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Pharmacokinetics of high-dose etoposide after short-term infusion

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Summary. The pharmacokinetics of high-dose etoposide (total dose, 2100 mg/m^2 divided into three doses given as 30-min infusions on 3 consecutive days) were studied in ten patients receiving high-dose combination chemotherapy followed by autologous bone marrow transplantation. In addition to etoposide, all subjects received 2×60 mg/kg cyclophosphamide and either $6 \times 1{,}000$ mg/m^2 cytosine arabinoside (ara-C), 300 mg/m^2 carmustine (BCNU), or 1,200 mg/m^2 carboplatin. Plasma etoposide concentrations were determined by ^{252}Cf plasma desorption mass spectrometry. In all, 27 measurements of kinetics in 10 patients were analyzed. According to graphic analysis, the plasma concentration versus time data for all postinfusion plasma etoposide values were fitted to a biexponential equation. The mean values for the calculated pharmacokinetic parameters were: $t_{1/2\beta}$, 256 ± 38 min; mean residence time (MRT), 346 ± 47 min; AUC, $4{,}972 \pm 629$ μg min ml^{-1} (normalized to a dose of 100 mg/m^2); volume of distribution at steady state (Vd_{ss}), 6.6 ± 1.2 l/m^2; and clearance (CL), 20.4 ± 2.4 ml min^{-1} m^{-2}. A comparison of these values with standard-dose etoposide pharmacokinetics revealed that the distribution and elimination processes were not influenced by the dose over the range tested (70–700 mg/m^2). Also, the coadministration of carboplatin did not lead to significant pharmacokinetic alterations. Although plasma etoposide concentrations at the time of bone marrow reinfusion (generally at 30 h after the last etoposide infusion) ranged between 0.57 and 2.39 μg/ml, all patients exhibited undelayed hematopoietic reconstitution.

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Introduction

Myelotoxicity is the major dose-limiting factor for most antineoplastic drugs. However, autologous bone marrow transplantation (ABMT) circumvents this factor and enables up to a 10-fold escalation of the starting dose. Recently, high doses of the epipodophyllotoxin derivate etoposide (VP16-213) have been used as a part of regimens preparatory to autologous and allogeneic bone marrow transplantation [1, 7, 17, 19, 20, 25]. In these studies, VP16 has been given as single short-term infusions, as continuous infusions, or as repeated short-term infusions.

We studied the pharmacokinetics of high-dose VP16 (700 mg/m^2) given as short-term infusions over 30 min on 3 consecutive days in combination with high-dose cyclophosphamide and either cytosine arabinoside, carboplatin, or BCNU followed by noncryopreserved ABMT [12]. Due to the time limitation for the liquid storage of bone marrow, the plasma levels of cytotoxic drugs are of special interest in this setting. Concurrent administration of cyclophosphamide does not alter the pharmacokinetics of etoposide [3, 24]; however, the influence of prior cisplatin therapy has been demonstrated in two studies [18, 21]. Thus, a further aim of this study was to investigate whether the coadministration of carboplatin causes similar alterations in etoposide pharmacokinetics.

Patients and methods

Patients. Ten adult patients displaying normal renal and hepatic function were included in this study. Their age ranged from 23 to 63 years (median, 43 years). Their underlying disease, age, body surface, and preparative chemotherapy are shown in Table 1.

Chemotherapy. Chemotherapy was started directly after bone marrow preservation. Etoposide (Vepesid) was dissolved in 250 ml 0.9% NaCl solution and infused after cyclophosphamide over 30–40 min. In this rapid-infusion technique, no instability was observed for etoposide. Carboplatin (1200 mg/m^2) was given as a 60-min infusion in 500 ml 5% dextrose solution. Problems of clinical management prevented us from keeping the sequence of drug administration uniform; patients 3, 5 and 8

