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Original Paper

Phase II Study of 21 Day Schedule Oral Etoposide in Children

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We report a multicentre phase II study of orally administered prolonged schedule etoposide in children with refractory or relapsed malignancy. 83 children were entered into the study. The largest diagnostic groups were neuroblastoma ($n=20$), rhabdomyosarcoma/soft tissue sarcoma ($n=16$) and brain tumours ($n=16$). Etoposide was administered twice daily at a dose of 50 mg/m^2/day for 21 days using the intravenous preparation given orally. Disease reassessment was performed after the second course. Etoposide plasma concentrations were measured by HPLC, 2 and 6 h after administration of therapy on days 7 and 14 in 15 patients. 61 patients completed two courses and were evaluable for response. There was 1 complete response (CR), 5 partial responses (PR) 22 stable disease (SD) and 33 progressive disease (PD). Of the 6 with responses, 3 had a diagnosis of medulloblastoma/cerebral primitive neuroectodermal tumour. 24 of 26 patients with SD/PR/CR received further courses with excellent palliative effect. The main toxicity observed was myelosuppression, with 8% and 7% of evaluable courses complicated by grade III–IV neutropenia and thrombocytopenia, respectively. Severe infection (grade III–IV) was rare, complicating only 2/94 evaluable courses. Plasma etoposide median concentrations at 2 h after administration on day 7 of course 1 were 1.5 (range 0.6–2.4) μg/ml. Total course 1 area under the etoposide plasma concentration versus time curve (AUC) values were estimated using a limited sampling model. Grade ≥ 2 leucopenia was only observed in patients with a day 7 2 h etoposide concentration of > 2 μg/ml or a course 1 AUC of > 35 mg/ml.min. It is concluded that given at a dose of 50 mg/m^2/day in two doses for 21 day courses, oral etoposide is well tolerated in children. A correlation between drug concentrations and toxicity was observed. Overall, a low response rate was seen (~10%), but disease stabilisation appears to occur, and useful palliative effect was frequently noted. The response in brain tumours was more encouraging (3/14 PR) and this group requires further evaluation. © 1997 Elsevier Science Ltd.

Key words: paediatric cancer, etoposide schedule, phase II, neuroblastoma, rhabdomyosarcoma, brain tumour

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INTRODUCTION

ALTHOUGH IN widespread clinical use in paediatric oncology, the optimum schedule for etoposide administration remains unclear. A variety of schedules are currently used, with doses ranging from 100 to 200 mg/m^2 intravenously daily for 1–5 days up to very high-dose therapy, around 3 g/m^2 with stem cell rescue. Some, but not all, preclinical studies have demonstrated that etoposide shows both dose and schedule dependency [1–5] and the schedule has been shown to be

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of importance in clinical practice [6,7]. One alternative is the use of prolonged oral administration at comparatively low doses [7–9]. This schedule can achieve prolonged drug serum levels which may be effective and well tolerated [10].

A paediatric pilot study in 22 patients with relapsed or refractory disease demonstrated the practicality of administering the intravenous preparation to children using an appropriate masking agent, and in heavily pretreated patients a dose of 50 mg/m^2/day for 21 days was associated with acceptable myelosuppression [11]. A subsequent phase I study in children with refractory solid tumours confirmed the feasibility of this schedule and concluded that a daily dose of 75 mg/m^2 produced dose-limiting diarrhoea [12].

For the present study, which included patients relapsing following bone marrow transplant and those with relapsed refractory leukaemia, a more conservative dose of 50 mg/m^2/day in two divided doses was chosen. The objectives of the study were to define the activity of prolonged oral etoposide in relapsed paediatric cancers and, in a subset of children, to investigate the pharmacokinetics and pharmacodynamics of oral etoposide.

PATIENTS AND METHODS

Eighty-three patients with relapsed or refractory disease were entered in this phase II trial. Patients were registered with the UKCCSG data centre as soon as possible after relapse. The study opened in March 1992 and closed to entry in October 1995. This study was approved by the individual participating hospitals' study review board and ethics committee and informed consent was obtained from patients, parents or legal guardians. 16 UKCCSG centres participated in this study.

