18-h plasma concentration measured in individual patients. Subsequent estimation of the plasma concentration on day 3 demonstrated that two-thirds of the patients were within 10% of the target concentration. There was a clear concentration dependent increase in myelosuppression, with 4/20 patients at 2 μg/ml and 11/20 at 3 μg/ml experiencing grade III/IV neutropenia. Interestingly, although a small number of patients are involved and the study is continuing, 13/19 patients at the 2-μg/ml level and 13/19 at the 3-μg/ml level have responded, suggesting that there may not be a concentration-dependent increase in anti-tumour activity. (Although target concentrations are escalated on cycle 3, most responding patients have achieved a response by then.) Additionally, as with the study of Ratain et al. [4], the degree of neutropenia showed a distribution much tighter than that obtained with standard dosing schemes. Further randomised studies using targeted therapy may permit the concentrations that result in anti-tumour activity and myelosuppression in different schedules to be established. The demonstration of significant anti-tumour activity at the lower plasma concentration, which typically involved doses of around 275 mg/m^2, suggests that anti-tumour activity, at least in untreated SCLC with 5-day exposure, may not be enhanced by dose increases. Indeed, such increases are likely to lead to increased toxicity, which may preclude the use of other agents. This aspect also requires further study in randomised trials.

Why is there such variability in the pharmacodynamic effects of etoposide with standard dosing?

Treatment with standardised doses of cytotoxics in a patient population typically leads to large variability in measured pharmacodynamic effects. A number of studies have described a correlation between etoposide pharmacokinetic

Table 2. Influence of renal function on etoposide pharmacokinetics and haematological toxicity. All patients have serum albumin levels of ≥35 g/l and AST/γGT values of <100 IU/l (V_d volume)

	Serum creatinine		
	<100 μmol/l	100–130 μmol/l	>130 μmol/l
Pharmacokinetic parameters (*n*)	34	10	5
AUC (μg ml^{-1} h 500 mg^{-1} m^{-2})	452	556*1	615*1
Clearance (ml min^{-1} m^{-2})	18.5	15.0*1	13.6*1
V_d (l/m^2)	8.6	8.5	8.6
Elimination half-life (h)	5.6	6.4	8.1*2
Haematological parameters (*n*)	50	13	6
Nadir haemoglobin (g/l)	11.3	11.1	10.8
% fall in haemoglobin	18.1	241.3	15.9
Nadir white cells (×10^9/l)	3.5	3.5	1.6*2
% fall in WBC	55.4	55.8	84.2*2
Nadir neutrophils (×10^9/l)	1.6	1.5	0.3*2
% fall in neutrophils	68.3	81.2	95.8*3
n <1×10^9/l	17/50	4/13	5/6*4
n <0.5×10^9/l	7/50	2/13	4/6*4
Nadir platelets (×10^9/l)	232	184	146
% fall in platelets	31.8	42.1	57.6*1

*1 P <0.05, *2 P <0.01, *3 P <0.001 (Mann-Whitney U-test) vs creatinine <100 μmol/l; *4 P <0.05 (Fischer's exact test, two-tailed) vs creatinine <100 μmol/l

parameters, such as AUC and clearance, and haematological toxicity [5, 6], although much of the variability remained unexplained. Stewart and colleagues [16] have further described the effect of serum albumin and bilirubin on etoposide protein binding and have demonstrated that haematological toxicity correlates better with exposure to free or non-protein-bound drug than with total etoposide exposure. This is largely because the protein binding of etoposide is very high (95%), such that small changes in binding can lead to large changes in free-drug exposure.

Effect of renal function

At St. Bartholomew's Hospital we investigated the effect of organ dysfunction on etoposide pharmacokinetics and myelosuppression. Previously untreated SCLC patients receiving single-agent i.v. etoposide were studied during their first cycle of treatment. Patients received a total dose of 500 mg/m^2 in two sequential randomised scheduling studies either as 5 daily 2-h infusions of 100 mg/m^2 or as 8 daily 75-min infusions of 62.5 mg/m^2. The influence of renal dysfunction in this group as measured by elevated serum creatinine levels is shown in Table 2. Patients with a serum creatinine value of >130 μmol/l had a significantly decreased total plasma clearance of drug resulting in an increased AUC, and this was associated with significantly lower white cell and neutrophil nadir counts [WBC, 3.5 vs 1.6 × 10^9/l (P <0.01); neutrophils, 1.6 vs 0.3 × 10^9/l (P <0.001)]. This resulted in 5/6 patients with impaired renal function experiencing grade III or IV neutropenia as compared with 17/50 patients with creatinine levels of <100 μmol/l. Patients at the upper end of the creatinine normal range (100–130 μmol/l) showed a less marked but significant increase in AUC but did not show any difference in haematological parameters as compared with those with creatinine level of <100 μmol/l. This increased exposure in renal impairment is in agreement with previous reports that etoposide renal clearance comprises around 30%–40% of the total plasma clearance and that the drug AUC is increased in patients with renal dysfunction. The demonstration of a clear increase in pharmacodynamic effect in this group emphasises the need for a dose reduction of 30%, which will normalise the increased AUC.

