Pergamon

European Journal of Cancer Vol. 32A, No. 13, pp. 2291 2297, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00301-2

Review

Etoposide for the Treatment of Paediatric Tumours: What is the Best Way to Give It?

S.P. Lowis[1] and D.R. Newell[2]

[1]Bristol Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ; and [2]Cancer Research Unit, University of Newcastle upon Tyne, Newcastle NE2 4HH, U.K.

Etoposide is one of the most important drugs available for the treatment of paediatric malignancies. Although there is evidence of schedule dependency for etoposide therapy in adults with small-cell lung cancer, the relevance of this observation to childhood cancers is uncertain. Prolonged parenteral or oral etoposide therapy has not yet shown a clear-cut advantage over intermittent treatment, and there are still no data to show that the administration of etoposide as a short intravenous (i.v.) daily infusion for 5 days does not represent acceptable therapy for primary disease. The pharmacokinetic variability seen with etoposide argues strongly for the use of pharmacologically guided dosing, and the introduction of etoposide phosphate will simplify both parenteral etoposide administration and the future evaluation of alternative etoposide schedules. Although the impact of molecular and cellular pharmacological investigations on the clinical use of etoposide has yet to be felt, the tools to perform these studies are now available and prospective trials can be designed. Such studies, performed in the setting of a pharmacologically guided trial to ensure control over pharmacokinetic variability, should identify the best way of treating children with etoposide. Copyright © 1996 Elsevier Science Ltd

Key words: etoposide, paediatric oncology, schedule dependency, pharmacokinetics, pharmacodynamics

Eur J Cancer, Vol. 32A, No. 13, pp. 2291–2297, 1996

INTRODUCTION

ETOPOSIDE IS ONE of the most widely used agents in paediatric oncology, and as a single agent, has activity against neuroblastoma, leukaemia, Ewing's sarcoma, soft tissue sarcoma, osteogenic sarcoma and Wilms' tumour. Combination of etoposide with cisplatin, carboplatin, cyclophosphamide or ifosfamide has activity against various solid paediatric tumours including medulloblastoma, primitive neuro-ectodermal tumours and germ cell tumours. In the United Kingdom, over 70% of children with malignant disease now receive etoposide at some point in their management and currently there are at least 20 protocols using etoposide with doses varying from 50 to 200 mg/m^2, given 1–21 times per course and over periods of 1 h to 21 days. Such diversity in dose, schedule and frequency of administration indicates that clinicians are conscious of the potential importance of etoposide scheduling and a need to identify the best way to give the drug. The purpose of the current paper is to review the evidence for and against schedule dependency for etoposide and identify directions for future clinical research.

Etoposide (VP16) is a semi-synthetic derivative of podophyllotoxin, which acts by inhibition of one of the most abundant nuclear proteins, DNA topoisomerase II. Etoposide is cell cycle specific, and leads to an accumulation of cells in G2/M [1]. Given that etoposide inhibits an enzyme, and that this inhibition is saturated at high drug concentrations, prolonged exposure should lead to greater cytotoxicity than that using a high concentration for a short period of time. Although *in vitro* studies have demonstrated the importance of both concentration and duration of exposure to etoposide cytotoxicity, no study has unequivocally demonstrated an advantage for prolonged treatment at low concentrations over the same overall exposure produced by a high concentration for a short period of time [2–7]. Thus,

Correspondence to S.P. Lowis.
Received 17 Jun. 1996; accepted 9 Jul. 1996.

the widely cited schedule dependency of etoposide cannot be clearly demonstrated *in vitro*.

Etoposide has, however, shown schedule dependency in one preclinical *in vivo* model system. Dombernowsky and Nissen [8] performed extensive studies with the L1210 murine leukaemia, and demonstrated differences in efficacy with a wide variety of dosing schedules. For example, administration of etoposide as a single dose led to a cure in three out of 24 animals (13%), whereas the optimum dose given every 3 h for 24 h on days 1 and 5 cured 16 out of 16 animals. Other schedules of administration led to cure rates between 19 and 63% and, in general, higher cure rates were seen where administration was separated by an interval of 4 days. Despite the limitations inherent in any preclinical model, the study by Dombernowsky and Nissen is important as it suggests that the therapeutic index of etoposide can be influenced by schedule. To investigate this possibility in the clinical setting, a number of trials have been performed.

CLINICAL STUDIES OF THE SCHEDULE DEPENDENCY OF ETOPOSIDE IN ADULTS

Cavalli and associates [9] were the first to study the schedule dependency of etoposide in patients; 60 patients with small cell lung cancer (SCLC) received etoposide as:

(1) 250 mg/m^2 intravenously over 5 min, once weekly;
(2) 500 mg/m^2 orally over 3 days weekly; or
(3) 850 mg/m^2 orally over 5 days every 3 weeks.

Response rates [complete response (CR) plus partial response (PR)] after 6 weeks were (a) 20%, (b) 65% and (c) 42%, respectively, with the rates for schedules (a) and (b) being significantly different. Assuming 50% oral bioavailability, the same exposure to etoposide would be expected with schedules (a) and (b), and the authors concluded that oral administration over 3 days was superior to a single i.v. dose. However, without appropriate phamacokinetic monitoring, the possibility of greater exposure in the oral group cannot be excluded.