Details of initial diagnosis and treatment are given in Table 1. In the brain tumour group there were 7 primitive neuroectodermal tumour (PNET)/medulloblastomas, 4 ependymomas, 3 brain stem gliomas, 1 astrocytoma and 1 pineoblastoma. Patients with relapsed disease had achieved an initial CR. Resistant disease describes those in whom first- or second-line therapy failed to achieve CR. There was no lower age limit and no tumour type was excluded. Entry of patients who had failed prior treatment with etoposide was encouraged in an attempt to demonstrate the activity of prolonged oral etoposide in disease refractory to conventional schedules.

Treatment

Oral etoposide was administered every 12 h for 21 days at a dose of 50 mg/m^2/day. The drug was administered in the form of commercially available parenteral preparation, dispensed in individual dose glass vials, which were subsequently mixed with an appropriate masking solution, such as juice or flavoured syrup. The family were dispensed a seven day supply of the solution.

Disease assessment

The method of assessment depended on the tumour type and site of disease. Measurable tumour was estimated in two maximum dimensions; bilateral bone marrow trephines and aspirates, and urinary catecholamines were performed in children with metastatic neuroblastoma. A unilateral aspirate was examined in cases of leukaemia. Patients were formally reassessed after two 21 day courses with a 7 day interval between courses. Complete response was defined as no evidence of residual disease, partial response as greater than a 50% reduction in measurable disease, stable disease as less than 50% reduction in measurable disease and progressive disease as a greater than 25% increase at disease site or sites. Neuroblastoma was staged according to the International Neuroblastoma Staging System recommendations [13] which includes mixed response (MR) defined as no new lesions with a greater than 50% reduction in any other disease and less than 25% increase in any existing lesion. In leukaemia, a bone marrow response was either a CR defined as less than 5% blasts, stable disease defined as no change in blast percentage or a decrease in blasts but not to 5%, or progressive disease defined as any increase in blast percentage.

A central review of relevant imaging studies was undertaken for patients classified as achieving partial or complete response.

Toxicity assessment

All data were collected prospectively. Full blood counts were performed weekly or more often as indicated clinically. Liver function tests and standard biochemistry were documented at the end of each course. Oral mucositis, diarrhoea, hair loss and infection were also recorded. Toxicity was gra-

Table 1. Patient details and diagnosis

Diagnostic group	No. of patients	Relapsed disease	Resistant disease	Prior etoposide	
				Yes	No
Neuroblastoma	20	14	6	20	0
Rhabdomyosarcoma and soft tissue sarcoma	16	11	5	11	5
Acute Lymphoblastic Leukaemia—ALL	4	2	2	4	0
Acute Myeloid Leukaemia—AML	6	5	1	6	0
Ewing's sarcoma	8	4	4	3	5
Brain tumours	16	16	0	9	7
Spindle cell carcinoma of thyroid	1	1	0	0	1
Squamous cell carcinoma	1	1	0	0	1
Teratoma	1	1	0	1	0
Retinoblastoma	1	1	0	1	0
Osteosarcoma	3	2	1	1	2
Hepatoblastoma	1	1	0	1	0
Hodgkin's lymphoma	1	0	1	1	0
NHL	2	2	0	2	0
Wilms' tumour	2	1	1	1	1
Total	83	62	21	61	22

Table 2. Details of patients undergoing pharmacokinetic studies

Patient	Age	Disease	Response (after 2 cycles of etoposide)	Initial liver function	
				Alkaline phosphatase	Albumin
1	15	Resistant liposarcoma	PD	193	37
2	12	Resistant neuroblastoma	SD	154	46
3	6	Relapsed brain stem glioma	SD	305	45
4	7	Relapsed medulloblastoma	PR	N/A	N/A
5	9	Resistant rhabdomyosarcoma	PD	N/A	35
6	4	Relapsed medulloblastoma	SD	423	67
7	7	Relapsed rhabdomyosarcoma	SD	80	44
8	12	Resistant rhabdomyosarcoma	PD	82	31
9	9	Resistant neuroblastoma	PD	N/A	N/A
10	14	Relapsed osteosarcoma	PD	N/A	N/A
11	12	Relapsed brain stem glioma	PD	177	50
12	14	Relapsed pineoblastoma	SD	195	53
13	7	Relapsed ependymoma	SD	110	39
14	7	Resistant neuroblastoma	SD	146	38
15	1.5	Relapsed PNET	PR	N/A	46

PD, progressive disease; SD, stable disease; PR, partial response; N/A, not applicable.

ded according to the World Health Organisation (WHO) grading system.