Effect of liver function

Patients with normal renal function (serum creatinine, <130 μmol/l) were then grouped according to indicators of liver function. The serum albumin level was the principal determinant such that this group included patients with a range of enzyme activity, whereas the markedly raised enzyme group had albumin levels of ≥35 g/l. [The normal group had aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) values of <35 IU/l (upper limit of normal, ULN)]. The results listed in Table 3 show that total etoposide pharmacokinetic parameters were unchanged in the two groups with abnormal hepatic function but that myelotoxicity was more severe, markedly so in the low-albumin group; 12/15 patients with albumin levels of <35 g/l experienced grade III/IV neutropenia as compared with 14/49 patients with normal liver function.

Toxicity in patients with normal organ function

Although the effect of renal and liver dysfunction is clearly demonstrated by these analyses, there remained 63 patients with normal organ function (serum creatinine, <130 μmol/l; albumin, <35 g/l; AST and GGT, <3 × ULN), approximately one-third of whom experi-

Table 3. Influence of liver function on etoposide pharmacokinetics and haematological toxicity. All patients have serum creatinine levels of <130 μmol/l (*Alb* Albumin)

	Liver function			
	Normal liver function	AST or γGT 35–100 IU/l Alb ≥35 g/l	Albumin <35 g/l[a]	AST or γGT >100 IU/l Alb ≥35 g/l
Pharmacokinetic parameters (*n*)	34	10	14	8
AUC (μg/ml^{-1} h 500 mg^{-1} m^{-2})	467	505	463	425
Clearance (ml/min^{-1} m^{-2})	18.2	16.5	18.6	19.7
V_d (l/m^2)	8.5	9.1	9.6	9.0
Elimination half-life (h)	5.8	5.9	5.9	5.9
Haematological parameters (*n*)	49	14	15	8
Nadir haemoglobin (g/l)	11.5	10.9	10.0*3	10.7
% fall in haemoglobin	18.6	18.5	27.6*1	12.7
Nadir white cells (×10^9/l)	3.7	3.2	1.5*2	2.5
% fall in WBC	56.0	50.0	78.5*3	90.1
Nadir neutrophils (×10^9/l)	1.7	1.0	0.6*3	0.8*1
% fall in neutrophils	70.7	76.6	89.3*3	97.3
n <1×10^9/l	14/49	7/14	12/15*5	5/8
n <0.5×10^9/l	6/49	4/14	7/15*5	3/8
Nadir platelets (×10^9/l)	227	208	191	171
% fall in platelets	35.5	25.3	49.7	65.6

*1 $P<0.05$, *2 $P<0.01$, *3 $P<0.001$ (Mann-Whitney *U*-test) vs normal liver function; *4 $P<0.05$, *5 $P<0.01$ (Fischer's exact test, two-tailed) vs normal liver function

[a] In all, 7 patients have AST and γGT values of <35 IU/l, 3 have AST or γGT levels of 35–100 IU/l and 5 have AST or γGT values of >100 IU/l; 2 patients have bilirubin levels of >35 μmol/l and both have AST or γGT values of >100 IU/l

enced a nadir neutrophil count of $<1 \times 10^9$/l. Regression analysis of biochemical parameters, age and performance status found age to be the only variable significantly predictive of nadir white cell and neutrophil counts. A division of this group according to age (Table 4) clearly shows decreasing drug clearance with increasing age (19.6 ml min^{-1} m^{-2} at <65 years vs 16.2 ml min^{-1} m^{-2} at ≥65 years, $P<0.05$), resulting in a trend towards an increase in AUC that does not quite reach statistical significance ($P = 0.06$) and in significantly worse leukopenia and neutropenia [WBC, 4.0 vs 3.0 × 10^9/l ($P<0.01$); neutrophil count 2.3 vs 1.1 × 10^9/l ($P<0.001$)]. In all, 14/32 patients aged 65 years and over experienced grade III/IV leukopenia and neutropenia as compared with 7/31 patients aged <65 years. It is noteworthy that pre-treatment counts were also lower in those patients aged >65 years, such that although the percentage drop in white blood cells and neutrophils was similar in both younger and older patients, the nadir counts remained significantly lower in the latter group.

