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SHORT COMMUNICATION

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Pharmacokinetics of etoposide in cancer patients treated with high-dose etoposide and with dexrazoxane (ICRF-187) as a rescue agent

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Abstract *Purpose*: The pharmacokinetics of etoposide were studied in cancer patients with brain metastases treated with high-dose etoposide in order to determine if the pharmacokinetics were altered by the use of dexrazoxane as a rescue agent to reduce the extracerebral toxicity of etoposide. *Methods*: Etoposide plasma levels were determined by HPLC. *Results*: The etoposide pharmacokinetics described by a monophasic first-order elimination model were found to be similar to other reported data in other settings and at similar doses. *Conclusions*: The pharmacokinetics of etoposide were unaffected by dexrazoxane rescue.

Keywords Etoposide · Dexrazoxane · Pharmacokinetics · Toxicity · Rescue

Abbreviations $AUC_{0-\infty}$ Area under the curve from time zero to infinity · C_{max} Maximum plasma concentration of drug · Cl_{tot} Total plasma clearance · *HPLC* High-pressure liquid chromatography · P_{oct} Octanol-water partition coefficient · $t_{1/2\beta}$ Beta phase plasma elimination half-time · t_r Retention time

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Introduction

We have previously determined that dexrazoxane (ICRF-187, Zinecard, Cardioxane) is rapidly metabolized to metal ion-chelating products in cancer patients with brain metastases treated with high-dose etoposide [13]. This study also showed that the pharmacokinetics of dexrazoxane are not altered by etoposide. Dexrazoxane is clinically used to reduce doxorubicin-induced cardiotoxicity [15, 16] and may act by reducing iron-based oxygen radical-induced oxidative stress on the heart muscle. Dexrazoxane, which is a strong catalytic inhibitor of DNA topoisomerase II [4], has been shown to antagonize etoposide DNA strand breaks and cytotoxicity [9, 14]. Our previous in vivo experiments have shown that dexrazoxane protects against etoposide-induced lethality and allows a 3.6-fold etoposide dose escalation [6]. Furthermore, in murine models in which tumor cells were inoculated into the central nervous system, treatment with the combination of high-dose etoposide and dexrazoxane resulted in highly significant increases in lifespan [7].

Dexrazoxane is hydrophilic (log P_{oct} −1.8 [4]) and likely does not cross the blood-brain barrier, but the lipophilic etoposide does. Thus, dexrazoxane protects normal tissues and is unable to antagonize etoposide in the central nervous system. The concept of dexrazoxane rescue from high-dose etoposide treatment has been the subject of a small phase I/II clinical trial of patients with brain metastases from primary small-cell lung cancer which provided the patient population for this study [13]. Thus etoposide pharmacokinetics were determined in patients undergoing dexrazoxane rescue from high-dose etoposide treatment in order to determine if dexrazoxane affected etoposide pharmacokinetics.

Patients and methods

The patient eligibility and characteristics have been described previously [13]. Briefly, the trial inclusion criteria were: histologically

Table 1 Etoposide pharmacokinetics in patients treated with high-dose etoposide combined with dexrazoxane rescue (*n* number of plasma concentration–time points for each patient used to obtain the pharmacokinetic parameters, *ND* not determined)

Patient no.	Dexrazoxane (mg/m^2)	Etoposide (mg/m^2)	Sex	*n*	$t_{1/2\beta}$ (h)	C_{max} (μM)	$AUC_{0-\infty}$ ($\mu M \cdot h$)	Cl_{tot} ($ml \cdot min \cdot m^{-2}$)
1[a]	1500	500	M	5	ND	150	ND	ND
2	1500	500	M	6	7.2	160	1770	8.0
3	1500	650	F	5	3.8	88[b]	560[b]	25[b]
4	1000	1000	M	8	7.4	85[b]	980[b]	15[b]
5	1500	500	F	6	2.6	180	820	17
Mean					5.2	133	1030	16.2
SD					2.4	43	520	7.0
Population[c]					5.9	125	1150	12

[a]For patient 1 the etoposide beta phase was not determined as etoposide plasma concentrations were only determined out to 4 h
[b]These values have been normalized to a dose of 500 mg/m^2 of etoposide assuming that they were proportional to the dose
[c]Population pharmacokinetics from all of the data combined (Fig. 1)

verified small-cell lung cancer together with CT- or MR-evaluable brain metastasis and age more than 18 years. Patients in the study group were treated every 3 weeks. The pharmacokinetic studies were done only on the first day of treatment. Three patients were dosed with 500 mg/m^2 etoposide and 1500 mg/m^2 dexrazoxane, one patient was dosed with 1000 mg/m^2 etoposide and 1000 mg/m^2 dexrazoxane, and one patient was dosed with 650 mg/m^2 etoposide and 1500 mg/m^2 dexrazoxane. The patients received different doses of etoposide and dexrazoxane in order to minimize the toxicity of the combination. For example, when the highest dose of etoposide was used, the dose of dexrazoxane was correspondingly reduced. Both etoposide and dexrazoxane were administered through a vascular port catheter. Dexrazoxane was administered over 15 min, followed by infusion of etoposide over 90 min within 15 min of completion of the infusion of dexrazoxane.

The study was not designed solely for evaluating the pharmacokinetic interaction of dexrazoxane and etoposide. It was a phase I/II study designed to investigate the feasibility of treating patients with dexrazoxane prior to treatment with high-dose etoposide. The patient had to understand the objective of the study, and must have signed an informed consent. The study was approved by the Danish Medical Authorities and by the local ethics committee.