Mead and associates [10] performed a randomised trial of etoposide given orally to patients with extensive SCLC. Patients received a total dose of 500 mg/m^2 as either a single dose or over 5 days, combined with cyclophosphamide and doxorubicin, every 21 days. No notable differences in response rates or survival were seen between the two arms of this study. However, response rates were less than that for similar patients in the study by Slevin and associates ([11], see below) and it is possible that the relatively low dose of etoposide (the administered dose was the same as that given in the Slevin study [11], but the oral route of administration results in a lower total exposure) used by Mead and associates may have reduced the impact of the drug in this regimen.

The pivotal study of etoposide schedule dependency was performed by Slevin and associates [11] who conducted a randomised trial of the effect of schedule upon efficacy in previously untreated SCLC. Patients were treated with etoposide alone either as a single i.v. dose of 500 mg/m^2 over 24 h, or as 5 daily infusions of 100 mg/m^2, each over 2 h every 3 weeks. Response rates (CR + PR) in the two arms were highly significantly different, being 10% after the single dose and 89% after the five divided doses. Bone marrow toxicity in both arms was mild, with only 3 patients becoming neutropenic ($< 1 \times 10^9$ cells/l) after single dosing. No patient developed thrombocytopenia ($< 100 \times 10^9$ platelets/l). The median survival time after divided dosing was significantly better than after single dosing (10 months versus 6.3 months). Pharmacokinetic studies were performed in all patients, and equivalent exposure (area under the plasma concentration versus time curve—AUC) was seen in each arm, but the duration of exposure above a plasma level of 1 μg/ml was significantly greater with divided dosing than with the single dose. In a later study, the same group reported no additional benefit in response rates for a more prolonged schedule of administration (8 days versus 5 days) of the same total dose of 500 mg/m^2 [12]. This result was confirmed by Clark and colleagues [13], although in this study the haematological toxicity was significantly less in the 8-day arm than in the 5-day arm.

Supporting the conclusions of Slevin and colleagues [11] is a study of 1-day versus 5-day etoposide therapy for SCLC given in combination with doxorubicin and vincristine [14]. Response rates were significantly different (52 versus 75%) for the 1-day and 5-day arms, respectively, again suggesting a therapeutic advantage for prolonged administration. However, lack of pharmacokinetic monitoring and the use of different routes of administration in the two arms limits the interpretation of these data.

In the studies performed by Slevin and colleagues, divided dosing led to significantly longer exposure at or above a plasma level of 1 μg/ml than did single dose administration. One possible explanation put forward for the improved response rate, but similar toxicity, seen with divided dosing was that high etoposide concentrations are associated with toxicity, whereas time of exposure to low concentrations (1–5 μg/ml) determines antitumour effect. However, studies with continuous infusions (CI) of etoposide compared to divided short infusions given over the same time period have failed to show any differences in terms of toxicity or response. For example, Chatelut and colleagues [15] reported a study of etoposide administered as either a CI of 360 mg/m^2 over 72 h or as three separate doses of 120 mg/m^2 on consecutive days, in combination with cisplatin, to patients with previously untreated non-small-cell lung cancer. No difference in pharmacokinetic parameters, response rates or toxicity was seen in this study, and the authors concluded that there was no therapeutic advantage to be gained from using infusion therapy. The same conclusion was reached by Goldberg and colleagues [16] in a study of infusion versus repeated short infusion etoposide and cisplatin therapy for stage IV non-small cell lung cancer. Similarly, in an early study published by Schell and colleagues in 1982 [17], 77 patients with breast cancer who had previously failed chemotherapy received etoposide as either a 1-h infusion of 50–70 mg/m^2 for 5 days, or as a CI at the same dose over 5 days. Response rates (CR + PR) were equivalent in the two arms (13% and 14% for infusion and intermittent treatment, respectively) and, in this group of heavily pretreated patients, haematological toxicity was severe.

In summary, whilst the superiority of prolonged or repeated therapy as opposed to bolus administration appears logical for an enzyme inhibitor such as etoposide, preclinical and clinical data do not consistently show any benefit.

Specifically, only in SCLC, a highly chemosensitive tumour type, has an advantage for repeated or prolonged etoposide administration been unequivocally demonstrated. Randomised studies in other tumour types are needed to confirm this observation. There have been no randomised trials of the effect of etoposide schedule on the activity of the drug in paediatric tumours.

OTHER ADULT STUDIES

Continuous infusion studies

Thompson and colleagues have described studies of very prolonged infusion therapy in adults with advanced malignancies [18, 19]. Patients received etoposide as a continuous infusion initially at 25 mg/m^2/day until haematological toxicity was seen. Therapy was continued for a total of 3–80 weeks (median = 10), and etoposide doses of between 375 and 8838 mg/m^2 (median = 1115) were administered. Haematological toxicity was generally mild, since infusion was interrupted if the white cell count fell below 2×10^9/l. Responses were seen in patients with SCLC and non-Hodgkin's lymphoma; no other tumour type was found to respond to this regimen.

