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Clinical and pharmacokinetic study of fractionated doses of oral etoposide in pediatric patients with advanced malignancies

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Lauro J. Gregianin[1] [redacted], Algemir L. Brunetto[1] [redacted], Luciane Di Leone[2] [redacted], Teresa Dalla Costa[3] [redacted], Pedro P. Santos[4] [redacted], Gilberto Schwartsmann[2,5] [redacted]

[1] Pediatric Oncology Service, Hospital de Clínicas de Porto Alegre, Brazil
[2] South American Office for Anticancer Drug Development (SOAD), Porto Alegre, Brazil
[3] Faculty of Pharmacy, Federal University of Rio Grande do Sul, Brazil
[4] Pediatric Hematology-Oncology Service, Hospital da Crianca Conceicao, Porto Alegre, Brazil
[5] Department of Oncology, Faculty of Medicine, Federal University of Rio Grande do Sul; Comprehensive Cancer Center, The Lutheran University of Brazil, Porto Alegre, Brazil

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Summary

Background: The purpose of this phase I study was to evaluate the toxicity profile, dose-limiting toxicities (DLT), maximum tolerated dose (MTD), and plasma pharmacokinetics of oral etoposide, and to recommend a safe fractionated dose for phase II trials in pediatric patients with refractory solid tumors.

Material/Methods: All patients had tumors no longer amenable to established forms of treatment. The initial dose of etoposide was 20 mg/m^2 TID for 14 days every 21 days (dose-level I). Etoposide plasma pharmacokinetics were studied on day 1 of treatment and determined by HPLC.

Results: Seventeen children were enrolled, 13 of whom were included in the pharmacokinetic study, for a total of 64 courses. Nine patients were included at dose-level I; grade 2–3 leucopenia was observed in 5. The dose was then raised to 25 mg/m^2 (dose-level II) in another 8 patients; grade 3–4 leucopenia was observed in 4. This dose-level was therefore considered the MTD. The DLT was neutropenia. In patients at dose-level I and II the maximum plasma etoposide concentration was 2.97 and 8.59 μg/ml, respectively. Drug levels > 1 μg/ml were maintained for about 6.3 hours following drug administration at both dose-levels. Partial response was observed in 1 patient and 4 patients showed stable disease.

Conclusions: Prolonged oral etoposide was well tolerated by our patients. Considering the MTD, and the fact that the patients included at dose-level I achieved an adequate (>1 μg/ml) plasma concentration of etoposide for a sufficient time, this dose level was recommended for phase II studies in pediatric malignancies.

This work was performed at the Pediatric Oncology Service, Hospital de Clínicas de Porto Alegre; the Pediatric Hematology-Oncology Service, Hospital da Crianca Conceicao; and at the South American Office for Anticancer Drug Development (SOAD), Porto Alegre, Brazil.

key words: oral etoposide • children • phase I study

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Author's address: Dr. Lauro J. Gregianin, Rua Ramiro Barcelos, 2350, 3rd-floor, Porto Alegre, Brazil, email: lgregianin@hcpa.ufrgs.br

BACKGROUND

Etoposide, a semi-synthetic epipodophyllotoxin derivative, is an important component of chemotherapy regimens for the treatment of adult cancers, and in most pediatric cancers as well. It is part of standard chemotherapy for neuroblastoma, leukemia, Ewing's sarcoma, soft tissue tumors, osteosarcoma and Wilms tumor, and in second-line treatment for other pediatric malignancies [1].

The anti-tumor effect of etoposide results from inhibition of the nuclear enzyme topoisomerase-II, producing cleavable complexes that prevent DNA religation and replication. It is a cell-cycle specific agent, active in the G2 phase, and to a lesser extent in the S phase [2].

Various schedules have been used for the intravenous administration of etoposide in studies involving pediatric populations, with doses varying from 50 to 200 mg/m^2 for 3 to 5 days, repeated at 3- to 4-week intervals [1,3]. Plasma concentrations of about 1–5 μg/ml seem to be sufficient to elicit the antitumor effects. However, severe myelosuppression is observed more frequently at etoposide plasma concentrations higher than 5 μg/ml [1,4–6].

