Cancer Chemother Pharmacol (1996) 38: 459–465

ORIGINAL ARTICLE

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Phase I and pharmacologic study of 7- and 21-day continuous etoposide infusion in patients with advanced cancer

Received: 3 April 1995/Accepted: 6 December 1995

Abstract *Purpose.* This phase I study was undertaken to evaluate the safety and tolerability of prolonged infusional etoposide, and to evaluate its pharmacokinetic/pharmacodynamic profile in patients with advanced cancer. *Methods.* A group of 17 patients received a 7-day infusion of etoposide (schedule A) every 21 days at doses from 30 to 75 mg/m^2 per day, and a second group of 37 patients a 21-day infusion (schedule B) every 28 days at doses from 18 to 40 mg/m^2 per day. Patients had a median Karnofsky performance status (PS) of 80%, and 34 patients had no prior chemotherapy. Etoposide concentrations at steady state (Css) and other pharmacokinetic parameters (plasma clearance, CLp; area under the curve, AUC) were determined during the first treatment cycle. Correlation coefficients were calculated to measure the relationship between variables. *Results.* Myelosuppression was the major toxicity, and was associated with three deaths. The maximum tolerated dose due to neutropenia was 75 mg/m^2 per day for schedule A and 40 mg/m^2 per day for schedule B. There was significant interpatient pharmacokinetic variability in both infusional schedules. Even though etoposide dose levels did not significantly correlate with plasma levels, the Css was ≥ 1 μg/ml in the majority of the patients. A significant correlation between AUC and neutrophil absolute decrease was noted only in schedule B ($r = 0.56$, $P = 0.003$). There were several marginal relationships in schedule B: PS versus Css ($r = 0.31$, $P = 0.058$), PS versus AUC ($r = -0.38$; $P = 0.058$) and age versus CLp ($r = -0.31$, $P = 0.057$). *Conclusion.* Overall, significant correlations were found for several hematologic variables and etoposide dose levels, but not with the Css values. One major problem with the application of pharmacodynamic models to predict hematologic toxicity in clinical practice is the presence of significant interpatient variability.

Key words Chemotherapy · Etoposide infusion

This study was supported in part by grant CA-13148

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Introduction

Laboratory and clinical data indicate that etoposide is both phase-specific and schedule-dependent [3, 4, 7]. Recently, a great deal of attention has been given to its schedule dependency, resulting in clinical trials using prolonged oral administration [11, 12, 15, 30]. Significant activity with this approach has been observed in small-cell lung cancer, germ cell tumors and lymphoma. Prolonged exposure to low concentrations (~ 1 μg/ml in plasma) of the drug has been considered important for its antitumor efficacy. Considerable interpatient and intrapatient variability exists in the pharmacokinetics of oral etoposide, and its absorption

is not linear with increasing doses within the range of clinical use [13, 14, 26]. Therefore, continuous infusions may be more effective than oral administration for the maintenance of low concentrations for prolonged periods, and the antineoplastic activity could be higher. The objectives of the present study were to evaluate the safety and tolerability of etoposide in 7- and 21-day continuous infusion schedules, and to clarify the relationship between pharmacokinetic parameters and clinical toxicities in patients with advanced cancer.

Patients and methods

The eligibility criteria included histologically confirmed, inoperable advanced solid tumor, a Karnofsky performance status of $\geq 60\%$, and no previous antineoplastic therapy for at least 3 weeks. The patients were required to have adequate renal and hepatic function and bone marrow reserve. Informed consent was required. For the first part of the study, patients were allocated to two infusional schedules (A, 7 days; or B, 21 days) of etoposide. At least three etoposide-naive patients were entered at each escalated dose level. As the maximum tolerated dose (MTD) was approached and potential dose-limiting toxicity was observed, five patients or more per dose level were entered. No dose escalation was allowed within patients assigned to specific dose levels in this part of the study. The MTD was defined as that dose that produced dose-limiting toxicity in 50% or more of the evaluable patients at any dose level. Dose-limiting toxicities were defined as at least one of the following: (1) absolute neutrophil count (ANC) $< 500/\mu l$ or platelet count $< 50\,000/\mu l$, and (2) nonhematologic toxicity (except for alopecia) grade 2 or more.