Table 4. Influence of age on etoposide pharmacokinetics and haematological toxicity. All patients have serum creatinine levels of <130 μmol/l, albumin levels of ≥35 g/l and AST/γGT values of <100 IU/l

	Age <65 years	Age ≥65 years
Pharmacokinetic parameters (*n*)	24	20
AUC (μg/ml^{-1} h 500 mg^{-1} m^{-2})	437	518
Clearance (ml min^{-1} m^{-2})	19.6	16.2*1
V_d (l/m^2)	8.0	8.0
Elimination half-life (h)	5.5	6.1
Haematological parameters (*n*)	31	32
Pre-treatment haemoglobin (g/l)	14.1	13.7
Nadir haemoglobin (g/l)	11.2	11.5
% fall in haemoglobin	18.8	18.0
Pre-treatment white cells (×10^9/l)	9.5	8.4*
Nadir white cells (×10^9/l)	4.0	3.0**
% fall in WBC	55.6	56.2
Pre-treatment neutrophils (×10^9/l)	7.7	5.7**
Nadir neutrophils (×10^9/l)	2.3	1.1***
% fall in neutrophils	72.8	71.2
n <1×10^9/l	7/31	14/32
n <0.5×10^9/l	3/31	7/32
Pre-treatment platelets (×10^9/l)	396	319*
Nadir platelets (×10^9/l)	227	203
% fall in platelets	42.1	25.3

* $P<0.05$, ** $P<0.01$, *** $P<0.001$ (Mann-Whitney *U*-test) vs age <65 years

Effect of protein binding on dynamic effects

Although typical measures of systemic exposure can explain the increased toxicity observed in patients with renal impairment and elderly patients, the total etoposide AUC alone does not explain the marked myelotoxicity seen in patients with low albumin levels. Ratain et al. [4] have previously reported the influence of albumin on etoposide myelotoxicity, and Stewart and colleagues [16] have described the effect of albumin on etoposide protein binding.

Table 5. Influence of protein binding on haematological toxicity

	Normal organ function	Creatinine >130 μmol/l	Albumin <35 g/l
Number of patients	49	6	15
Nadir neutrophil count (×10⁹/l)	1.7	0.3***	0.6***
Total AUC per course (μg ml⁻¹ h)	467	615***	463
Clearance (ml min⁻¹ m⁻²)	18.2	13.6***	18.6
Protein binding	4.1	4.4	5.5**
Free AUC per course (μg ml⁻¹ h)	16.5	26.0**	27.5**

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ normal organ function

With this in mind, we investigated protein binding in these patients using plasma samples taken immediately prior to treatment and subsequently stored at −40° C. Protein binding was measured by spiking etoposide-free samples with etoposide to a concentration of 10 μg/ml and measuring the etoposide concentration in the ultrafiltrate following ultrafiltration (Shah, personal communication). The free-etoposide AUC was then derived by multiplying the total AUC by the free fraction (%). The results obtained for patients with normal organ function, impaired renal function and low serum albumin levels are given in Table 5.

The percentage free etoposide was 4.1% in patients with normal organ function, resulting in a median free AUC per course of treatment of 16.5 μg ml⁻¹ h. Although the degree of protein binding was not significantly altered in renal impairment, the increased total drug AUC resulting from reduced clearance led to a free-drug AUC of 28.0 μg ml⁻¹ h per course. The most dramatic evidence resulting from this analysis was the effect of albumin on protein binding. Etoposide binding was significantly decreased in this group, resulting in an increased free fraction. Thus, although the total drug AUC was not changed, this change in binding resulted in an increase in free-etoposide AUC to 27.5 μg ml⁻¹ h, a level similar to that seen in patients with renal impairment. There was also a smaller but significant increase in free etoposide in the group with normal albumin levels but AST or GGT values of >3 × ULN, suggesting that the increase in free etoposide observed in patients with liver dysfunction may have resulted from both decreased protein binding and reduced hepatic clearance, as has previously been suggested by Stewart and co-workers [17].