There is clear evidence that the antitumor effects of etoposide are dependent upon prolonged exposure of the intracellular target, the nuclear enzyme topoisomerase II, to the activity of the drug. Therefore, repeated drug administration may enhance etoposide's antineoplastic efficacy by producing therapeutic plasma levels for a longer period of time than in the case of a high concentration over a short period of time [4,7]. The pioneer clinical study exploring the schedule dependency of etoposide concluded that oral administration over 3 days was superior to a single intravenous dose in adults with small cell lung cancer (SCLC) [8]. This observation was later supported by Slevin et al, who reported on an important randomized study in patients with SCLC treated with etoposide, either as a single intravenous dose over 24 hours or as 5 daily infusions every 3 weeks, with response rates of 10% and 89% respectively [5]. Pharmacokinetic analysis identified a more prolonged exposure above the plasma level of 1 μg/ml with divided dosing than with a single dose. The most common toxicity was non-cumulative myelosuppresion.

In a comparative study of twice daily versus single daily dose of oral etoposide in SCLC patients, Clark et al. observed more rapid responses in the group with fractionated doses [9]. Other clinical trial conducted by Clark et al. in patients with SCLC observed a more rapid tumor response with prolonged duration of low doses of oral etoposide than with the once-daily schedule [10].

Prolonged oral etoposide therapy as an alternative to intravenous administration has been demonstrated to be feasible and relatively well tolerated in adult and in pediatric patients [11–13]. In a phase I study in children, Davidson observed an important palliative effect in 11 of 15 patients, who reported pain relief after oral etoposide; bone marrow suppression was the major toxicity [14]. Mathew et al. reported on a phase I and pharmacokinetic study in children with oral etoposide administered every 8 hours for 21 days [15]. The maximum tolerated dosage (MTD) was 60 mg/m^2/day; the dose-limiting toxicity was myelosuppression.

The efficacy of low doses of oral etoposide in refractory or relapsed pediatric tumors has been evaluated in patients with neuroblastoma and brainstem tumors with apparent antineoplastic activity [1,12,16–18].

In our institution, the clinical toxicity and plasma pharmacokinetic profile of etoposide when administered orally in fractionated doses was evaluated in a phase I trial conducted in adult patients with advanced solid tumors [19]. In that study, prolonged levels of etoposide could be obtained in plasma within the therapeutic range, without producing the high peak levels of the drug usually associated with severe myelosuppression. In a follow-up study, we demonstrated the occurrence of a high percentage of tumor responses with minimal toxicity in patients with AIDS-related Kaposi's sarcoma, who were treated according to the above-mentioned schedule [13]. Currently, in our institution other phase II trials of fractionated doses of oral etoposide are being conducted in patients with advanced solid tumors, such as ovarian and NSCL cancer.

In the present study, we report on the results of a phase I study of fractionated doses of oral etoposide in children with refractory advanced malignancies. This is the second published phase I trial of t. i. d. oral etoposide in a pediatric population of patients with refractory solid tumors, confirming the safety data reported in the first trial [15]. Furthermore, our regimen was slightly different than in the previous study, as the drug was given for 14 consecutive days, followed by a one-week rest period. Presently, we are initiating a phase II trial of etoposide, through international cooperative study groups, administered at the above-mentioned dose schedule as second-line therapy for patients with metastatic neuroblastoma who are not suitable for inclusion in trials with combination chemotherapy.

MATERIAL AND METHODS

Pediatric patients with refractory solid tumors were entered in the study between August 1998 and July 1999 at the Pediatric Oncology Units of Hospital de Clínicas de Porto Alegre and Hospital da Crianca Conceicao, and at the South-American Office for Anticancer Drug Development (SOAD), Porto Alegre, Brazil. The study was approved by the Institutional Review Board and the respective Ethics Committees, and written informed consent was obtained from all patients or parents.

The study entry criteria included age younger than 18 years, a diagnosis of advanced refractory solid tumor no longer amenable to established forms of treatment, World Health Organization (WHO) performance status

of 0 to 3, no concomitant infection or other active disease, adequate liver, kidney and cardiac function, life expectancy of at least 3 months, no prior cytotoxic therapy within 4 weeks of enrollment, no residual toxicity from previous cytotoxic therapy, no active disease in the CNS, no previous or concurrent malignancy, absence of severe concomitant medical problems or history of allergy to etoposide.