Etoposide was administered as a continuous infusion by a portable infusion pump (Medfusion WalkMed 400, Clinical System, St. Louis, Mo.) at different dose levels for 7 days (schedule A: 30, 45, 60, and 75 mg/m^2 per day) or 21 days (schedule B: 18, 25, 30, and 40 mg/m^2 per day). Treatment cycles were repeated on day 21 or day 28 for schedule A and B, respectively, if the ANC was $\geq 1500/\mu l$ and platelet count $\geq 150\,000/\mu l$, and any nonhematologic toxicity had reversed to baseline values. Etoposide was diluted with 5% dextrose solution at a maximum concentration of 0.4 mg/ml. A white granular precipitation was occasionally observed in the plastic containers at a concentration of 0.4 mg/ml, resulting in malfunctioning of the pump. This complication was immediately resolved by a change of the drug concentration to 0.2 mg/ml. The infusate was changed every 12 or 24 h depending on the total daily dose. Doses of etoposide were reduced by 25% or 50% for grade 3 and 4 neutropenia/thrombocytopenia or grade 2 and 3 nonhematologic toxicity, respectively.

Chemotherapy-naive patients with advanced non-small-cell lung cancer, and who fulfilled the other eligibility criteria, were included in the second part of the study. These patients were treated with schedule B (21-day infusion) using one dose level below the MTD. A 20% dose escalation was allowed in this part of the study in the absence of nonhematologic toxicity (except for alopecia), and if the ANC and platelet nadirs were $> 1500/\mu l$ and $> 100\,000/\mu l$, respectively.

Pretreatment evaluation included a history and physical examination, complete blood cell counts with differential (CBC), routine chemistry profile, urinalysis, and a chest roentgenogram. Additional radiographic studies were obtained as clinically indicated and as necessary to document measurable or evaluable disease. During treatment, a CBC with differential was obtained weekly, and a chemistry profile prior to each cycle of treatment. Creatinine clearance was estimated prior to treatment using a previously published formula [5]. Toxicity was graded weekly according to National Cancer Institute criteria. Febrile neutropenic episodes were considered severe or life-threatening when there was evidence of a significant infection (e.g. pneumonia, bacteremia), fever $> 40^\circ$C for more than 24 h in the absence of a source of infection, or fever accompanied by hypotension. Response was assessed after completion of each cycle of treatment or following every two cycles if computed tomograpic measurements were required. Treatment response was assessed according to standard criteria [20]. Patients with no clinical evidence of tumor progression received a second cycle of treatment and those with no response after two cycles were removed from the study. Etoposide was continued until patients demonstrated evidence of tumor progression or experienced unacceptable toxicity.

Each patient during the first cycle of treatment underwent pharmacokinetic evaluation. Heparinized blood samples were obtained from the arm opposite that used for drug infusion at 4, 6, 24, 48, and 96 h, and on day 7 after the start of the etoposide infusion. In addition, weekly blood samples were taken in the morning in those patients on the 21-day schedule. Etoposide concentrations were determined using a high-performance liquid chromatography (HPLC) assay reported previously [18]. The lower limit of sensitivity was 0.05 μg/ml.

Etoposide concentration at steady state (Css) was defined as the mean of the measured plasma concentration at ≥ 24 h after the initiation of the infusion [1]. The etoposide plasma clearance at steady state (CLp) was determined by using the formula:

$$\text{CLp (ml/min per m}^2) = \frac{\text{Infusion rate(mg/m}^2\text{ per min)}}{\text{Css (mg/ml)}}$$