Pharmacokinetic predictors of tumour response

In all, 67 of the patients in this group who were from the same randomised scheduling study and had pharmacokinetics studies performed were analysed separately to determine if any kinetic parameter were predictive of response. Although the numbers were small, those patients not responding to treatment had a lower AUC per course than did responders (367 vs 451 μg ml⁻¹ h, $P = 0.01$), associated with increases in the volume of distribution and plasma etoposide clearance. As all patients in this study received the same total dose of etoposide a dose-response relationship clearly would not exist, but, as with haematological toxicity and those studies that have reported responses associated with steady-state plasma concentration rather than with dose, there is clear evidence of a systemic exposure-response relationship.

Conclusions

The data presented herein confirm the dose response of etoposide with regard to haematological toxicity, but in the standard dose range typically used, evidence of an anti-tumour dose response is less convincing. More prolonged schedules exhibit less myelosuppression as evidenced by the increased MTD for both oral and infusional drug. Although this schedule of administration has resulted in responses in tumours previously unresponsive to chemotherapy, its value as first-line treatment is yet to be defined in randomised studies.

Standard dosing of etoposide leads to large variability in pharmacodynamic effects, and this variability can be reduced and the drugs activity more reliably predicted by individualising the dose on the basis of a pharmacokinetic parameter. Although this is a difficult and labour-intensive practise, it will permit the relationship between pharmacokinetic parameters and dynamic effects to be defined much more clearly and will make treatment optimisation in individual patients possible. The demonstration in our own studies and those of Stewart et al. [16] that free drug is a much more important measure of exposure than total drug suggests that it is this parameter that may be important in individualised therapy. Future randomised studies should determine the value of adaptively controlled dosing and the role of free drug with regard to both toxicity and anti-tumour activity.

In a previous article from this department we concluded that much remained to be learned about this fascinating compound. Although our level of knowledge has been furthered significantly since that time, this statement still stands.

References

1. Slevin ML, et al (1989) 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
2. Hainsworth JD, et al (1989) Chronic daily administration of oral etoposide – a phase I trial. J Clin Oncol 7: 396–401

3. Bennett CL, et al (1987) Phase I clinical and pharmacological study of 72-hour continuous infusion of etoposide in patients with advanced cancer. Cancer Res 47: 1952–1956
4. Ratain MJ, et al (1991) Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. J Clin Oncol 9: 1480–1486
5. Miller AA, Stewart CF, Tolley EA (1990) Clinical pharmacodynamics of continuous-infusion etoposide. Cancer Chemother Pharmacol 25: 361–366
6. Stewart CF, et al (1991) Relation of systemic exposure to unbound etoposide and hematologic toxicity. Clin Pharmacol Ther 50: 385–393
7. Dombernowsky P, Nissen NI (1973) Schedule dependency of the antileukemic activity of the podophyllotoxin derivative VP 16-213 in L1210 leukaemia. Acta Pathol Microbiol Immunol Scand [A] 81: 715–724
8. Hill BT, et al (1981) A comparative assessment of the in vitro effects of drugs on cells by means of colony assays or microfluorimetry. Cancer Chemother Pharmacol 7: 21–26
9. Cavalli F (1982) VP16-213 (etoposide): a critical review of its activity. Cancer Chemother Pharmacol 7: 81–85
10. Wolff SN, et al (1986) Randomized dose-response evaluation of etoposide in small cell carcinoma of the lung: a Southeastern Cancer Study Group trial. Cancer Treat Rep 70: 583–587
11. Niederle N, et al (1991) Etoposide in patients with previously untreated non-small-cell lung cancer: a phase I study. Cancer Chemother Pharmacol 28: 59–62
12. Joel SP, et al (1991) The bioavailability of oral etoposide during prolonged administration and development of a limited sampling strategy for estimation of AUC after an oral dose (abstract). Proc Am Assoc Cancer Res 32: 178
13. Hande KR, et al (1993) Bioavailability of low dose oral etoposide. J Clin Oncol 11: 374–377
14. Minami H, et al (1993) Phase I clinical and pharmacokinetic study of a 14-day infusion of etoposide in patients with lung cancer. J Clin Oncol 11: 1602–1608
15. Kunitoh H, Watanabe K (1993) A phase I/II study of long-term continuous infusion of etoposide combined with cisplatin in advanced non-small cell lung cancer (NSCLC) (abstract). Proc Am Soc Clin Oncol 343
16. Stewart CF, et al (1989) Altered protein binding of etoposide in patients with cancer. Clin Pharmacol Ther 45: 49–55
17. Stewart CF, et al (1990) Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. J Clin Oncol 8: 1874–1879