Pharmacokinetic studies

The pharmacokinetics of etoposide were studied in 15 patients (Table 2)—course 1: day 7 (n=15), day 14 (n=10); course 2: day 7 (n=10), day 14 (n=7). Blood samples were collected 2 and 6 h after drug administration and etoposide concentrations measured by a validated HPLC assay [5]. In addition to the etoposide concentration, the area under the etoposide concentration versus time curve (AUC) was calculated using the equation:

$$AUC_{0-12\,h}(\text{mg/ml min}) = (0.195 \times C_2) + (0.499 \times C_6) - 0.063$$

Where the $AUC_{0-12\,h}$ is the 0–12 h AUC, i.e. the AUC prior to the next dose, and C_2 and C_6 are the etoposide concentrations (μg/ml) at 2 and 6 h, respectively [14]. The etoposide AUC for the course of therapy was calculated by multiplying the day 7 single-dose AUC value (or the mean of the day 7 and day 14 values if both were available) by 42, i.e. the total number of doses.

Results

Sixty-five patients completed two courses of treatment and were evaluable for toxicity. 61 patients were evaluable for response, as 4 patients did not complete adequate restaging assessment. In 18 cases disease progression occurred following or during the first course and these patients were not evaluable for subsequent toxicity assessment, and were counted as non-responders.

Response

Details of responses are shown in Table 3. In total, 1 patient achieved a CR (AML) and 5 a PR (3 PNET/medulloblastoma, 1 Ewing's, 1 neuroblastoma) (10%, 95% CI 4–20%). Details of the initial disease assessment and reassessment in these 6 patients are shown in Table 4. The patient achieving a complete response had AML (M_4). Following three courses of chemotherapy, including etoposide, on the AML X trial, a bone marrow aspirate revealed refractory disease with 9% myeloblasts. In addition, the patient had persistent splenomegaly. Two courses of cytosine/asparaginase were then given, following which a bone marrow aspirate showed persistent disease, still with 9% blasts and characteristic eosinophils. The patient was then entered in to the current trial.

Twenty-two patients had stable disease, whilst 33 had progressive disease. Prior etoposide therapy in conventional regimens did not appear to influence response.

Twenty-one of 61 (36%) patients who had received prior etoposide achieved either CR/PR or SD, compared with 6/22 (27%) who had not received prior etoposide therapy. 5 of the 6 patients who achieved CR/PR had received prior etoposide.

Toxicity

Details of toxicities are shown in Table 5. The major toxicity seen was myelosuppression. Neutropenia appeared to be more

Table 3. Response after two courses according to disease

Disease type (No. of evaluable patients)	Complete response	Partial response	Stable disease	Progressive disease
Neuroblastoma (n=15)	0	1	6	8
Rhabdomyosarcoma/Soft tissue sarcoma (n=11)	0	0	3	8
Brain tumours (n=14)	0	3	6	5
Ewing's sarcoma (n=6)	0	1	2	3
AML (n=5)	1	0	1	3
ALL (n=2)	0	0	0	2
Other (n=8)	0	0	4	4
Total	1	5	22	33

marked than thrombocytopenia, with 44% of courses complicated by at least grade I neutropenia, although only 8% of courses were complicated by grades III–IV. Serious infection was uncommon. Nausea or vomiting affected 21% of courses, although a disproportionate number of the brain tumour patients suffered nausea and vomiting which may have been associated with their disease. Alopecia was not inevitable and after two courses 61% of patients had not suffered any hair loss.