The study performed by Thompson and colleagues was undertaken with the intention of maintaining plasma etoposide concentrations between 0.5 and 1 μg/ml for as long as possible. Patients were entered at a starting dose of 25 mg/m^2/day, which proved to be the MTD, with myelosuppression as the dose limiting toxicity. A dose of 25 mg/m^2/day corresponds to a total administered dose of 525 mg/m^2 every 3 weeks, which is the MTD found in the majority of studies of etoposide administered by conventional intermittent schedules. In practice, from the data presented by Thompson and colleagues, patients actually received a mean dose of only 336 mg/m^2 over 21 days, which is below the MTD reported for etoposide in most conventional schedule studies. Furthermore, the response rate seen was not dramatically better than that reported for conventional regimens.

Oral etoposide therapy as an alternative to parenteral administration

In adults there have been a large number of studies of oral etoposide and, because of the schedule dependency of systemic therapy, a number of these have involved SCLC. In general, oral administration appears to have similar activity to parenteral etoposide, although comparisons with historical data are complicated by varying bioavailability and scheduling [20–25]. Recently, the issue of prolonged oral versus intermittent systemic etoposide treatment for SCLC has been addressed in a randomised trial of cisplatin and etoposide therapy [26]. The two arms of the trial were 130 mg/m^2 etoposide i.v. plus 25 mg/m^2 cisplatin i.v. daily for 3 days, repeated every 21 days, versus 50 mg/m^2 etoposide orally daily for 21 days plus 33 mg/m^2 cisplatin i.v. daily for 3 days, repeated every 28 days. The response rates in the two arms were similar, and prolonged oral administration of etoposide was the more toxic treatment.

The use of oral etoposide in adults has recently been reviewed by Hainsworth and Greco [27] who concluded that prolonged oral etoposide therapy was both feasible and relatively well tolerated. However, these authors felt that the potential benefit of prolonged oral administration was likely to be limited to etoposide-sensitive tumours. There is still a need for further prospective randomised studies of intermittent versus prolonged exposure etoposide therapy in which (a) bioequivalent etoposide doses are compared, (b) there is pharmacokinetic monitoring to ensure bioequivalence, (c) concomitant therapy is equivalent, both in terms of the drugs used and the doses given, and (d) overall dose intensity, for each drug is equal in both arms.

ETOPOSIDE SCHEDULES EXPLORED FOR THE THERAPY OF PAEDIATRIC TUMOURS

Continuous infusion studies

Campbell and colleagues [28] reported a dose escalation study involving 96-h infusion therapy consisting of doxorubicin, cisplatin and etoposide, with bolus ifosfamide, in heavily pretreated patients with refractory neuroblastoma. Doses of etoposide were escalated to 500 mg/m^2/course, with cisplatin 160 mg/m^2/course, doxorubicin 40 mg/m^2/course, and ifosfamide 10 g/m^2/course. Toxicity was severe, with all patients developing grade IV neutropenia, 47% with associated fever. Six per cent of patients developed severe mucositis. With the highest etoposide dose, a response was seen in 3 of 5 patients [2 CR and 1 VGPR (very good PR)] and the overall response rate was 43%, which compares favourably with previous reports of regimens containing etoposide in the relapse setting. Meresse and colleagues [29] reported a series of patients with refractory neuroblastoma treated with CI etoposide and high-dose cyclophosphamide. All patients received both drugs as first-line therapy. Etoposide was given at a dose of 50 mg/m^2/day for 5 days, and cyclophosphamide was given at 2 g/m^2/day for 3 days. Myelotoxicity was significant in all patients, with neutropenia ($< 0.5 \times 10^9$ cells/l) lasting for a median of 14 days. Febrile episodes developed in 96% of courses, with documented septicaemia in 15 of 56. Vomiting, diarrhoea and mucositis were seen in 33%, 10% and 14% of courses, respectively. The overall response rate was 36% (1 CR + 9 PR), comparable with previous studies. However, the fact that responses were seen, despite previous treatment failure with conventional methods of administration, was taken as evidence of improved therapeutic efficacy.

Infusions of longer than 5 days have not been studied in children, but the case for investigating prolonged parenteral etoposide administration in children at this time is not strong, considering results observed in adults [18, 19].

Oral etoposide therapy

To date, relatively few trials of the efficacy of oral etoposide have been carried out in children. Davidson and colleagues [30] reported a series of 22 children with relapsed or refractory disease treated with etoposide at doses of 50–100 mg/m^2/day for 21 days. Patients had diagnoses of neuroblastoma ($n = 11$), soft tissue sarcoma ($n = 5$), leukaemia ($n = 4$), Hodgkin's disease ($n = 1$) and germ cell tumour ($n = 1$). Only one patient, with neuroblastoma, achieved a PR, although he was, in fact, unable to tolerate the oral preparation, and subsequently received an equivalent daily intravenous dose. 6 other patients with neuroblastoma had mixed responses. 8 patients, including all 4 with leukaemia, had progressive disease, but useful palliation was documented in 11 of 15 patients who had pain prior to commencing therapy. The major toxicity of this therapy was bone mar-

row suppression, which occurred in 3 out of 4 patients who received 80 mg/m^2/day. At lower doses, toxicity was less severe, and 2 children completed 8 and 9 courses with good palliation. The overall efficacy of this regimen was disappointing, since no patient receiving oral etoposide attained a response, but the excellent palliation seen, and the ease of this method of administration were important considerations. Furthermore, the patients included in this study had all received aggressive multi-agent chemotherapy, including etoposide in conventional doses and schedules, and the *a priori* likelihood of response from any single agent was, therefore, small. Based upon this pilot study, a phase II trial of etoposide at a dose of 50 mg/m^2/day in patients with relapsed and refractory disease was, therefore, initiated by the New Agents Group of the UKCCSG. This trial has recently been closed, but the results have not yet been published.