The area under the etoposide curve (AUC) was calculated as follows [6] :

$$\text{AUC (mg h/l)} = \text{Css} \times \text{infusion duration}$$

We correlated different pharmacokinetic parameters at each dose level of etoposide in the first treatment cycle with the degree of hematologic toxicity. The absolute decrease (before treatment minus nadir counts) and relative decrease (absolute decrease divided by before treatment count) were calculated. To minimize the impact of interpatient variability in pretreatment blood parameters, we also calculated the survival fractions (nadir count divided by pretreatment count) of neutrophils, platelets and hemoglobin. The interpatient variability of etoposide plasma levels was expressed as the coefficient of variation [8]. For each treatment schedule, correlation analysis yielded estimates of correlation coefficients between pharmacokinetic parameters, observed hematologic toxicities, performance status, serum albumin, and estimated creatinine clearance. Pearson's correlation coefficients were obtained for continuous variables (i.e. blood counts) and Spearman's correlation coefficients for variables related to graded toxicity [8, 24]. The Pearson's rank (Spearman's) and partial correlation coefficients were calculated to measure the relationship between variables [10]. The two-sample Wilcoxon's (rank sum) test was used to compare outcomes in the groups classified by performance status or other parameters [31].

Results

The characteristics of the 54 evaluable patients are shown in Table 1. All of the patients were ambulatory, and 34 (63%) had not received any prior chemotherapy. Patients who had had prior radiation therapy (44%) had less than 25% of bone marrow exposure and were entered onto this study ≥ 6 weeks from the last treatment. Of the 22 patients treated on schedule B at a dose level of 30 mg/m^2 per day, 17 belonged to the second part of the study. At this dose level, 20 patients (91%) were chemotherapy-naive. A total of 113 treatment cycles were administered, with a median number of 2 per patient.

Table 1 Patient characteristics and treatment schedules

	No. of patients
Evaluable patients[a]	54
Male/female	50/4
Karnofsky performance status (%)	
100–80	36
70–60	18
Prior therapy	
None	23
Chemotherapy	20
Radiation therapy	24
Disease site	
Lung	31
Colorectal	5
Renal	3
Esophagus	3
Pancreas	3
Other	9
Treatment schedule (mg/m^2 per day)	
A. 7-day infusion: 30 (3) [b], 45 (3), 60 (5), 75 (6)	17
B. 21-day infusion: 18 (3), 25 (4), 30 (22), 40 (8)	37

[a] Age (years): median, 60; range 31–73
[b] Numbers in parentheses indicate number of patients at each dose level

The dose-limiting toxicity of etoposide on these continuous infusion schedules was neutropenia. Table 2 lists the hematologic toxicities for the first cycle of treatment. In schedule A, grade 3 or worse neutropenia occurred in 11 of 42 cycles (26%), most of them at the dose level of 75 mg/m^2 per day. At this dose, grade 4 neutropenia occurred in 3 of 6 patients during the first cycle. The median neutrophil nadir at this dose level during the first cycle of treatment was 495/μl (range 12–2240/μl); these nadirs occurred in a median of 16 days (range 14–21 days). There were eight febrile neutropenic episodes in this schedule; but only three at dose levels 45–75 mg/m^2 per day were severe or life threatening. Thrombocytopenia of $< 75\,000$/μl ($\geq$ grade 2) occurred in three cycles of treatment, but was only associated with one bleeding complication. This patient developed gastrointestinal bleeding from a gastric ulcer when the platelet count was 53 000/μl. Anemia of grade 2 or more was observed in 45% of the treatment cycles, and four patients required blood transfusions. One possible toxic death was observed in this schedule, and was related to neutropenia and gastrointestinal bleeding. Significant myelosuppression was the reason for dose reduction by 25–50% in six subsequent cycles of therapy, and treatment delays for 1 week on three occasions. Nonhematologic drug toxicities, except for alopecia, were infrequent and mild. Grade 1 nausea and vomiting occurred in six cycles; symptoms were easily controlled by prochlorperazine. One patient experienced grade 1 diarrhea immediately after cycle 1.