Subsequent outcome

Information was available on the subsequent outcome of 26 of the 28 patients documented as having either a response

Table 4. Assessment and reassessment details of responding patients (CR or PR)

Patient	Diagnosis	Method of assessment	Initial disease assessment	Reassessment	Response
1	Medulloblastoma	MRI brain and spine	Large areas of tumour in frontal horns with scattered deposits in temporal and occipital horns. Invasion of disease around shunt insertion site. Lesion in hypothalamus which had seeded into 3rd ventricle	Dramatic response of the tumour seeding previously present in the frontal horns and lateral ventricle, with faint enhancement in right lateral ventricle. Moderate sized subdural collections with faint areas of enhancement.	PR
2	Ewing's sarcoma with lung metastases	Chest X-ray	Left large anterior mediastinal mass and at least one pulmonary metastasis	Left upper zone opacification almost completely resolved and left mid-zone metastases difficult to identify	PR
3	Neuroblastoma. Abdominal primary with bone and bone marrow metastases	Meta-iodobenzylguanidine, bone marrow aspirates and trephine	4/4 marrow specimens positive Meta-iodobenzylguanidine uptake	1/4 marrow specimens positive Meta-iodobenzylguanidine uptake largely unchanged	PR
4	Medulloblastoma	MRI scan	Posterior fossa tumour extending to cerebellopostine angle and 3rd ventricle. Tumour volume 32 cm^3	Reduction in size to 14.2 cm^3	PR
5	PNET brain	CT scan	Large enhancing right frontal mass lesion extending into ethmoid sinus	Dramatic response with almost complete resolution of intracranial component of frontal tumour. Mass lesion in the nasal space also smaller	PR
6	AML	Bone marrow aspirate	9% blasts	<5% blasts	CR

MRI, magnetic resonance imaging; CT, computed tomography; PNET, primitive neuroectodermal tumour; AML, acute myeloid leukaemia.

Table 5. Toxicity

	No. of evaluable courses	Grade 0	Grade I	Grade II	Grade III	Grade IV
Neutropenia	88	49 (55.6%)*	21 (23.8%)	11 (12.5%)	5 (5.6%)	2 (2.3%)
Thrombocytopenia	89	78 (87.6%)	3 (3.3%)	2 (2.2%)	4 (4.5%)	2 (2.2%)
Infection	92	79 (85.6%)	7 (7.6%)	4 (4.3%)	1 (1.1%)	1 (1.1%)
Nausea and vomiting	97	77 (79.3%)	6 (6.1%)	11 (11.3%)	3 (3.1%)	0
Mucositis	99	92 (92.9%)	2 (2.02%)	4 (4.04%)	0	1 (1.01%)
Diarrhoea	108	105 (97%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0
Alopecia (course 2 only)	36	22 (61%)	3 (8%)	7 (19%)	4 (11%)	0
Renal function	69	69 (100%)	0	0	0	0
Liver function	34	30 (88%)	4 (11.7%)	0	0	0

*% of courses complicated by toxicities (WHO grade).

or stable disease. 2 patients received only two complete courses—1 patient died suddenly two weeks after the second course without clinical evidence of disease progression, and 1 did not receive further courses because of myelosuppression. 24 of the 26 patients went on to receive between 3 and 18 courses with a median of 5. 19 of these 24 have since developed progressive disease and died. 5 patients are still alive, 5 on treatment and 1-off treatment. This last patient had a relapsed ependymoma and underwent further neurosurgery after three courses of oral etoposide with which her disease remained stable. 2 further patients also underwent attempts at curative therapy after receiving oral etoposide with radical radiotherapy and intrathecal monoclonal antibody therapy, but have since developed progressive disease.

