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Short Communication

Phase I and Pharmacokinetic Study of a Water-soluble Etoposide Prodrug, Etoposide Phosphate (BMY-40481)

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Etoposide phosphate is a water-soluble prodrug of etoposide. A phase I and pharmacokinetic study has been performed over the dose range 25–110 mg/m²/day for 5 days (etoposide equivalent doses). The maximum tolerated dose (MTD) was 110 mg/m²/day for 5 days every 3 weeks and the dose-limiting toxicity was neutropenia. Other toxicities were mild, with the exception of 2 patients who displayed significant hypersensitivity reactions. The etoposide phosphate:etoposide area under the plasma concentration versus time curve (AUC) ratio was <1% and the pharmacokinetic parameters for etoposide were within previously reported ranges. Pharmacodynamic analyses demonstrated that etoposide AUC and baseline white blood cell count were significant determinants of leucopenia (model $r^2 = 0.51$).

Key words: etoposide, etoposide phosphate, pharmacokinetics, phase I trial
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INTRODUCTION

ETOPOSIDE PHOSPHATE (BMY-40481) is an analogue of etoposide, with a phosphate group in the 4' position of the E ring, that is readily soluble in water [1]. It has no intrinsic cytotoxic activity *in vitro*, but addition of alkaline phosphatase restores its potency to that of etoposide. Evaluation of etoposide phosphate and etoposide *in vivo* in murine and human tumour xenograft models showed equivalent antitumour activity [2]. Etoposide phosphate is hydrolysed to etoposide when incubated in plasma obtained from mice, rats, dogs, monkeys and human donors. Following intravenous or intraperitoneal administration to mice, etoposide phosphate is largely converted to etoposide within 15 min. These preclinical data suggest that etoposide phosphate has potential as a water soluble prodrug for etoposide.

PATIENTS AND METHODS

Eligibility criteria for entry on to this study were histologically documented advanced solid tumour resistant to standard chemotherapy, age 18–75 years, performance status (WHO) 0–2, a life expectancy of 3 months, normal haematological status, hepatic and renal function. Written informed consent was obtained and the protocol approved by the institutional Ethics Committee. This study was performed under the auspices of the Cancer Research Campaign Phase I/II Clinical Trials Committee. Response to treatment, and toxicities encountered, were graded by the criteria of the World Health Organisation [3].

Doses of etoposide phosphate in this study were expressed as etoposide equivalent doses (i.e. a dose of 100 mg/m² equals 113.6 mg/m² etoposide phosphate). The starting dose was 25 mg/m²/day for 5 days every 3 weeks, and at 25, 50, and 75 mg/m²/day etoposide phosphate was dissolved in 250 ml normal saline solution and infused intravenously over 30 min. Patients entering the study at 90 and 110 mg/m²/day received the drug in 500 ml normal saline solution given over 60 min.

Pharmacokinetic and pharmacodynamic analyses were performed as previously described [4, 5]. For etoposide analyses [6], the plasma and urine assays were linear (0.2–20 μg/ml) for all analytical runs with coefficients of determination (r^2) of ≥0.99 with intra- and interassay coefficients of variation (CVs) for

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Table 1. Haematological toxicity following etoposide phosphate

	Dose (mg/m²/day)	Courses	WHO grade (% of courses) 0	1	2	3	4
Total white cells	25	3	67	33	0	0	0
	50	23	39	43	18	0	0
	75	22	50	23	14	14	0
	90	22	9	36	50	5	0
	110	12	25	8	50	8	8
Granulocytes	25	3	67	33	0	0	0
	50	23	57	39	0	4	0
	75	22	45	23	18	9	5
	90	22	9	27	23	41	0
	110	12	25	8	25	25	17
Platelets	25	3	100	0	0	0	0
	50	23	96	0	0	0	4
	75	22	95	5	0	0	0
	90	22	100	0	0	0	0
	110	12	100	0	0	0	0
Haemoglobin	25	3	67	33	0	0	0
	50	23	48	30	22	0	0
	75	22	9	36	41	14	0
	90	22	41	27	27	5	0
	110	12	25	33	42	0	0

quality assurance samples at 5 μg/ml of <10%. For etoposide phosphate analyses [4, 5], corresponding data were $r^2 \geq 0.99$ for 0.02–2.0 μg/ml and CVs <11% at 0.5 μg/ml, respectively.