Pretreatment evaluation included a complete medical history and physical examination, a complete biochemical and hematological evaluation, urinalysis, chest X-ray and/or CT scan, and appropriate imaging procedures to obtain a bidimensional evaluation of tumor size. Blood count and biochemistry were repeated weekly throughout the treatment.

Toxicity was evaluated during each cycle of therapy and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [20], while tumor responses were categorized according to WHO criteria [21]. Toxicity was assessed weekly during all courses. Tumor responses were reviewed prior to each treatment course by clinical examination of target lesions and classified using the two largest diameters of the lesions measured by imaging studies every two courses of chemotherapy. A complete response was defined as complete disappearance of all measurable lesions for at least 4 weeks. Partial response is a decrease of at least 50% but less than 100% in the product of the perpendicular diameters of the measurable lesions, and the absence of new lesions for at least 4 weeks. Minor response was a reduction of less than 50% in the product of the perpendicular diameters of the lesions. Stable disease was defined as no progression of measurable disease over a period of at least 4 weeks. Progressive disease was defined as no response and an increase of at least 25% in the product of two perpendicular diameters of the lesions, or the appearance of disease in any new localization after at least two cycles of treatment.

A commercially available etoposide intravenous formulation (100 mg/5 ml, Bristol Myers Squibb Brazil AS, Sao Paulo, Brazil) was given orally to the patients in the study. A pharmacist provided the exact dose of etoposide in a syringe and each patient was instructed to dilute the contents of the syringe in orange juice at home immediately before ingestion. Based on previous reports, a biovailability of about 50% could be anticipated after oral intake [3,22].

All patients were treated as outpatients, except for day 1 of the first course, when they were hospitalized to allow blood sampling for pharmacokinetic evaluation. Parents were instructed to administer etoposide preparation orally every 8 hours for 14 consecutive days, followed by a 1 week treatment-free period. The courses were repeated every 3 weeks unless the patients experienced greater than grade 2 hematological toxicity, in which case treatment was suspended until after complete hematological recovery.

Based on previous studies in adult patients with AIDS-related Kaposi's sarcoma, in which a daily dose of 50 mg/m^2 (25 mg/m^2 twice daily) produced manageable toxicity, the phase I study in adults with refractory solid tumors, and the results of the study by Mathew et al. on a pediatric population, the initial dose used in this study was 20 mg/m^2 (daily dosage of 60 mg/m^2), which was labeled dose level I [15,19,22]. Dose level II was 25 mg/m^2 every 8 hours. At least 5 patients were included in each dosage level before a higher dosage was implemented [23]. Intrapatient dose escalation was not allowed. Treatment was continued indefinitely in patients who presented evidence of tumor response or disease stabilization.

The MTD was defined as the dosage that produced grade 4 hematological toxicity, grade 3 mucositis, diarrhea or skin toxicity, and grade 2 hepatic, renal, pulmonary, cardiac or neurological toxicity in at least half of the patient population treated at the given dose level. The recommended dose for phase II trials had to be a dose level which caused manageable toxicity, and yet could produce adequate plasma levels of etoposide for a prolonged time, as shown by the results of our pharmacokinetic studies.

Etoposide plasma concentrations were measured using a previously described HPLC method with slight modifications [24]. Blood samples (5 ml) were collected immediately before the first dose of etoposide and at four pre-set time-points (1, 3, 5 and 8 hours) after the first dose. Since the peak etoposide plasma concentration is best evaluated within the first 2–3 hours after drug administration, an additional time-point was added at hour 2 for subsequent patients at dose level II.

Considering the limitations of volume that can be collected from pediatric patients, the volume of each sample was restricted to 5 ml. Each sample was immediately centrifuged for 10 minutes at 3,000 rpm and the plasma was divided into 1.5 ml aliquots. Etoposide was extracted with 3 × 2.5 ml of chloroform after the addition of 20 µg teneposide as an internal standard. Following evaporation to dryness, each extract was dissolved in 65 µl HPLC-grade methanol, further diluted with 35 µl distilled water, and 20 µl aliquots were then analyzed for etoposide.