In 1994, Mathew and associates reported a second phase I study of single agent oral etoposide in children with refractory solid tumours [31]. 20 patients received etoposide at doses of 50, 60 and 75 mg/m^2 for 21 days every 4 weeks, and pharmacokinetic studies were performed on days 1, 7, 14 and 21. Etoposide was administered three times daily, aiming to maximise the duration of exposure above 1 μg/ml. The major dose-limiting toxicity in this study was haematological, with 2/7 patients developing grade 4 neutropenia at the 75 mg/m^2 dose level, but diarrhoea was also a problem. The maximum tolerated dose was defined as 60 mg/m^2/day with this three-times daily regimen. One complete response, two partial responses and two 'objective responses' were observed in this study. The CR and two objective responses were in patients with neuroblastoma and 4 additional patients had stable disease, which in one case was for 27 courses of oral etoposide. Pharmacokinetic studies were performed in 17 patients and, although full pharmacokinetic data were not reported, the median duration of plasma concentrations in each 24-h period during which etoposide plasma concentrations were greater than 1 μg/ml were 9.4, 15.4 and 13.5 h for doses of 50, 60 and 75 mg/m^2/day, respectively.

Mahmoud and colleagues [32] have reported preliminary results from 25 children with relapsed ALL treated with a novel re-induction regimen, with 3 patients in second relapse. Etoposide was administered orally at a dose of 50 mg/m^2/day, on days 1–22, with vincristine, dexamethasone and L-asparaginase given on days 8–36. 21 of 22 evaluable patients attained CR with this regimen, which compares favourably with other remission re-induction protocols. However, toxicity was severe, with 22/25 patients developing grade 4 haematological toxicity and 4 patients unable to tolerate the regimen, as a result of severe diarrhoea. One patient died of disseminated fungal disease during induction, and 9 developed sepsis (5 bacterial, 4 fungal).

In principle, oral etoposide for paediatric tumours is an attractive option in the setting of palliative therapy. However, it is essential in each patient to ensure that safe plasma levels of etoposide are not being exceeded, and pharmacokinetic monitoring is helpful in this respect. As first-line therapy, it is unlikely that prolonged oral etoposide will offer any advantage over intermittent systemic treatment, and alternative approaches have a higher priority.

THE OPTIMISATION OF ETOPOSIDE THERAPY WHEN GIVEN IN COMBINATION SCHEDULES

The majority of clinical protocols using etoposide involve multi-agent chemotherapy. In addition to the issues of schedule dependency raised above, drug interactions can occur in combination protocols both at the whole body and the cellular level. In particular, a number of paediatric protocols involve the co-administration of etoposide and platinum complexes. Adults with SCLC who received cisplatin prior to etoposide have a significantly superior response rate and survival than patients receiving the drugs in the opposite sequence [33]. The reasons for this difference are unclear. Relling and colleagues have shown that in children the co-administration of etoposide and cisplatin leads to a reduction in etoposide clearance [34]. A plausible explanation is that cisplatin causes an acute reduction in the renal and/or metabolic clearance of etoposide, which leads to higher drug levels and hence an improved clinical outcome. Prospective trials are needed to address this possibility.

The combination of carboplatin with etoposide in children during high-dose marrow-ablative therapy may lead to a prolongation of the time to engraftment [35], which may also be related to reduced etoposide clearance. More gener-

Table 1. Pharmacokinetic–pharmacodynamic relationships for etoposide therapy

Authors	Schedule	Pharmacokinetic parameter	Pharmacodynamic parameter	Model	Coefficient of determination	[Ref.]
Brindley *et al.*	i.v. daily × 5	C24h	Leucopenia	Linear	$r^2 = 0.49$	[36]
Bennett *et al.*	3 day CI	Css	Leucopenia	Non-linear	$r^2 = 0.49$	[37]
Desoize *et al.*	5 day CI	C days 3–5	Response	NA*	NA	[38]
Miller *et al.*	24 h CI	AUC	Leucopenia	Linear	$r^2 = 0.50$	[39]
			Thrombocytopenia	Linear	$r^2 = 0.46$	
			Anaemia	Linear	$r^2 = 0.70$	
Mick and Ratain	3 day CI	C24h	Leucopenia	Non-linear	NA	[40]
Stewart *et al.*	i.v. days 1, 3, 5	Unbound AUC	Leucopenia	Non-linear	$r^2 = 0.59$	[41]
Miller *et al.*	i.v. daily × 3	Unbound AUC	Neutropenia	Linear	$r^2 = 0.94$	[42]
Minami *et al.*	14 day CI	Css	Leucopenia	Non-linear	$r^2 = 0.41$	[43]
			Thrombocytopenia	Non-linear	$r^2 = 0.46$	
Millward *et al.*	14 day p.o.	Day 1 AUC	Neutropenia	Non-linear	$r^2 = 0.77$	[44]
Joel *et al.*	i.v. daily × 5 or 8	Unbound AUC	Neutropenia	Non-linear	$r^2 = 0.39$	[45]

C24h, concentration at 24 h; Css, concentration at steady state; C, concentration; AUC, area under the plasma concentration versus time curve; NA, not applicable.