RESULTS

31 patients (15 males, 16 females; median age 52 (26–73) years; 7 with ovarian cancer performance status 0,1 patient; 1,13 patients; 2,17 patients; prior chemotherapy, 19 patients) received 85 courses. 2 patients were withdrawn because of hypersensitivity reactions during the first dose of etoposide phosphate. Following 50 mg/m², one patient developed facial flushing and parasthesiae of the lips and eyelids after 10 min of the infusion. Symptoms resolved with discontinuation of the infusion and intravenous hydrocortisone. At 90 mg/m², 1 patient developed nausea and retching 5–10 min after the start of the infusion which was followed by transient loss of consciousness with central cyanosis and twitching of the limbs. The infusion was discontinued and the patient recovered over 10–20 min. This patient had previously and subsequently received etoposide at the same dose and rate of infusion, without apparent hypersensitivity. One confirmed partial response was observed in a patient with recurrent ovarian carcinoma after platinum chemotherapy who had a partial response of a retroperitoneal pelvic mass.

Haematological toxicity was dose-limiting and is summarised in Table 1. Nausea/vomiting WHO grade III was recorded following etoposide phosphate in 2/7 patients at 75 mg/m²/day, 2/8 patients at 90 mg/m²/day, and 5/7 patients at 110 mg/m²/day. Minor (WHO grade I) diarrhoea was recorded in 2 patients following etoposide phosphate (75 and 90 mg/m²/day) and stomatitis in 1 patient (90 mg/m²/day). Localised phlebitis at the site of venous access was noted in 9 patients following etoposide phosphate, but was not severe or apparently dose-related. Miscellaneously recorded, and possibly treatment-related, toxicities (all <WHO grade III) were malaise (6 patients), altered taste (3 patients), radiation recall reaction (skin erythema:1 patient) and elevated alkaline phosphatase and aspartate transaminase (2 patients, both WHO grade I). Alopecia was recorded at all dose levels ≥ 50 mg/m²/day, but could not be quantified because of the varying prior chemotherapy received.

Pharmacokinetic parameters are defined in Table 2. The etoposide phosphate maximum concentration (CMAX) and the area under the plasma concentration versus time curve (AUC) (0–T), where T varied from 10–70 min post initiation of infusion, were less than 1 μg/ml and 1 μg/ml.h, respectively. There was no clear dose dependency for AUC (0–T) and in all patients etoposide phosphate was undetectable (<0.02 μg/ml) within 70 min of the end of the infusion. The pharmacokinetic parameters for etoposide following the intravenous infusion of etoposide phosphate on day 1 are summarised in Table 2. The mean values for the ratio of the CMAXs of etoposide phosphate:etoposide, corrected for the molecular weight difference, ranged from 0.014 to 0.1. The mean values for the ratio AUC (0–T) of etoposide phosphate to AUC(INF) of etoposide, corrected for the molecular weight difference, ranged from 0.001

Table 2. Pharmacokinetic parameters (mean ± S.D.) for etoposide after the i.v. administration of etoposide phosphate on day 1

Dose (mg/m²)	CMAX (μg/ml)	TMAX* (h)	AUC(INF) (μg/ml h)	MRT(INF) (h)	T-HALF (h)	CLT/F (ml/min/m²)	VSS/F (l/m²)	CLR (ml/min/m²)	UR (%)
25 (n = 1)	3.7	0.75	17.6	5.1	3.6	23.9	7.3	7.1	30
50 (n = 4)	9.5 ± 2.3	0.77 (0.52, 0.92)	41.8 ± 13.1	6.0 ± 1.7	5.3 ± 1.8	21.9 ± 8.8	7.4 ± 1.5	10.4 ± 10.8	40 ± 25
75 (n = 5)	16.9 ± 1.2	0.55 (0.50, 0.77)	66.7 ± 18.9	6.4 ± 1.1	5.7 ± 1.5	19.8 ± 4.8	7.4 ± 1.2	5.7 ± 2.2	27 ± 6
90 (n = 6)	18.3 ± 2.0	1.03 (0.90, 1.17)	86.7 ± 12.8	6.4 ± 0.8	6.0 ± 0.5	17.5 ± 2.5	6.7 ± 0.9	6.7 ± 1.6	37 ± 9
110 (n = 3)	17.8 ± 0.9	1.08 1(1.07, 1.17)	72.8 ± 19.4	6.5 ± 2.2	7.0 ± 1.8	26.3 ± 6.1	9.8 ± 0.7	15.2 ± 10.4	53 ± 31

CMAX, maximum concentration; TMAX, time of maximum concentration; AUC(INF), area under the plasma concentration versus time curve from 0 to infinity; MRT(INF), mean residence time;T-HALF, half life; CLT/F, apparent systemic clearance; VSS/F, apparent steady state volume of distribution; CLR, renal clearance; UR, cumulative amount excreted within the 24 h collection period as a percentage of administered dose, for further details see [4] and [5]. n, number of patients studied on each day at each dose level.