HPLC analyses were carried out using a µBondpak C18 reversed-phase column (3.9 × 150 mm, 10 µm particles; Waters-Millipore Corporation, Milford, MA, USA) connected to an L-6000 solvent delivery system, an L-4000 UV detector and a D-2500 chromato-integrator (Hitachi Ltd, Tokyo, Japan). The analytical column was protected with a µBondpak C18 Guard-Pak Insert (Waters-Millipore Corporation, Milford, MA, USA). The mobile phase consisted of 65% (v/v) methanol in distilled water. The flow rate was 0.7 ml/min. The detection wavelength was 254 nm. The detection limit for etoposide in plasma was 0.1 µg/ml.

Plasma etoposide concentrations (µg/ml) for each time-point were calculated by measuring etoposide HPLC

Table 1. Patients characteristics.

Number of patients	17
Age, years	
• Median	8.5
• Range	3.5–17.1
Male/Female	10/7
WHO performance status	
• 0	8
• 1	5
• 2	4
Tumor types	
• Neuroblastoma	5
• Osteosarcoma	4
• Retinoblastoma	2
• Ewing's Sarcoma	1
• Pleuropulmonary blastoma	1
• PNET	1
• Wilms tumor	1
• Yolk sac tumor	1
• Papillary carcinoma	1
Previous therapy	
• Chemotherapy	
One regimen	7
Two regimens	10
• Surgery	14
• Radiotherapy	10

peak areas, comparing them with a calibration curve and correcting for loss of the internal standard. For each time-point, the plasma etoposide concentrations were averaged, and the means of at least three independent determinations were semi-logarithmically plotted against time using PCNONLIN 4.2 computer software for the analysis of drug pharmacokinetics (SCI Software, ClinTrials Inc, Lexington, KY, USA).

From the plasma concentration versus time curves the half-life ($t_{1/2}$) was estimated and the area under the curve (AUC) was calculated by the trapezoidal method from time 0 (t_0) to the time of the last sample (t_n). The remaining AUC from tn to infinity was estimated by dividing the concentration at tn by the elimination rate constant (k_2). The apparent volume of distribution (Vd) was calculated by dividing the administered drug dose by the product of AUC and k_2. The total body clearance (Cl_t) was calculated by dividing the administered dose by the AUC. Because the bioavailability was not determined in this study, the estimated values of Vd and Cl_t actually represent the ratio between these parameters and the bioavailability (f).

Peak plasma concentrations (C_{max}), the time at which C_{max} was reached (t_{max}), and the time during which the etoposide plasma concentration was >1 μg/ml were determined for each patient. The mean residence time (MRT) was obtained by dividing the AUMC (area under the first moment curve) by the AUC, both of which were obtained by the trapezoidal method. Student's two-tailed t-test was used to evaluate statistically significant differences ($p < 0.05$) between pharmacokinetic parameters determined at each dose level.

RESULTS

Seventeen children and adolescents with a wide variety of solid tumors were qualified for toxicity and response evaluation. The patients' characteristics at the start of treatment are listed in Table 1. This was a heavily pretreated population; all the qualified patients had failed to respond to one or more combination chemotherapy regimens, and 10 had received radiotherapy previously. The total number of courses of etoposide administered during the study was 64 (44 at dose level I and 20 at dose level II), with a median of 2 courses per patient (range 1 to 12). As mentioned earlier in this article, intrapatient dose escalation was not allowed.

The number of courses of oral etoposide per patient ranged from 1 to 12 (median of 2 courses). The first six patients received dose level I (20 mg/m^2) and developed manageable toxicity; the dose was then escalated to dose level II (25 mg/m^2) in the next 8 consecutive patients. Thereafter, dose level I was extended to 3 additional patients, after which this dose level was defined as MTD and recommended for phase II trials.

Concomitant medication was administered to all these patients, and during the day of pharmacokinetic evaluation. Nine patients received analgesics, and 2 patients used laxatives, but no patients received antacids during the period of blood sampling for pharmacokinetic evaluation.