In schedule B, grade 3 or worse neutropenia occurred in 18 of 71 cycles of treatment (25%); most of them at the dose levels of 30–40 mg/m^2 per day. During the first part of the study, grade 4 neutropenia occurred in one of five patients initially entered at the dose level of 30 mg/m^2 per day. At this dose, 17 additional patients were entered in the second part of the study, with an overall grade 4 neutropenia of 14% (Table 2) during the first cycle of treatment. The median neutrophil nadir for cycle 1 at 30 mg/m^2 per day was 1595/μl (range 40–3850/μl); these nadirs occurred in a median of 26 days (range 20–29 days). Etoposide infusion at this dose level was discontinued before day 21 in 6 of 48 cycles (13%) because of significant myelosuppression, and treatment delays were required on two occasions. A 20% dose increment was feasible in only 6 of the 17 patients eligible for dose escalation at the 30 mg/m^2 dose level. At 40 mg/m^2 per day, 5 of 8 patients had grade 3 or worse neutropenia during the first cycle of treatment, despite discontinuation of the infusion in three cases because of neutrophil counts of less than 1000/μl. The median neutrophil nadir for cycle 1 at this dose level was 778/μl (range 40–4680/μl), and the nadirs occurred in a median of 21 days (range 16–27 days). Of the ten febrile neutropenic episodes in this schedule, seven were considered severe or life threatening and eight of them occurred at 30–40 mg/m^2 per day. Two toxic deaths were observed during or immediately after

Table 2 Hematologic toxicity of the first cycle of treatment (NCI Common Toxicity Criteria: neutrophils: grade 0, ≥ 2.0; grade 1, 1.5–1.9; grade 2, 1.0–1.4; grade 3, 0.5–0.9; grade 4, < 0.5; platelets: grade 0, normal range; grade 1, 75 – normal; grade 2, 50–74.9; grade 3, 25–49.9; grade 4, < 25; hemoglobin: grade 0, normal; grade 1, 10 – normal; grade 2, 8–10; grade 3, 6.5–7.9; grade 4, < 6.5)

Schedule	No. of patients[a]	Neutrophils 0	1	2	3	4	Platelets 0	1	2	3	4	Hemoglobin 0	1	2	3	4
A. (mg/m^2 per day × 7)																
30	3 (3)	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0
45	3 (2)	2	0	0	0	1	2	0	0	0	1	1	1	0	1	0
60	5 (3)	1	1	0	1	2	3	2	0	0	0	0	2	3	0	0
75	6 (4)	1	0	0	2	3	2	2	1	1	0	0	4	2	0	0
B. (mg/m^2 per day × 21)																
18	3 (2)	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0
25	4 (1)	2	0	0	1	1	2	1	1	0	0	1	1	1	1	0
30	22 (2)	8	3	3	5	3	20	1	0	1	0	1	12	6	3	0
40	8 (2)	2	0	1	4	1	6	1	0	1	0	0	2	1	4	1

[a] Numbers in parentheses indicate patients who had had prior chemotherapy

Table 3 Etoposide plasma concentrations (Css). Values are from the first cycle of treatment (μg/ml)

	Schedule A (mg/m^2 per day)				Schedule B (mg/m^2 per day)			
	30 ($n = 3$)	45 ($n = 3$)	60 ($n = 6$)	75 ($n = 6$)	18 ($n = 3$)	25 ($n = 4$)	30 ($n = 22$)	40 ($n = 8$)
Mean	1.9	9.9	2.5	2.4	2.5	1.3	1.4	3.6
SD	1.6	10	0.9	0.5	2.6	0.2	0.4	7.3
Median	1.4	6.2	2.4	2.4	1.2	1.4	1.3	1.1
Range	0.5–3.7	2.2–21	1.4–3.6	1.8–2.9	0.7–5.5	0.9–1.4	0.5–2.1	0.7–21
Coefficient of variation (%)	86	101	35	20	107	16	28	201

cycle 1 at the 25–30 mg/m^2/per day dose levels and were related to neutropenia complicated in one patient by an infectious pneumonia and sepsis in the other. Thrombocytopenia of $< 75\,000/\mu l$ ($\geq$ grade 2) was observed on three occasions during the first cycle of treatment (Table 2), but only one grade 4 episode occurred in one patient after a 20% dose escalation (36 mg/m^2 per day). No bleeding complications were observed. Anemia of grade 2 or more was observed frequently at the 30–40 mg/m^2 per day dose levels, and there was a suggestion of a cumulative effect with repeated cycles of treatment. Blood transfusions ($n = 36$) were required by 12 patients.