Dexrazoxane hydrochloride (Cardioxane) for the clinical studies was obtained from Chiron (Amsterdam, The Netherlands) as a lyophilized powder in 500-mg vials. It was reconstituted in 25 ml sterile water, and the total amount of drug was then mixed with isotonic glucose to a total volume of 250 ml prior to infusion. Etoposide (Vepesid) was obtained from Bristol-Myers Squibb (New York, N.Y.) as a ready-to-administer liquid solution (100 mg etoposide in 5 ml).

Etoposide was determined by isocratic (methanol/water/glacial acetic acid 49/50/1 v/v/v, 1 ml/min, pH 3.5, t_r 14 min) HPLC on a 125 Å 10 µm µBondapak 3.9×300 mm reversed-phase phenyl column (Waters, Canada) [11] with absorbance detection at 235 nm. The HPLC calibration plots using integrated peak areas (2 to 300 μM etoposide) were prepared by adding etoposide (Sigma, St. Louis, Mo.) to blank plasma. The calibration plots ($n=8$) for etoposide were linear (r^2 0.995) with a between-day variation in the slopes of 3% (±SD). Absolute recoveries from spiked plasma ranged from 80% to 97% over a 10 to 300 μM etoposide concentration range with a limit of quantitation of 2 μM.

Blood samples were withdrawn at predetermined times (0, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16 and 24 h) starting directly after completion of the infusion of dexrazoxane (defined as time zero) [13]. A blood sample was also taken as an HPLC control before infusion of any drugs. Blood sampling was from a peripheral vein during infusion of drugs and after completion of treatment the blood was withdrawn from a vascular port catheter. The plasma was acetonitrile-precipitated (2:1 v/v), allowed to settle for 5 min and then centrifuged at 10,000 *g* for 10 min. The supernatant was evaporated to dryness under nitrogen and reconstituted in eluent to stabilize it just prior to analysis. The plasma decay curves for etoposide were fitted to a constant rate i.v. infusion no lag-time monophasic first-order elimination model (WinNonlin 4, Pharsight, Mountain View, Calif.) weighted with the reciprocal of the calculated concentration. Errors quoted are SDs unless otherwise indicated.

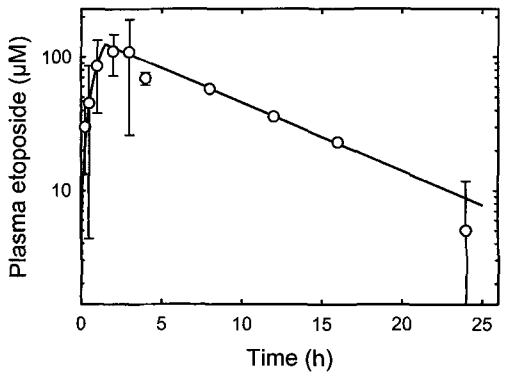

Fig. 1 Normalized (to 500 mg/m^2 etoposide) average plasma concentrations of etoposide after i.v. dosing. The smooth solid line was calculated from a constant rate i.v. infusion no lag-time monophasic first-order elimination model of all of the data from five patients. The best fit to this data yielded $t_{1/2\beta}$ 5.9±1.2 h, C_{max} 125±12 μM, $AUC_{0-\infty}$ 1150±203 $\mu M \cdot h$, and Cl_{tot} 12±2 $ml \cdot min^{-1} \cdot m^{-2}$, where the errors are SEs obtained from the modeling. The error bars on the data points represent the SDs and where no error bars are shown (8, 12, and 16 h) the results are from a single patient (patient no. 4). Other data points are averages from two to five data points

Results and discussion

The etoposide pharmacokinetics were well described with first-order monophasic elimination kinetics due to the extended infusion time (1.5 h) which prevented an accurate determination of the alpha phase kinetics. Fitting of the data to a two-compartment biphasic model did not significantly improve the fit of the data. The results of etoposide pharmacokinetic modeling for the five patients and the population pharmacokinetics for all patients are given in Table 1. The patient numbering was the same as that used in our previous study [13]. The data for the patients dosed at 650 and 1000 mg/m^2 of etoposide are included in Table 1 by normalizing the concentration of etoposide to 500 mg/

m^2 as previous studies have shown that the elimination pharmacokinetic parameters are independent of dose [2, 3, 5, 12]. The average normalized (to 500 mg/m^2) plasma levels of etoposide for all five patients are plotted in Fig. 1.

The pharmacokinetics of high-dose etoposide have been well studied [1, 3, 8, 10, 12] and reviewed [2, 5]. In a review citing 17 studies, the mean $t_{1/2\beta}$ values ranging from 3.4 to 43 h were referenced with a median value of 5.8 h cited [5]. Similarly, the plasma Cl_{tot} of 16.2 ± 7.0 $ml \cdot min^{-1} \cdot m^{-2}$ is similar to a median value of 23.7 $ml \cdot min^{-1} \cdot m^{-2}$ of reported mean values ranging from 3.9 to 48 $ml \cdot min^{-1} \cdot m^{-2}$ [5]. The average C_{max} value of 133 ± 43 μM of this study is also similar to a value of 93 ± 37 μM for patients also dosed at 500 mg/m^2 but with an infusion of 2–3 h [3]. The observational limitations of this study are noted. Thus, while this study was not specifically designed to test whether dexrazoxane affected the pharmacokinetics of high-dose etoposide treatment, the pharmacokinetics of etoposide were similar to other reported data in other settings and at similar doses.

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