Hematological and non-hematological toxicity in this trial are summarized in Tables 2 and 3, respectively. Grade 1 and 2 hematological toxicities were observed in 7 out of 9 patients at dose level I. Two patients developed grade 3 neutropenia, and 1 patient grade 3 anemia. Grade 4 thrombocytopenia was observed in 1 patient. Non-hematological toxicities were mild. Infection of grades 2 and 3 were documented in 2 patients. Two patients had grade 2–3 nausea/vomiting at dose level I, 3 patients developed grade 2 diarrhea, and 4 patients had anorexia. A transient elevation of transaminases was

Table 2. Hematological toxicity by dose level: worst National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade during entire treatment by patient.

Dose level	Number of patients/ courses	Neutropenia					Anemia					Thrombocytopenia				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
20 mg/m^2	9/44	3	1	3	2	0	3	2	3	1	0	7	1	0	0	1
25 mg/m^2	8/20	2	2	0	1	3	1	1	3	1	2	4	1	0	2	1

Table 3. Non-hematological toxicity by dose level: worst National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade during entire treatment by patient.

Dose level	Number of patients/ courses	Infection					Vomiting					Diarrhea				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
20 mg/m²	9/44	7	0	1	1	0	5	2	1	1	0	4	2	3	0	0
25 mg/m²	8/20	4	1	0	3	0	4	1	2	1	0	7	0	0	1	0
Dose level	**Number of patients/ courses**	**Anorexia**					**Abdominal pain**					**Mucositis**				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
20 mg/m²	9/44	5	2	1	0	1	6	2	0	1	0	7	1	1	0	0
25 mg/m²	8/20	8	0	0	0	0	3	2	1	2	0	7	0	0	1	0

observed in 3 patients (grades 1, 2 or 3) (data not given in Table 3).

At dose level II, neutropenia of grades 1, 3, and 4 was observed in 2, 1, and 3 patients, respectively, and grade 4 anemia in 2 patients. The only other hematological toxicity observed was thrombocytopenia, grade 3 in 2 patients, and grade 4 in 1 patient. Non-hematological toxicity was also observed. Three patients developed grade 3 infections. Grade 2–3 nausea/vomiting was observed in 3 patients. Two patients had grade 3 abdominal pain. Grade 3 mucositis was documented in 1 patient, and grade 3 diarrhea in another. There were no cases of secondary acute myelogenous leukemia in patients included in the study.

Table 4 lists the objective responses observed in patients included in the trial. One partial response was observed in a 6-year-old girl with Wilms tumor with metastatic dissemination to inferior cava vein, extended to the right atrium. She received 6 courses of oral etoposide, after which significant reductions in the intra-vascular and intra-atrial tumor masses were documented by ultrasound. The collateral venous circulation on the chest wall disappeared. This partial response was sustained for 3 months, after which tumor progression was identified.

Stable disease was documented in 4 patients with papillary carcinoma, PNET, neuroblastoma and Ewing's sarcoma, and these responses were sustained for 3, 6, 10 and 20 months, respectively. The first three patients developed progressive disease, but the last patient has survived to this writing with stabilized disease for 20 months after the beginning of therapy. This is a 17-year-old boy with a Ewing's sarcoma affecting the 3rd and 4th cervical vertebra with metastases to the skull. He received 12 courses of oral etoposide as proposed by the protocol, and then the bone metastases were surgically resected. The CT scan showed stable disease at the primary site. He received 6 additional courses of oral etoposide. The symptoms of paresthesia and pain in the left arm disappeared, and he now has normal physical activity.

All patients with a documented response had previously received etoposide in intravenous infusion. All the remaining patients showed disease progression.

Table 4. Clinical responses.

Responses rate (WHO)	No. of patients	%
PR	1	6
SD	4	23
PD	12	7

PR – Partial Response; SD – Stable Disease; PD – Progressive Disease

Table 5. Pharmacokinetics parameters of 6 patients at dose level I.