Nonhematologic toxicities were modest. Alopecia was seen in all patients who completed at least one cycle of treatment. Nausea and vomiting was observed in 17% of all cycles, but it was significant (grade 2) in only three patients who received etoposide infusions of 30–40 mg/m^2 perday. Grade 3 mucositis occurred in two patients treated at 40 mg/m^2 per day and was associated with neutropenia in both cases. Other toxicities (grade 2 or more) observed in this schedule included grade 2 diarrhea in two patients (20 mg/m^2 per day) and grade 3 cutaneous reaction in one patient (30 mg/m^2 per day). Other side effects (anorexia, fatigue, weight loss) were observed and may not have been related to etoposide in all instances.

Objective responses were noted in one patient on schedule A and in four on schedule B. All responses were partial, with a median duration of response of 3 months (range 208 months). Two of these responses occurred in patients with advanced non-small-cell lung cancer, and one each in patients with small-cell lung cancer, adenocarcinoma of the colon and adenocarcinoma of unknown primary.

The etoposide plasma concentrations for both infusional schedules are listed in Table 3. There was considerable variation between patients. Dose levels (mg/m^2) in each treatment schedule did not significantly correlate with plasma etoposide concentrations. Nevertheless, the Css was ≥ 1 μg/ml in the majority of the patients. Etoposide concentrations at steady state were highly variable within each dose level. Expressed as a coefficient of variation, the interpatient variability ranged from 20% to 101% in schedule A, and 16% to 201% in schedule B. The interpatient variability was not clearly related to the creatinine clearance, serum albumin, age or performance status. Considerable interpatient variability was also noted with etoposide AUC and plasma clearance in both treatment schedules. There were several marginal relationships in patients treated on schedule B: performance status versus Css ($r = 0.31$, $P = 0.058$), performance status versus AUC ($r = -0.38$, $P = 0.058$) and age versus CLp ($r = -0.31$; $P = 0.057$). Pharmacokinetic data on 22 patients at the 30 mg/m^2 per day dose level (schedule B) are shown in Table 4. The AUCs, etoposide plasma concentrations (Css) and total plasma clearance rates were tested for their possible correlation with age, performance status, creatinine clearance, and serum albumin. No significant correlations were found between these variables at this dose level.

Table 4 Pharmacokinetic parameters of the 21-day continuous infusion of etoposide at 30 mg/m^2 per day ($n = 22$). Values are from the first cycle of treatment on schedule B

	Css (μg/ml)	CLp (ml/min/m^2)	AUC (mg h/l)
Mean	1.4	28.8	657
SD	0.4	11.7	170
Median	1.3	25.8	657
Range	0.5–2.1	16–67	262–932
Coefficient of variation (%)	28	40	25

Pharmacodynamic correlations were evaluated in all patients during the first cycle of treatment. We attempted to identify any significant pharmacokinetic relationship with hematological toxicity. This analysis was performed on each treatment schedule, and in the 22 patients treated at 30 mg/m^2 per day on schedule B. As expected, due to the considerable interpatient variability of the pharmacokinetic parameters, few weak correlations were observed. A significant correlation between AUC and neutrophil absolute decrease was noted in schedule B ($r = 0.56$, $P = 0.003$), but only a trend with all patients on both schedules ($r = 0.26$, $P = 0.09$). Another weak correlation was between Css and neutrophil absolute decrease in schedule B ($r = 0.31$, $P = 0.06$), but not in schedule A. The relationship between Css and other hematologic parameters was not significant. Significant correlations were found for several hematologic parameters and etoposide dose levels (Table 5). Several

Table 5 Correlation coefficients for etoposide dose levels and hematologic toxicity for the first cycle of treatment