*Median (minimum, maximum) values reported. Note: the infusion time was increased from 30 to 60 min at 90 mg/m² and above.

to 0.007. Thus, in every case, the etoposide phosphate AUC (0–T) was less than 1% of the etoposide AUC(INF). Regression analysis of etoposide AUC(INF) against dose of etoposide phosphate indicated a proportional relationship.

Stepwise linear regression analysis of the relationship between leucocyte nadir, patient factors and etoposide pharmacokinetics, was performed. Examination of Akaike's information criteria and root mean square error values, as well as plots of predicted versus observed nadir values, indicated that linear regression analysis was the best model for predicting leucocyte nadir (model $r^2 = 0.51$) when compared with published non-linear models [7].

DISCUSSION

Following the intravenous infusion of etoposide phosphate, there is rapid disappearance of etoposide phosphate from the systemic circulation and quantitative appearance of etoposide. The principle toxicity seen was myelosuppression and, as expected after etoposide, leucopenia and granulocytopenia were more pronounced than thrombocytopenia. The occurrence of hypersensitivity reactions following etoposide phosphate indicates that the diluents used for the intravenous formulation of etoposide may not be the sole cause of the toxicities ascribed to i.v. etoposide therapy [8–13]. It is possible that etoposide itself may be responsible for some reactions, although cross-sensitivity to etoposide and etoposide phosphate was not apparent in our patients.

The dose-limiting toxicity of etoposide is myelosuppression and many studies have attempted to identify pharmacokinetic and other patient factors that could explain interpatient variability in the haematological toxicity of etoposide. Although other investigators have demonstrated that a non-linear model was superior in predicting the leucocyte nadir [7], results from this study indicated that the stepwise linear regression model was the best model for predicing the leucocyte nadir and the optimal linear model explained 51% of the observed variability, and included AUC(INF) and pretreatment leucocyte count.

1. Doyle TW, Vyas DM. Second generation analogs of etoposide and mitomycin C. *Cancer Treat Rev* 1990, **17**, 127–131.
2. Rose WC, Basler GA, Trail PA, Saulnier M, Crosswell AR, Casazza AM. Preclinical antitumor activity of a soluble etoposide analog, BMY-40481-30. *Invest New Drugs* 1990, **8** (suppl. 1), 25–32.
3. World Health Organisation. *Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO, Offset Publication 48.
4. Budman DR, Igwemezie LN, 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, 5 in patients with solid tumors. *J Clin Oncol* 1993, **12**, 1902–1909.
5. Fields SZ, Igwemezie LN, Kaul S, *et al.* Phase I study of etoposide phosphate (etopophos) as a 30-minute infusion on days 1, 3 and 5. *Clin Cancer Res* 1995, **1**,105–111.
6. Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH. Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. *Cancer Chemother Pharmacol* 1989, **23**, 367–372.
7. Mick R, Ratain MJ. Modelling interpatient pharmacodynamic variability of etoposide. *J Natl Cancer Inst* 1991, **83**, 1560–1564.
8. O'Dwyer PJ, Weiss RB. Hypersensitivity reactions induced by etoposide. *Cancer Treat Rep* 1984, **68**, 959–961.
9. Ogle KM, Kennedy BJ. Hypersensitivity reactions to etoposide: a case report and review of the literature. *Am J Clin Oncol* 1988, **11**, 663–665.
10. Tester WJ, Cohn JB, Fleekop PD, Rabinowitz MS, Lieberman JS. Successful rechallenge to etoposide after an acute vasomotor response. *J Clin Oncol* 1990, **8**, 1600–1601.
11. Eschalier A, Lavarenne J, Burtin C, Renoux M, Chapuy E, Rodriguez M. Study of histamine release induced by acute administration of antitumor agents in dogs. *Cancer Chemother Pharmacol* 1988, **21**, 246–250.
12. Hudson MM, Weinstein HW, Donaldson SS, *et al.* Acute hypersensitivity reactions to etoposide in a VEPA regimen for Hodgkin's disease. *J Clin Oncol* 1993, **11**, 1080–1084.
13. Wolff SN, Fer MF, McKay CM, Hande KR, Hainsworth JD, Greco FA. High-dose VP-16-213 and autologous bone marrow transplantation for refractory malignancies: a Phase I study. *J Clin Oncol* 1983, **1**, 701–705.

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