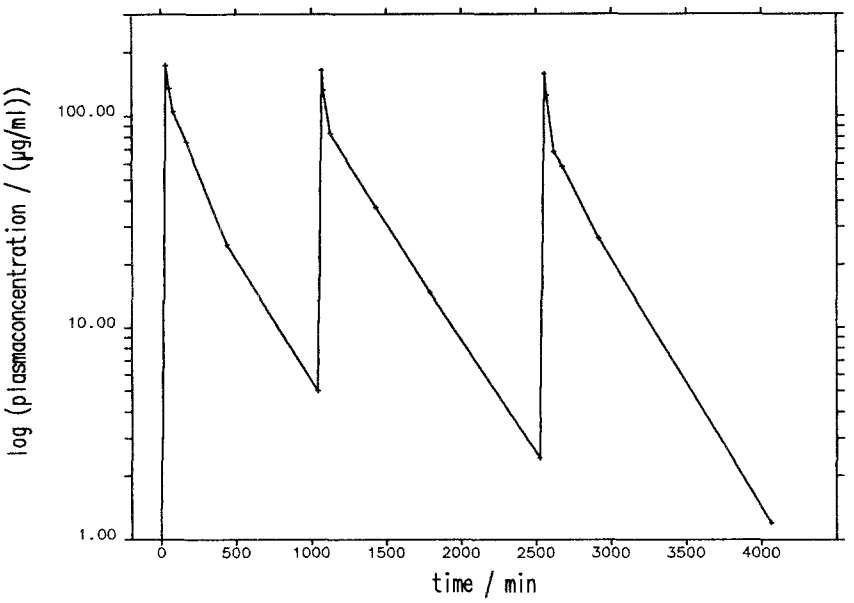

Fig. 1. Plasma etoposide concentrations in a patient treated with 700 mg/m^2 per infusion on 3 consecutive days

Table 1. Characteristics of patients

Patient	Diagnosis	Age (years)	Sex	Body surface (m^2)	Chemotherapy on day		
					–3	–2	–1
1	AML 2.CR	56	F	1.6	C, VP, A	C, VP, A	VP, A
2	ALL 2.CR	26	F	1.55	C, VP, A	C, VP, A	VP, A
3	SCLC	49	F	1.7	C, VP, CP	C, VP	VP
4	AML 1.CR	63	F	1.8	C, VP, A	VP, A	VP, A
5	SCLC	55	M	1.9	C, VP, CP	C, VP	VP
6	SCLC	58	M	2.1	C, VP, CP	C, VP	VP
7	AML 1.CR	40	F	1.8	C, VP, A	C, VP, A	VP, A
8	MT	28	F	1.7	/	C, VP, CP	C, VP
9	LEC	34	M	1.8	C, VP, B	CP, VP, C	VP
10	AML 2.CR	23	F	1.7	C, VP, A	C, VP, A	VP, A

AML, Acute myeloid leukemia; ALL, acute lymphoblastic leukemia; SCLC, small-cell lung cancer; MT, malignant thymoma; LEC, lymphoepithelioma; CR, complete remission; C, cyclophosphamide; VP, etoposide; A, cytosine arabinoside; CP, carboplatin; B, BCNU

received carboplatin immediately after the first etoposide treatment, and subjects 6 and 9 were given carboplatin just prior to the second infusion of etoposide.

Blood samples. Blood samples were taken from a peripheral vein using an indwelling catheter and were collected in tubes containing sodium citrate and then centrifuged. The plasma obtained was frozen at –20° C until analysis. Samples were drawn before and immediately after the infusions and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, and 24 h after the end of the infusions. In five cases, further samples were taken immediately before bone marrow reinfusion. When deviations from this sampling scheme occurred, the exact sampling times were used for calculations.

Etoposide assay. Plasma etoposide concentrations were determined by ^{252}Cf plasma desorption mass spectrometry (PDMS) according to slightly modified methods used in our previous etoposide studies [4, 11]. The etoposide assay was performed in a four-step procedure: sample extraction, sample purification by thin-layer chromatography (TLC), target preparation, and quantitative detection. Initially, 1 ml plasma labelled with the homologous compound teniposide was extracted with 2 ml chloroform at pH 4.5 [4]. The organic phase was removed and the solvent was evaporated under vacuum. The organic extract was redissolved in 50 µl $CHCl_3$ and then separated on reversed-phase thin-layer plates (Merck RP-18F_{254}S) using a mobile phase consisting of methanol, acetonitrile, and water (8 : 2 : 1, by vol.). The selected flow conditions led to a joint spot of etoposide and teniposide, which was scratched off and redissolved for target preparation. A special matrix-assisted preparation technique for the final PDMS target was developed to improve the sensitivity and reproducibility of this method [11]. The quantitative result was obtained by comparing the intensities of the two mass lines corresponding to the molecular ions of etoposide and teniposide. The method was tested by varying the concentration of etoposide from 1 to 100 µg/ml in a blank plasma sample. A linear calibration curve was observed.