Patient #	k_2 (h^{-1})	t* (h)	AUC (μg.h/ml)	C_{max} (μg/ml)	t_{max} (h)	AUMC ($\mu g.h^2$/ml)	MRT (h)	Cl_f/f (l/h/m²)	Vd/f (l/m²)	t>1 μg/ml (h)
1	0.16	4.3	13.5	1.98	1.0	45.40	3.7	2.9	18.2	4.7
2	0.311	2.2	12.5	2.66	3.0	59.55	4.7	0.9	3.0	5.9
3	0.16	4.3	26.2	2.97	5.0	180.11	6.8	0.7	4.5	7.6
4	0.107	6.4	13.1	1.82	1.0	128.83	9.7	1.4	13.5	4.8
5	0.135	5.1	22.3	2.74	1.0	183.58	8.2	1.0	7.5	7.6
6	0.13	5.3	26.8	3.4	1.0	238.9	8.9	0.6	4.6	7.6
Mean	**0.167**	**4.6**	**19.0**	**2.59**	**2.0**	**139.39**	**7.0**	**1.25**	**8.5**	**6.3**
SD	**0.073**	**1.4**	**6.7**	**0.59**	**1.6**	**75.93**	**2.4**	**0.85**	**6.0**	**1.4**

k_2 – elimination constant; t* – half-life; AUC – area under the plasma concentration versus time curve; C_{max} – peak plasma concentration; t_{max}, time to maximum peak concentration; AUMC – area under the first moment curve; MRT – mean residence time; Cl/f – total body clearance related to bioavailability; Vd/f – apparent volume of distribution related to bioavailability; t>1 mg/ml – period of etoposide plasma concentrations >1 mg/ml; SD – standard deviation

Table 6. Pharmacokinetics parameters of 7 patients at dose level II.

Patient #	k_2 (h^{-1})	t* (h)	AUC (μg.h/ml)	C_{max} (μg/ml)	t_{max} (h)	AUMC ($\mu g.h^2$/ml)	MRT (h)	Cl_t/f (l/h/m²)	Vd/f (l/m²)	t>1 μg/ml (h)
1	0.199	3.4	9.3	1.46	2.0	53.78	5.8	3.5	18.0	3.4
2	0.15	4.6	15.2	2.11	1.0	108.97	7.1	1.1	7.6	5.2
3	0.256	2.7	14.5	2.74	3.0	40.61	2.8	1.1	4.4	6.7
4	0.203	3.4	22.8	7.65	2.0	105.62	4.6	1.5	7.5	7.8
5	0.103	6.7	19.3	3.94	1.0	177.87	9.1	1.0	10.0	6.2
6	0.3	2.3	40.9	8.59	2.0	165.01	4.0	0.6	2.1	7.3
7	0.278	2.4	23.1	5.57	1.0	83.17	3.5	0.5	1.8	7.6
Mean	**0.212**	**3.6**	**20.7**	**4.58**	**1.7**	**105.0**	**5.3**	**1.3**	**7.3**	**6.3**
SD	**0.071**	**1.5**	**10.1**	**2.77**	**0.7**	**51.91**	**2.2**	**1.0**	**5.5**	**1.5**

k_2 – elimination constant; t* – half-life; AUC – area under the plasma concentration versus time curve; C_{max} – peak plasma concentration; t_{max} – time to maximum peak concentration; AUMC – area under the first moment curve; MRT – mean residence time; Cl/f – total body clearance related to bioavailability; Vd/f – apparent volume of distribution related to bioavailability; t>1 mg/ml – period of etoposide plasma concentrations >1 mg/ml; SD – standard deviation