	Schedule A ($n = 17$)		Schedule B ($n - 37$)	
	Correlation coefficient[a]	*P*-value	Correlation coefficient[a]	*P*-value
Grade neutropenia	0.54	0.026	0.27	0.10
Grade anemia	0.36	0.15	0.50	0.002
Grade thrombocytopenia	0.41	0.10	0.01	0.92
Neutrophil, nadir	− 0.59	0.014	− 0.38	0.022
Hemoglobin, nadir	− 0.19	0.47	− 0.52	0.001
Platelet, nadir	− 0.38	0.13	− 0.11	0.53
Neutrophil, survival fraction	− 0.53	0.028	− 0.36	0.029
Hemoglobin, survival fraction	− 0.50	0.042	− 0.43	0.008
Platelet, survival fraction	− 0.56	0.019	− 0.23	0.17
Neutrophil, absolute decrease	0.44	0.07	0.20	0.23
Hemoglobin, absolute decrease	0.58	0.014	0.37	0.026
Platelet, absolute decrease	0.62	0.008	0.29	0.08
Neutrophil, relative decrease	0.53	0.027	0.36	0.030
Hemoglobin, relative decrease	0.50	0.039	0.44	0.006
Platelet, relative decrease	0.56	0.019	0.22	0.18

[a] Spearman's correlation coefficient for graded variables and Pearson's correlation coefficient for all other variables

Table 6 Correlation coefficients of age and estimated creatinine clearance on various measures of hematologic toxicity for patients treated on Schedule B at 30 mg/m^2 per day ($n = 22$) during the first cycle of treatment

	Age[a]		Creatinine clearance[b]	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Grade neutropenia	0.34	0.11	− 0.66	0.001
Neutrophil, nadir	− 0.52	0.014	0.51	0.014
Neutrophil, survival fraction	− 0.49	0.020	0.33	0.13
Neutrophil, relative decrease	0.49	0.020	− 0.33	0.13
Hemoglobin, survival fraction	− 0.42	0.05	0.41	0.06
Hemoglobin, absolute decrease	0.46	0.033	− 0.39	0.07
Hemoglobin, relative decrease	0.41	0.05	− 0.41	0.05
Platelet, nadir	− 0.55	0.007	0.39	0.07

[a] Age (years) : median, 60; range, 43–73
[b] Estimated creatinine clearance (ml/min) : median, 66; range, 35–178

neutrophil variables (nadir, survival fraction, relative decrease) and hemoglobin variables (survival fraction, absolute and relative decrease) were significantly correlated in both treatment schedules. Table 6 shows that age and creatinine clearance were correlated with several variables of hematologic toxicity in those patients treated at 30 mg/m^2 per day (schedule B). Examination of age versus creatinine clearance in this group of patients revealed a significant correlation ($r = -0.61$, $P = 0.003$).

Discussion

The results of this study indicate that etoposide may be given by continuous infusion for 7 or 21 days with tolerable toxicity. Besides alopecia, myelosuppression was the most frequent drug-related toxicity being associated with three toxic deaths, one in schedule A and two in schedule B. The dose-limiting toxicity in both treatment schedules was neutropenia. Other significant toxicities included anemia during the last two dose levels of each schedule (Table 2) and nausea and vomiting on schedule B. The maximum tolerated dosages were 75 mg/m^2 per day for schedule A and most probably 40 mg/m^2 per day for schedule B. There was one grade 4 neutropenia at this dose level, but three out of four patients with grade 3 neutropenia had early discontinuation of the infusion because of counts less than 1000 cells/μl.

Similar toxicity data have been obtained in a Japanese phase I study in which etoposide was administered at doses of 300–700 mg/m^2 over 14 days continuous infusion [21]. The MTD in this study was 50 mg/m^2 perday, and neutropenia and mucositis were the dose-limiting side effects. Grade 3 mucositis occurred in two of our eight patients at doses of 40 mg/m^2 per day over 21 days. Apparently this toxicity becomes dose limiting either when the chronic infusion dose is $\geq$ 40 mg/m^2 per day or with very high-dose schedules [22]. The toxicity of schedule B at doses

of ≤ 30 mg/m^2 per day is comparable with that found by Thompson et al. [29] with a similar chronic infusion regimen. In that study, etoposide was administered by continuous infusion at 18–25 mg/m^2 per day for at least 21 days, or until the leukocyte count decreased to $< 2000/\mu l$, the platelet count to $< 75\,000/\mu l$, or tumor progression. Similar degrees of neutropenia and anemia were observed, and significant mucositis was uncommon. In contrast to this study, only 40% of our patients treated on schedule B at ≥ 30 mg/m^2 per day potentially could have been treated for much longer periods (> 21 days).