Table 2. Pharmacokinetic variability of etoposide in children

Authors	Number of patient	Ages (years)	Dose (mg/m^2/day)	Clearance (ml/min/m^2)			[Ref.]
				Mean ± S.D.	Median	Range	
D'Incalci *et al.*	6	4–10	95–216	—	39	20–46	[46]
Evans *et al.*	9	0.25 18	200–250	20 ± 12*	—	—	[47]
Sinkule *et al.*	8	4–22	200	21 ± 5	—	—	[48]
Lowis *et al.*	33	0.4–16	89–208	—	26	14–54	[49]
Relling *et al.*	16	1–10	260	—	20†	16–50	[34]
					16‡	11–19	
					20§	16–26	
Rodman *et al.*	29	2–24	320–500	—	14	7–30	[35]
Boos *et al.*	11	0.7 ± 0.2	125	22 ± 9	19	—	[50]
	39	4.9 ± 4.6	125	19 ± 5	18	—	

* Values are mean ± S.D. † With concurrent cyclophosphamide: course 2 of a 6-course multi-agent regimen. ‡ With concurrent cisplatin: course 4 of a 6-course multi-agent regimen. § With concurrent cyclophosphamide: course 6 of a 6-course multi-agent regimen.

ally, etoposide is used in combination with several cytotoxic drugs. The clinical justification for multi-agent therapy is often not proven whereas the potential for drug interactions, sometimes with adverse clinical consequences, is clear. Simplified clinical protocols, with full laboratory support, which address well-defined questions, are needed.

FUTURE DIRECTIONS FOR CLINICAL RESEARCH WITH ETOPOSIDE IN PAEDIATRIC ONCOLOGY

A number of recent developments have highlighted ways in which the treatment of paediatric malignancies with etoposide might be improved. Overall, the priorities for research are:

(1) to improve the consistency of therapy by reducing intra- and interpatient pharmacokinetic and pharmacodynamic variability;
(2) to enhance the activity of etoposide against tumours with intrinsic or acquired drug resistance; and
(3) to minimise the doses of etoposide given to patients with chemocurable tumours in order to reduce the risk of second malignancies.

In responding to these priorities, it is important to note that there is considerable evidence for exposure–toxicity relationships for etoposide, but much less data to support exposure–response relationships [36–45]. These data are summarised in Table 1. For leucopenia and neutropenia, 50% of the variability in toxicity can be accounted for by variation in etoposide levels (i.e. median $r^2 = 0.5$ for pharmacokinetic–pharmacodynamic relationships). Etoposide plasma clearance in children shows marked interpatient variability [34, 35, 46–50], and dosing on the basis of surface area, or in infants body weight [50], does not compensate for inter-individual differences. As shown in Table 2, most studies have found that surface area-normalised etoposide clearance in children varies 3–4-fold. Pharmacologically guided dosing, to compensate for pharmacokinetic variability, should result in greater reproducibility and thereby improve the therapeutic index of the drug. Studies in adults have shown that pharmacologically guided dosing does allow safer administration of etoposide [51], and paediatric trials have confirmed the feasibility of adaptive dosing, with feedback control for the related epipodophyllotoxin teniposide [52], a drug for which there is strong evidence of a pharmacokinetic–response relationship in paediatric tumours [53]. More practical, limited sampling strategies have been reported [44, 54–57] and future protocols incorporating etoposide, regardless of the schedule being studied, should consider pharmacologically guided dosing as an option.

Although pharmacologically guided dosing may compensate for pharmacokinetic variability, the response of the tumour cell will also depend upon molecular and cellular determinants of chemosensitivity. For example, a large body of preclinical data implicates the intracellular activity of topoisomerase II as a determinant of the activity of etoposide. Prospective documentation of the levels of topoisomerase II in tumour samples and their relationship to subsequent tumour response is another high priority for clinical research, although such studies are complicated by the fact that etoposide is often used in combination with other drugs.

In vitro sensitivity to etoposide is also influenced by the levels of the MDR1 drug efflux pump. In an attempt to overcome resistance due to the action of the MDR1 glycoprotein, studies have been performed with modulators such as verapamil, cyclosporin A and PSC833 [58]. Trials in children with refractory tumours have been performed using cyclosporin A and verapamil [59, 60], but it is clear that pharmacokinetic interactions between the 'modifier' and the cytotoxic drug can significantly complicate the interpretation of results. As with studies to investigate the potential of different routes of etoposide therapy, clinical trials with resistance modifiers must include pharmacokinetic monitoring to ensure that bioequivalent etoposide exposures are compared.