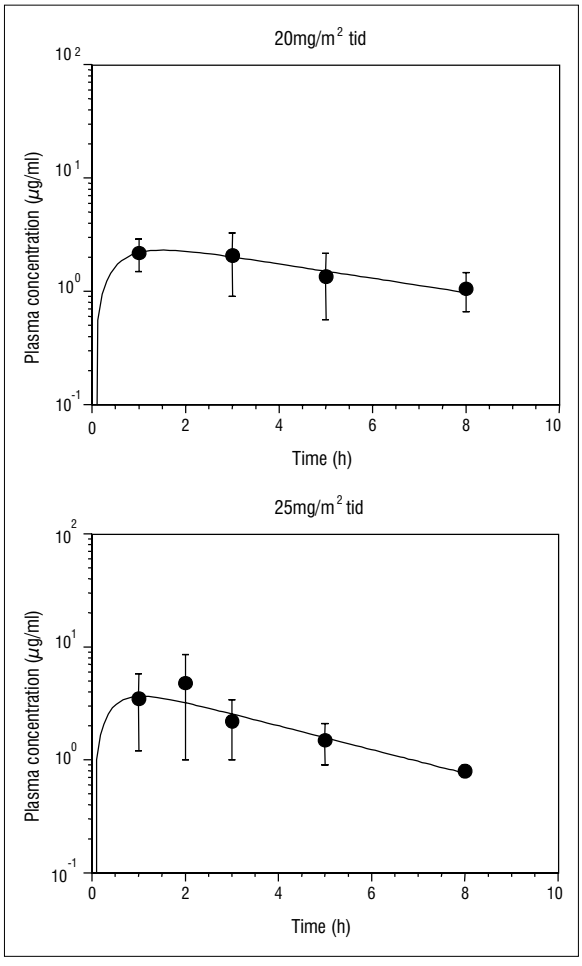

Figure 1. Plasma concentration versus time profiles for oral etoposide in children with refractory solid tumors. Etoposide was administered orally at a dosage of 20 mg/m² (dose level I) or 25 mg/m² (dose level II) every 8 hours daily for 14 days. Blood samples were obtained at baseline and during the first 8 hours after the first oral administration.

Etoposide plasma pharmacokinetics were assessed in 6 and 7 patients at dose levels I and II, respectively. The relevant individual pharmacokinetic parameters are presented in Tables 5 and 6, after the administration of dose levels I and II, respectively. The mean etoposide plasma concentration versus time curves, obtained by averaging the plasma etoposide concentrations of the patients at dose levels I and II, are shown in Figure 1, fitted to a one-compartment model.

Etoposide absorption was first-order, and occurred at a mean rate of 1.82 and 2.36 h^{-1} for doses level I and II, respectively. The elimination rate constant was 0.167±0.073 h^{-1} and 0.212±0.071 h^{-1} for dose levels I and II, respectively. The drug disappeared from the plasma with a mean $t_{1/2}$ of 4.6±1.4 h at dose level I and 3.6±1.5 h at dose level II. The mean AUC at dose levels I and II was 19±6.7 and 20.7±10.1 μg·h/ml, respectively. The mean C_{max} was 2.59±0.59 μg/ml, and was reached approximately 2 hours after being administered to patient on dose level I. For dose level II patients, the mean C_{max} was 4.58±2.77 μg/ml, which was observed on the average 1.7 hours after first dose administration. The etoposide levels remained greater than 1 μg/ml for a average of 6.3±1.4 hours at dose levels I and II.

The highest C_{max} observed at dose level I was 2.97 μg/ml. Etoposide plasma concentrations greater than 5 μg/ml were observed in 3 out of 7 patients receiving 25 mg/m² dose (dose level II). There were no significant differences ($p > 0.05$) in the pharmacokinetic parameters obtained from patients at dose level I when compared with the group receiving dose level II.

Discussion

Although the majority of children with cancer can be cured, there is still a need for new agents and/or protocols to treat patients with relapsed or refractory tumors. The results of phase I studies with new drugs in adults may be a predictor of MTD and toxicities for the pediatric population, but it is very important to consider the wide differences in prior therapies, metabolism and body composition between these two populations before extrapolating to children the adult dose for phase II

[25]. It is only reasonable to identify the MTD and toxicities in pediatric phase I studies, as well as the pharmacokinetic profile of drugs, in order to define the dose for subsequent phase II trials for this specific population.

Etoposide is highly schedule-dependent in terms of its antitumor activity, showing superior results with multiple drug administrations as compared to single high dose administration [3]. Pharmacokinetic analysis suggests that this could be related to the greater anti-tumor effect obtained when etoposide plasma concentrations between 1 and 5 μg/ml are sustained, avoiding the myelotoxicity observed with high plasma levels (> 5 μg/ml) [3,5,6,26].

The etoposide preparation used for intravenous administration is of similar composition to the oral solution and may be taken orally [27,28]. Therapeutic plasma levels can be achieved by the oral route, assuming a bioavailability of 50% [3,29,30]. In view of the foregoing, we decided to evaluate the administration of fractionated doses of etoposide every 8 hours in children with refractory or relapsed solid malignancies. The determination of drug plasma concentration is essential to identify an appropriate dose. Our goal was to establish a tolerable dose of oral etoposide for future studies.