Pharmacokinetics

Median (range) plasma etoposide concentrations at 2 h on day 7 of course 1 were 1.5 (0.6–2.4) μg/ml. 2 h median concentrations on day 14 of course 1 (1.1 (0.8–2.8) μg/ml) and days 7 (1.2 (0.8–2.4) μg/ml) and 14 (1.7 (0.7–2.6) μg/ml) of course 2 were similar. The predicted total AUC for course 1 was 23 (19–49) mg/ml min which was produced by a total dose of 1050 mg/m^2. In 9 patients who were studied on three or four occasions, the intrapatient coefficient of variation (CV) for the 2 h plasma etoposide concentration and the predicted AUC were 12% (0–48%) and 8% (3–60%), respectively. For comparison, the CVs for the interpatient variation in the 2 h plasma etoposide concentration (1.6±0.5 μg/ml) and predicted AUC (0.7±0.2 mg/ml min) on day 7 of course 1 were both 33%. Thus, overall, the median intrapatient variability in etoposide pharmacokinetics was approximately one-third of the interpatient variation.

The relationship between etoposide pharmacokinetics and haematological toxicity during and after the first course of therapy was examined in the 15 patients studied. Of note was the observation that the only 3 patients with ≥ grade 2 leucopenia were those 3 patients with 2 h plasma etoposide concentrations >2 μg/ml or a predicted AUC for the whole course of >35 mg/ml min (Figure 1).

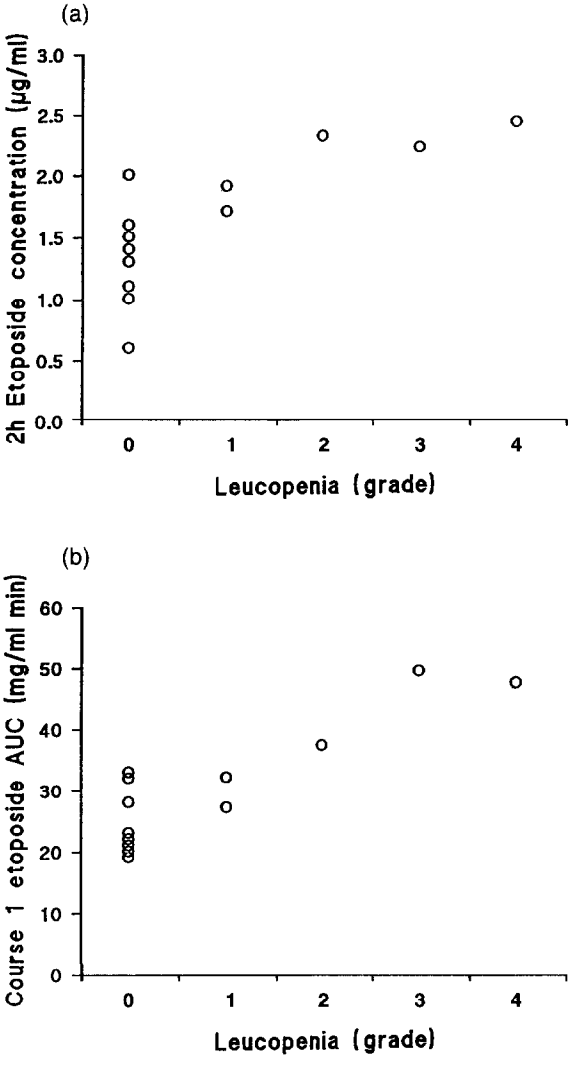

Figure 1. Degree of leucopenia in relation to etoposide concentration and AUC.

DISCUSSION

The dose of etoposide used in this study was selected on the basis of adult phase I trials [15] and a small paediatric pilot study [11]. It has been suggested that a slightly higher dose will be tolerated by children without unacceptable myelotoxicity using a three times a day schedule which avoids high peak plasma levels of etoposide [12]. This is consistent with relatively minor myelosuppression in patients receiving low-dose etoposide by 24 h continuous infusion [16].

A number of adult solid tumours have been treated with 21-day etoposide, and response rates range from 4 to 60% [17–21]. In paediatric studies it is impractical to use the 50 or 100 mg capsules, partly because of their large size and unpalatability but also because of problems with dose modification in relation to surface area. Despite its unpleasant taste in unmasked form, the liquid preparation proved remarkably palatable and in the present study was well tolerated by the majority of children. Only one child refused to take the treatment.