Finally, the recent identification of etoposide phosphate, a water-soluble prodrug, which is activated by plasma phosphatase enzymes, is of potential significance to paediatric oncology. Etoposide phosphate can be administered in a purely aqueous vehicle, thereby avoiding potential toxicities of the excipients used in current parenteral etoposide formulations [61]. Pharmacokinetic studies in adults have confirmed that etoposide, given intravenously as etoposide phosphate, is fully bio-equivalent [62–65], and high priority should now be given to the investigation of this in children.

1. Drewinko B, Barlogie B. Survival and cell cycle progression delay of human lymphoma cells *in vitro* exposed to VP 16-213. *Cancer Treat Rep* 1976, **60**, 1295–1306.

2. D'Incalci M, Erba E, Vaghi M, Morasca L. *In vitro* cytotoxicity of VP16 on primary tumour and metastasis of Lewis lung carcinoma. *Eur J Cancer* 1982, **18**, 377–380.
3. Matsushima Y, Kanzawa F, Hoshi A, *et al.* Time-schedule dependency of the inhibiting activity of various anticancer drugs in the clonogenic assay. *Cancer Chemother Pharmacol* 1985, **14**, 104–107.
4. Roed H, Vindelov LL, Christensen IJ, *et al.* The effect of the two epipodophyllotoxin derivatives etoposide (VP16) and teniposide (VM26) on cell lines established from patients with small cell carcinoma of the lung. *Cancer Chemother Pharmacol* 1987, **19**, 16–20.
5. Wolff SN, Grosh WW, Prater K, Hande KR. *In vitro* pharmacodynamic evaluation of VP 16-213 and implications for chemotherapy. *Cancer Chemother Pharmacol* 1987, **19**, 246–249.
6. Lowis SP, Newell DR, Pearson ADJ. Exposure and schedule dependency of etoposide in neuroblastoma and leukaemia cells *in vitro*. *Eur J Cancer* 1995, **31A**, 622–626.
7. Ohishi Y, Fujiwara K, Kohno I. Effect of the exposure dose of etoposide on the cell growth and cell kinetics of human ovarian cancer cells. *Cancer Chemother Pharmacol* 1996, **38**, 141–146.
8. Dombernowsky P, Nissen NI. Schedule dependency of the antileukemic activity of the podophyllotoxin-derivative VP 16-213 (NSC-141540) in L1210 leukemia. *Acta Path Microbiol Scand A* 1973, **81**, 715–724.
9. Cavalli F, Sonntag RW, Jungi F, Senn HJ, Brunner KW. VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosing schedules. *Cancer Treat Rep* 1978, **62**, 473–475.
10. Mead GM, Thompson J, Sweetenham JW, Buchanan RB, Whitehouse JMA, Williams CJ. Extensive stage small cell carcinoma of the bronchus. A randomized study of etoposide given orally by one-day or five-day schedule together with intravenous adriamycin and cyclophosphamide. *Cancer Chemother Pharmacol* 1987, **19**, 172–174.
11. Slevin ML, Clark PI, Joel SP, *et al.* A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989, **7**, 1333–1340.
12. Clark PI, Slevin ML, Joel SP, *et al.* A randomized trial of two etoposide schedules in small cell lung cancer: the influence of pharmacokinetics on efficacy and toxicity. *J Clin Oncol* 1994, **12**, 1427–1435.
13. Clark PI, Cottier B, Joel SP, Slevin ML. Two prolonged schedules of single agent oral etoposide of differing duration and dose in patients with untreated small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1991, **10**, 268 (abstract).
14. Abratt RP, Willcox PA, de Groot M, *et al.* Prospective study of etoposide scheduling in combination chemotherapy for limited disease small cell lung cancer. *Eur J Cancer* 1991, **27**, 28–30.
15. Chatelut E, Chevreau C, Blancy E, *et al.* Pharmacokinetic and toxicity of two modalities of etoposide infusion in metastatic non-small cell lung carcinoma. *Cancer Chemother Pharmcol* 1990, **26**, 365–368.
16. Goldberg RM, Jett JR, Therneau TM, *et al.* Bolus versus infusion regimens of etoposide and cisplatin in treatment of non-small cell lung cancer: a study of the North Central Cancer Treatment Group. *J Natl Cancer Inst* 1990, **82**, 1899–1903.
17. Schell FC, Yap HY, Issell B, Esparza L. Phase II study of VP16-213 (etoposide) in refractory metastatic breast carcinoma. *Cancer Chemother Pharmacol* 1982, **7**, 223–225.
18. Thompson DS, Hainsworth JD, Hande KR, Holzmer MC, Greco FA. Prolonged administration of low dose infusional etoposide in patients with advanced malignancies. *Cancer* 1994, **73**, 2824–2831.
19. Thompson DS, Hainsworth JD, Hande KR, Holzmer MC, Greco FA. Prolonged administration of low dose, infusional etoposide in patients with etoposide-sensitive neoplasms: a phase I/II study. *J Clin Oncol* 1993, **11**, 1322–1328.