The level of compliance with the oral route was satisfactory in this study, as only one patient discontinued treatment because of grade 2 abdominal pain. The patients were treated with the oral regimen in the outpatient clinic, which minimized the inconvenience and costs associated with hospitalization. This is an important aspect of patient care, which favorably affects quality of life.

The initial dose of etoposide in our study was chosen on the basis of a prior study by Schwartsmann et al. in adult patients, which suggested a daily dose of 60 mg/m^2 (divided into three daily doses of 20 mg/m^2 each) for patients with heavily pretreated malignancies [19]. The hematological toxicity was reversible at that dose, while escalation to dose level II (25 mg/m^2 every 8 hours) produced severe myelotoxicity. Grade 4 neutropenia was documented in 3 out of 8 patients; accordingly, these authors recommend a dose of 20 mg/m^2 given three times daily for 14 days for further trials. The non-hematological toxicity was tolerable and manageable, even for patients scheduled to receive dose level II.

The results of our study in pediatric patients confirmed our previous experience with using fractionated doses of oral etoposide in the adult population. Not only the MTD, but also the recommended dose of etoposide for phase II trials were similar to those established for the adult population [19]. Moreover, in a phase I study in children, Mathew et al. also recommended the dosage of 20 mg/m^2 of etoposide t. i. d. for future pediatric studies, although the drug was maintained for three consecutive weeks instead of the two weeks applied in our study [15]. In this study, hematologic toxicity was not considered dose-limiting unless it persisted for longer than 7 days or caused therapy to be interrupted.

In our study, one patient with Wilms tumor experienced partial response, sustained for three months, and another patient with a Ewing's sarcoma had stable disease with regression of symptoms that lasted for at least 20 months. A boy with stage 4 neuroblastoma had stabilization of the disease which persisted for 10 months. Two other patients had stabilized disease that lasted for less than 6 months. Despite the fact that all these patients had received intravenous etoposide in previous schedules, we observed that prolonged administration of oral etoposide at low dose exhibit some degree of antitumor activity. A similar observation has also been made by other authors [15,17,31]. Notably, no secondary acute myeloid leukemia was observed in our study, although low-dose oral etoposide at frequent intervals is reported to present an increased risk of secondary leukemia [31]. This may be attributed to the short follow-up, and also the small number of patients included in our study.

The results from our pharmacokinetic analysis are in accordance with data reported in the literature [3,28], and suggest that safe plasma concentrations may be obtained with a t.i.d. schedule in children, as there is no evidence of drug accumulation upon repeated drug administrations [26]. As in our previous studies in adults, etoposide was administered using a similar mixture of the contents of the ampoule with orange or lemon juice, which maintains a pH of about 5.0 to facilitate oral absorption, while making the solution palatable for oral use. The mean elimination half-life of etoposide appears shorter in our pediatric population than that observed in adults [28].

The pharmacokinetic parameters observed at dose level I did not significantly differ from that obtained after dose level II. Etoposide plasma concentrations above 1 μg/ml were observed and sustained for an average of 6.3 hours after the administration of either dose of the drug, which is similar to observations reported in other studies [11,28]. High plasma concentrations (above 5 μg/ml), associated with severe myelosuppression, were observed in three patients after the first administration of etoposide at dose level II. In patient #6, the pharmacokinetic analysis performed after administration of 25 mg/m^2 of oral etoposide showed a C_{max} of 8.59 μg/ml. After this course of chemotherapy, the patient presented with grade 3 neutropenia. Patient #4, whose C_{max} after the first dose of etoposide was 7.65 μg/ml, developed grade 2 neutropenia. All other patients for whom C_{max} was less than 5 μg/ml had grade 1 neutropenia as the worst myelotoxicity.

CONCLUSIONS

The present study showed that etoposide at the dose of 20 mg/m^2 every 8 hours given for 14 consecutive days in 21-day courses had manageable toxicity in children with refractory advanced malignancies, and seemed to fulfill the pharmacokinetic requirements we had previously

defined as a means to improve the therapeutic index of etoposide, i.e, the attainment of sustained, low cytotoxic plasma levels of the drug. This dose regimen will be used in our future phase II studies in a pediatric population.

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