Neutropenia is also the dose-limiting factor after 21 days for chronic administration of oral etoposide at a dose of 50 mg/m^2 per day, limiting the duration of treatment [11]. This dose is biologically equivalent to approximately 40 mg/m^2 per day intravenously [14]. This time limitation over 21 days with both routes of administration may possibly be for pharmacological reasons. Higher peak levels of oral etoposide (3–5 μg/ml) are seen with a 50 mg/m^2 daily dose, which most likely would result in more myelosuppression than continuous low-dose infusion. When administered by continuous infusion at doses below 30 mg/m^2 per day, such peak levels are avoided, and usually constant low plasma levels (~ 1 μg/ml) are achieved. In fact, the difference in myelosuppression between schedules A and B with comparable total etoposide dosages would tend to support earlier observations of an improved therapeutic index with prolonged exposure to a low plasma concentration (~ 1 μg/ml) of etoposide. Nevertheless, when infusional etoposide is administered at ≥ 30 mg/m^2 per day over 21 days, then a prolonged concentration – time exposure may also result in significant myelosuppression. The influence of duration of exposure on the neutrophil counts at certain dose levels is supported by our data. AUC was significantly correlated with the neutrophil absolute decrease ($P = 0.003$) in patients treated on the 21-day schedule.

This study demonstrates the presence of significant interpatient pharmacokinetic variability for 7- or 21-day etoposide infusions. This variability has been demonstrated previously for etoposide with short- and long-term infusions, and with chronic oral administration [1, 18, 19]. We were unable to identify clinical parameters (age, performance status, serum albumin, creatinine clearance) which could predict this interpatient variability. Other possible explanations for this variability include prior antineoplastic therapy (e.g. radiotherapy) and infusion pump-related factors. In this study, dose level was the only parameter that was clearly correlated with myelosuppression. Etoposide Css values were not significantly correlated with hematologic toxicity, in contrast to the findings of other investigators [1, 19, 21]. The relationship between Css and neutrophil absolute decrease in schedule B showed a trend but was not significant. Even in a population of patients with minimal prior therapy treated with the same dosage (schedule B, 30 mg/m^2 per day), plasma levels of etoposide were not able to predict for hematologic toxicity. There was a significant relationship between several hematologic variables and age or creatinine clearance in those patients treated on schedule B at 30 mg/m^2 per day. This is probably the result of a decline in glomerular filtration rate with age [9] and the fact that renal clearance accounts for 30–67% of etoposide clearance [25].

Other investigators have proposed pharmacodynamic models to predict for hematologic toxicity based on drug measurements and clinical parameters [17, 19, 23]. However, one major problem with the application of this concept is the presence of significant interpatient pharmacokinetic and pharmacodynamic variability. Our incomplete understanding of such variability is of major concern with etoposide and other antineoplastic agents. One important aspect is etoposide plasma protein binding [27, 28], and the wide interpatient variability in the percentage of unbound drug in cancer patients. Another area of concern is the partial understanding of nonrenal clearance of etoposide and its metabolites [16].

Continuous infusion is attractive for many reasons for patients with etoposide-sensitive neoplasms [29], but its contribution in clinical practice remains to be determined. It is a cumbersome and expensive therapeutic approach. Critical issues with the current etoposide formulation are the limited stability at concentrations of ≥ 0.4 mg/ml, and potential cracking of plastic devices with the use of undiluted preparation for prolonged infusions. It is possible that with the new water-soluble derivative, etoposide phosphate, some of these inconveniences are eliminated [2].

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