20. Carney DN, Grogan L, Smit EF, *et al.* Single agent oral etoposide for elderly small cell lung cancer patients. *Semin Oncol* 1990, **17**(Suppl. 2), 49–53.
21. Clark PI, Cottier B. 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* 1992, **19**(Suppl. 14), 36–39.
22. Sessa C, Zucchetti M, Torri V, *et al.* Chronic oral etoposide in small cell lung cancer: clinical and pharmacokinetic results. *Annals Oncol* 1993, **4**, 553–558.
23. Johnson PWM, Seymour MT, Waines A, Squires L, Slevin ML. Etoposide as a single agent in small cell lung cancer (SCLC): as good as combination chemotherapy? *Proc Am Soc Clin Oncol* 1992, **11**, 291 (abstract).
24. Grant SC, Gralla RJ, Kris MG, Orazem J, Kitsis EA. Single agent chemotherapy trials in small cell lung cancer, 1970–1990. The case for studies in previously treated patients. *J Clin Oncol* 1992, **10**, 484–498.
25. Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP16 in refractory small cell lung cancer: a Hoosier Oncology Group Study. *Semin Oncol* 1990, **17**(Suppl. 2), 32–35.
26. Miller AA, Herndon II J, Hollis DR, *et al.* Schedule dependency of 21-day oral versus 3-day intravenous etoposide in combination with intravenous cisplatin in extensive-stage small-cell lung cancer: a randomized phase III study of the Cancer and Leukemia Group B. *J Clin Oncol* 1995, **13**, 1871–1879.
27. Hainsworth JD, Greco FA. Etoposide: twenty years later. *Annals Oncol* 1995, **6**, 325–341.
28. Campbell LA, Seeger RC, Harris RE, Villablanca JG, Matthay KK. Escalating dose of continuous infusion combination chemotherapy for refractory neuroblastoma. *J Clin Oncol* 1993, **11**, 623–629.
29. Meresse V, Vassal G, Michon J, *et al.* Combined continuous infusion etoposide with high-dose cyclophosphamide for refractory neuroblastoma: a phase II study from the Societe Francaise d'Oncologie Pediatrique. *J Clin Oncol* 1993, **11**, 630–637.
30. Davidson A, Lewis I, Pearson ADJ, Stevens MCG, Pinkerton CR. 21-day schedule oral etoposide in children—a feasibility study. *Eur J Cancer* 1993, **29A**, 2223–2225.
31. Mathew P, Ribeiro RC, Sonnichsen D, *et al.* Phase I study of oral etoposide in children with refractory solid tumours. *J Clin Oncol* 1994, **12**, 1452–1457.
32. Mahmoud H, Relling M, Crist W, Rivera G, *et al.* Effective retrieval therapy including daily oral etoposide for children with relapsed acute lymphoblastic leukemia. *Med Pediatr Oncol* 1993, **21**, 555.
33. Maksymiuk AW, Jett JR, Earle JD, *et al.* Sequencing and schedule dependent effects of cisplatin plus etoposide in small-cell lung cancer: results of a North Central Cancer Treatment Group randomized clinical trial. *J Clin Oncol* 1994, **12**, 70–76.
34. Relling MV, McLeod HL, Bowman LC, Santana VM. Etoposide phrmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharm Ther* 1994, **56**, 503–511.
35. Rodman JH, Murry DJ, Madden T, Santana VM. Altered etoposide pharmacokinetics and time to engraftment in pediatric patients undergoing autologous bone marrow transplantation. *J Clin Oncol* 1994, **12**, 2390–2397.
36. Brindley CJ, Antoniw P, Newlands ES, Bagshawe KD. Pharmacokinetics and toxicity of the epipodophyllotoxin derivative etoposide (VP16-213) in patients with gestational choriocarcinoma and malignant teratoma. *Cancer Chemother Pharmacol* 1985, **15**, 66–71.
37. Bennett CL, Sinkule JA, Schilsky RL, Senekjian E, Choi KE. Phase I clinical and pharmacological study of 72 hr continuous infusion of etoposide in patients with advanced cancer. *Cancer Res* 1987, **47**, 1952–1956.
38. Desoize B, Marechal F, Cattan A. Clinical pharmacokinetics of etoposide during 120 hours continuous infusions in solid tumours. *Br J Cancer* 1990, **62**, 840–841.
39. Miller AA, Stewart CF, Tollet EA. Clinical pharmacodynamics of continuous infusion etoposide. *Cancer Chemother Pharmacol* 1990, **25**, 361–366.
40. Mick R, Ratain MJ. Modelling interpatient pharmacodynamic variability of etoposide. *J Natl Cancer Inst* 1991, **83**, 1560–1564.
41. Stewart CF, Arbuck SG, Fleming RA, Evans WE. Relation of systemic exposure to unbound etoposide and haematologic toxicity. *Clin Pharm Ther* 1991, **50**, 385–393.
42. Miller AA, Tolley EA, Niell HB, Stewart CF, Griffin JP. Pharmacodynamics of three daily infusion of etoposide in