Pharmacokinetic calculations. The time dependence of the postinfusion plasma etoposide concentration is described by a biexponential equation over the period examined:

$$c = Ae^{-\alpha t} + Be^{-\beta t},$$

where c is the concentration at time t, A and B are the concentration constants, parameter α is the distribution-phase rate constant, and β is the elimination-phase rate constant. The intercepts A and B, obtained from the postinfusion curve, were corrected for the infusion time [14]:

$$A_{corr} = A\alpha T/(1-e^{-\alpha t}), \quad B_{corr} = B\beta T/(1-e^{-\beta t}),$$

Table 2. Pharmacokinetic parameters measured in 10 patients receiving high-dose etoposide

Patient	*n*	Infusion time (min)	Dose (mg/m²)	Peak level (μg/ml)	AUC (μg min ml⁻¹)	MRT (min)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	Vd_{ss} (l/m²)	CL (ml min⁻¹ m⁻²)
1	3	40,40,40	700	158 ±1	5314 ±111	333 ±28	24 ±6	243 ±31	5.9 ±0.6	18.8 ±0.4
2	3	27,28,35	700	165 ±6	5213 ±412	350 ±25	26 ±9	260 ±7	6.4 ±0.2	19.3 ±1.5
3	3	85,45,55	700	135 ±20	4707 ±650	350 ±21	25 ±9	253 ±17	6.6 ±0.7	20.7 ±2.4
4	3	55,40,45	700	162 ±18	4922 ±508	326 ±25	24 ±2	245 ±20	6.2 ±1.0	20.5 ±2.0
5	3	30,40,45	700	138 ±4	4396 ±320	332 ±33	24 ±6	243 ±23	7.1 ±41	22.9 ±1.6
6	3	40,65,55	700	160 ±5	6542 ±314	439 ±45	22 ±12	330 ±54	6.3 ±0.7	15.2 ±0.6
7	2	40,40	700	172 ±6	5027 ±176	268 ±15	40 ±5	184 ±19	5.0 ±0.5	19.9 ±0.7
8	2	30,33	800	219 ±16	4611 ±508	301 ±40	18 ±5	233 ±27	6.2 ±0.2	22.0 ±2.4
9	2	30,30	700	116 ±22	4091 ±201	428 ±29	24 ±3	316 ±18	9.8 ±0.3	24.5 ±1.2
10	3	90,60,45	700	131 ±15	4895 ±490	336 ±18	29 ±12	236 ±18	6.2 ±0.3	20.6 ±1.9
All patients		27–90	700	156 ±27	4972 ±629	346 ±47	26 ±5	256 ±38	6.6 ±1.2	20.4 ±2.4

Data represent mean values ± SD for all kinetics measured in each patient. AUC values were normalized to a dose of 100 mg/m² (corresponding to standard-dose etoposide treatment). *n*, Number of evaluations of 24-h kinetics

Table 3. Mean pharmacokinetic parameters measured in patients treated with standard-dose etoposide, high-dose etoposide without carboplatin, and the combination of high-dose etoposide and carboplatin

Treatment	AUC (μg min ml⁻¹)	MRT (min)	$t_{1/2\beta}$ (min)	CL (ml min⁻¹ m⁻²)	Vd_{ss} (l/m²)
Standard-dose etoposide	4494 ±1060 (*n* = 22)	372 ±104 (*n* = 30)	281 ±82 (*n* = 30)	22.5 ±5.0 (*n* = 22)	7.0 ±1.25 (*n* = 10)
High-dose etoposide without carboplatin	5016 ±757 (*n* = 22)	344 ±59 (*n* = 22)	256 ±44 (*n* = 22)	20.3 ±2.9 (*n* = 22)	6.5 ±1.20 (*n* = 22)
High-dose etoposide + carboplatin	4962 ±934 (*n* = 5)	350 ±49 (*n* = 5)	257 ±31 (*n* = 5)	20.9 ±3.8 (*n* = 5)	6.8 ±1.5 (*n* = 5)

AUC values were normalized to a dose of 100 mg/m². *n*, Number of measurements evaluated

where T represents the infusion time. The pharmacokinetic parameters were calculated using the following equations:

$AUC = A_{corr}/\alpha + B_{corr}/\beta$,
$AUMC = A_{corr}/\alpha^2 + B_{corr}/\beta^2 + AUC \times T/2$,
$MRT = AUMC/AUC$,
$CL = Dose/AUC$, and
$Vd_{ss} = CL\ (AUMC/AUC–T/2)$,

where *AUMC* represents the area under the moment curve, *MRT* stands for the mean residence time, and CL represents clearance.