It must be concluded that response rates were disappointing and this schedule appears to be less active than a recently reported 3×3 intravenous schedule (100 mg/m^2 three times a week for three consecutive weeks) in which a 42% response rate was observed in children with relapsed or refractory soft tissue sarcomas [22]. Better activity has also been described using an oral 3×3 schedule (200 mg/m^2) in relapsed neuroblastoma [23]. It is of note that a recent study in neuroblastoma cell lines failed to show any advantage of an AUC achieved by prolonged continuous low-dose exposure compared to a shorter administration period [24]. The encouraging response rate quoted by Mathew and associates [12] included patients with stable disease, and if these were excluded, overall response rates are comparable to those seen in our study.

Of the individual diagnostic groups, the only noteworthy response rates were observed in the patients with brain tumours (3/14). The 3 patients with a partial response having medulloblastoma/PNET all had previously received conventional schedule etoposide. Similar response rates with oral etoposide in recurrent medulloblastoma/PNET have been reported [25]. Encouraging responses have also been documented in patients with recurrent chiasmatic/hypothalamic gliomas after two 21 day courses of oral etoposide at 50 mg/m^2 [26]. There are few studies which have evaluated single-agent etoposide in central nervous system (CNS) tumours. Single courses of high-dose (600–1000 mg/m^2) etoposide produced 1 PR and 4 SD in 24 patients [27]. Standard dose etoposide (50–100 mg/m^2×5 days) produced 3 PR and 6 SD in 22 patients [28]. Both these studies involved a range of tumour

types and no conclusion can be drawn about any schedule effect when the present study data are included. Cytotoxic levels of etoposide have recently been documented in the cerebrospinal fluid of children with leukaemia receiving 25–50 mg/m^2 orally [29].

Although the study was not designed to evaluate symptomatic benefit, a palliative effect of 21 day oral etoposide was noted by investigators in many of the cases with advanced chemorefractory disease. The simple outpatient nature of the therapy and the comparative lack of toxicity makes this regimen an attractive option for children where no curative therapy is available. Dramatic symptom relief enabling a reduction or even withdrawal of opiate analgesia was not uncommon.

The use of this schedule outside the palliative situation cannot be discussed without consideration of the possible carcinogenic effects. Secondary AML related to etoposide seems to be schedule dependent and in childhood ALL is almost exclusively limited to those receiving a regimen where repeated doses are given [30]. Although the relationship to pharmacokinetic parameters is unknown, it seems possible that this prolonged low-dose schedule might be similarly implicated and in the current study one case of secondary AML was reported. This patient was diagnosed with a supratentorial PNET in 1987 and received cisplatin-based therapy. Following a relapse in 1991, he received further chemotherapy including 12 courses of etoposide given 3 weekly at a dose of 100 mg/m^2 daily×3. Following an initial response, he relapsed again and was entered into the current study. He received two courses as per protocol but had progressive disease. He then received thiotepa, during the course of which treatment he developed AML.

The pharmacokinetic studies performed demonstrated a relationship between etoposide levels and myelotoxicity, but because of the small number of responses it was not possible to consider the relationship between drug levels and activity. Variability in absorption has been described in adults [31, 32], but newer forms of etoposide, such as etoposide phosphate, may produce more reproducible bioavailability [33]. If oral etoposide is used, the limited sampling schedules (2 and 6 h can be employed on day 7 to identify patients at risk of $\geq$ grade 2 leucopenia. Re-evaluation of etoposide concentrations on day 14 could establish whether or not any dose reduction results in safer levels (2 h concentration 1.25–1.75 μg/ml, AUC 0.5–0.8 mg/ml min per dose). By using such therapeutic drug monitoring, untoward morbidity can be avoided, an important consideration in the setting of palliative therapy.

In conclusion, oral etoposide at 50 mg/m^2 day for 21 days was well tolerated but, with the exception of brain tumours, overall response rates in children with a wide range of relapsed or resistant cancers were disappointing. The evidence to date suggests that this schedule can have a valuable role in palliative care and further investigation seems justified in children with poor-risk brain tumours.

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