patients with extensive-stage small-cell lung cancer. *Cancer Chemother Pharmacol* 1992, **31**, 161–166.
43. Minami H, Shimokata K, Saka H, *et al.* Phase I clinical and pharmacokinetic study of a 14-day infusion of etoposide in patients with lung cancer. *J Clin Oncol* 1993, **11**, 1602–1608.
44. Millward MJ, Newell DR, Yuen K, *et al.* Pharmacokinetics and pharmacodynamics of prolonged oral etoposide in women with breast cancer. *Cancer Chemother Pharmacol* 1995, **37**, 161–167.
45. Joel SP, Shah R, Clark PI, Slevin ML. Predicting etoposide toxicity: relationship to organ function and protein binding. *J Clin Oncol* 1996, **14**, 257–267.
46. D'Incalci M, Farina P, Sessa C, *et al.* Pharmacokinetic of VP16-213 given by different administration methods. *Cancer Chemother Pharmacol* 1982, **7**, 141–145.
47. Evans WE, Sinkule JA, Crom WR, *et al.* Pharmacokinetics of teniposide (VM26) and etoposide (VP16-213) in children with cancer. *Cancer Chemother Pharmacol* 1982, 7, 147–150.
48. Sinkule JA, Hutson P, Hayes FA, Etcubanas E, Evans WE. Pharmacokinetics of etoposide (VP16) in children and adolescents with refractory solid tumours. *Cancer Res* 1984, **44**, 3109–3113.
49. Lowis SP, Pearson ADJ, Newell DR, Cole M. Etoposide pharmacokinetics in children: the development and prospective validation of a dosing equation. *Cancer Res* 1993, **53**, 4881–4889.
50. Boos J, Krumpelmann S, Schulze-Westhoff P, *et al.* Steady-state levels and bone marrow toxicity of etoposide in children and infants: does etoposide require age dependent dose calculation? *J Clin Oncol* 1995, **13**, 2954–2960.
51. Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F. Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. *J Clin Oncol* 1991, **9**, 1480–1486.
52. Rodman JH, Sunderland M, Kavanagh RL, *et al.* Pharmacokinetics of continuous infusion methotrexate and teniposide in paediatric cancer patients. *Cancer Res* 1990, **50**, 4267–4271.
53. Rodman JH, Abromowitch M, Sinkule JA, *et al.* Clinical pharmacodynamics of continuous infusion teniposide: systemic exposure as a determinant of response in a phase I trial. *J Clin Oncol* 1987, **7**, 1007–1014.
54. Stromgren AS, Sorensen BT, Jakobsen P, Jakobsen A. A limited sampling method for estimation of the etoposide area under the curve. *Cancer Chemother Pharmacol* 1993, **32**, 226–230.
55. Gentili D, Zucchetti M, Torri V, Sessa C, *et al.* A limited sampling model for the pharmacokinetics of etoposide given orally. *Cancer Chemother Pharmacol* 1993, **32**, 482–486.
56. Joel SP, Heap L, Robbins S, Clarke PI, Slevin ML. A limited sampling strategy for the calculation of etoposide pharmacokinetics. *Proc Am Soc Clin Oncol* 1990, **9**, 260.
57. Joel SP, Dolega-Ossowski E, Jones K, *et al.* 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* 1991, **32**, 178.
58. Lum BL, Fisher GA, Brophy NA, *et al.* Clinical trials of modulation of drug resistance. *Cancer* 1993, **72**, 3302–3314.
59. Cowie F, Pinkerton CR, Dick G. Continuous infusion of cyclosporin A to reverse etoposide resistance in pediatric tumours. *Anti-Cancer Drugs* 1994, **5**(Suppl. 1), 65.
60. Cowie FJ, Pinkerton CR, Philips M, *et al.* Continuous-infusion verapamil with etoposide in relapsed or resistant paediatric cancers. *Br J Cancer* 1995, **71**, 877–881.
61. Schacter LP, Igwemezie LN, Seyedsadr M, *et al.* Clinical and pharmacokinetic overview of parenteral etoposide phosphate. *Cancer Chemother Pharmacol* 1994, **34**(Suppl.), S58–S63.
62. Budman DR, Igwemezie LM, Kaul S, *et al.* Phase I evaluation of a water soluble etoposide prodrug, etoposide phosphate, given as a 5-minute infusion on days 1, 3, and 5 in patients with solid tumours. *J Clin Oncol* 1994, **12**, 1902–1909.
63. Hainsworth JD, Levitan N, Wampler GL, *et al.* Phase II randomised study of cisplatin plus etoposide phosphate or etoposide in the treatment of small-cell lung cancer. *J Clin Oncol* 1995, **13**, 1436–1442.
64. Kaul S, Igwemezie LM, Stewart DJ, *et al.* Pharmacokinetics and bioequivalence of etoposide following intravenous administration of etoposide phosphate and etoposide in patients with solid tumours. *J Clin Oncol* 1995, **13**, 2835–2841.
65. Millward MJ, Newell DR, Mummaneni V, *et al.* Phase I and pharmacokinetic study of a water soluble etoposide prodrug, etoposide phosphate (BMY-40481). *Eur J Cancer* 1995, **31A**, 2409–2411.

Acknowledgements—The authors would like to thank the North of England Children's Cancer Research Fund and the North of England Cancer Research Campaign for financial support. The authors would like to acknowledge also Professor Andrew D.J. Pearson for his advice, support and encouragement.