Statistical analysis. Student's two-way *t*-test was used to investigate the statistical significance of differences in the pharmacokinetic data. A *P* value of ≤ 0.05 was considered to indicate a positive correlation.

Results

In this study, 27 measurements of kinetics in 10 patients were analysed. In general, etoposide infusions were given on 3 consecutive days; a typical example of 3-day kinetics is shown in Fig. 1. In Table 2 the pharmacokinetic data on all subjects are listed individually as the mean values for all kinetics measured in the same patient. Standard deviations were computed to indicate the extent of individual variability. In contrast to our former studies, inter- and intrapatient deviations did not differ substantially.

Table 3 compares the mean values for pharmacokinetic parameters measured in our standard- and high-dose

etoposide studies. In our standard-dose studies [18], the influence of renal insufficiency and interactions with cisplatin on the pharmacokinetics of etoposide were investigated. Because these two factors alter the AUC and CL values, the corresponding kinetics were not included in the calculation of these values for this comparison. The statistical comparison revealed that the pharmacokinetics of etoposide were not influenced significantly by the dose in the tested range of 70–700 mg/m^2. In five cases of high-dose treatment, etoposide was given in combination with carboplatin (1,200 mg/m^2), which did not lead to significant alterations in etoposide pharmacokinetics (Table 3). Plasma etoposide concentrations at bone marrow reinfusion, generally carried out at 30 h after the last etoposide infusion, were measured in five cases; they ranged from 0.57 to 2.39 μg/ml (mean, 1.09 ± 0.68 μg/ml).

Discussion

In the present study, the pharmacokinetics of high-dose etoposide given at doses of 700–800 mg/m^2 as short-term infusions was studied by analyzing 27 measurements of 24-h kinetics. A comparison of these data with our former standard-dose data revealed that the processes of distribution and elimination of etoposide were not significantly influenced by extremely different doses. This result is in agreement with the findings of other authors who have investigated the kinetics of high-dose etoposide treatment. In contrast to our schedule of drug administration, most other studies have used longer infusion times [6, 8–10]. Gouyette et al. [7] gave 350 mg/m^2 etoposide in 30-min infusions and also found no change in pharmacokinetics. Cunningham et al. [3], who investigated the steady-state kinetics of etoposide (1 g/m^2 given in five infusions over 20 h), observed a significant increase in the volume of distribution at steady state.

The influence of prior cisplatin therapy on etoposide pharmacokinetics – an increase in the AUC value and a decrease in the CL and Vd_{ss} values – has been demonstrated in different studies [18, 21]. Impaired renal function due to the nephrotoxicity of cisplatin may explain this reduction in the clearance of etoposide. In the present study, we also investigated the effect of coadministration of high-dose carboplatin (1,200 mg/m^2) and found no alteration in the pharmacokinetics of etoposide. The sequence of drug administration was indeed not uniform (see Patients and methods), but our result is in agreement with data presented by Newell et al. [16], who studied the influence of carboplatin (600–900 mg) on standard-dose etoposide (120 mg/m^2). As carboplatin does not impair renal function, an influence on etoposide clearance was neither expected nor observed. Moreover, the processes of distribution of etoposide were not altered by carboplatin.

Liquid storage of bone marrow limits the storage time to 96 h. Therefore, bone marrow reinfusion was undertaken at 30 h after the last etoposide treatment. At this time, plasma etoposide concentrations ranged from 0.57 to 2.39 μg/ml. These plasma levels did not delay the hematologic recovery of our patients. The median time required to achieve neutrophil counts of >500/μl and >1,000/μl was 20 (range, 12–39) and 26 (range, 15–47) days, respectively. The median time required to achieve an unsupported platelet count of >20,000/μl was 20 (range, 10–55) days [13]. This is well within the range reported for recovery after the reinfusion of cryopreserved marrow, which is generally carried out at 48 h after the last course of chemotherapy [2, 5, 15, 22, 23].

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